NuGOweek 2022

18th edition

29 August - 1 September 2022
Tarragona, Spain

Food bioactives for disease prevention – from mechanisms to chrononutrition

Book of Abstracts

Organisers

NuGO

NuGO is an Association of Universities and Research Institutes focusing on the joint development of the research area of molecular nutrition, personalised nutrition, nutrigenomics and nutritional systems biology

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NuGOweek 2022 INDEX BoA

(digital version)

WELCOME TO THE NUGOWEEK 2022 – 18TH EDITION

Dear NuGOweek participants,

Three years have passed since we met in Bern to celebrate the last in-person edition of the NuGO week. The COVID-19 pandemic has kept us away of enjoying science face to face and we all got used to online meetings to discuss our research. For this reason, we are so excited to finally celebrate the NuGO week LIVE again in the fabulous city of Tarragona, Spain!

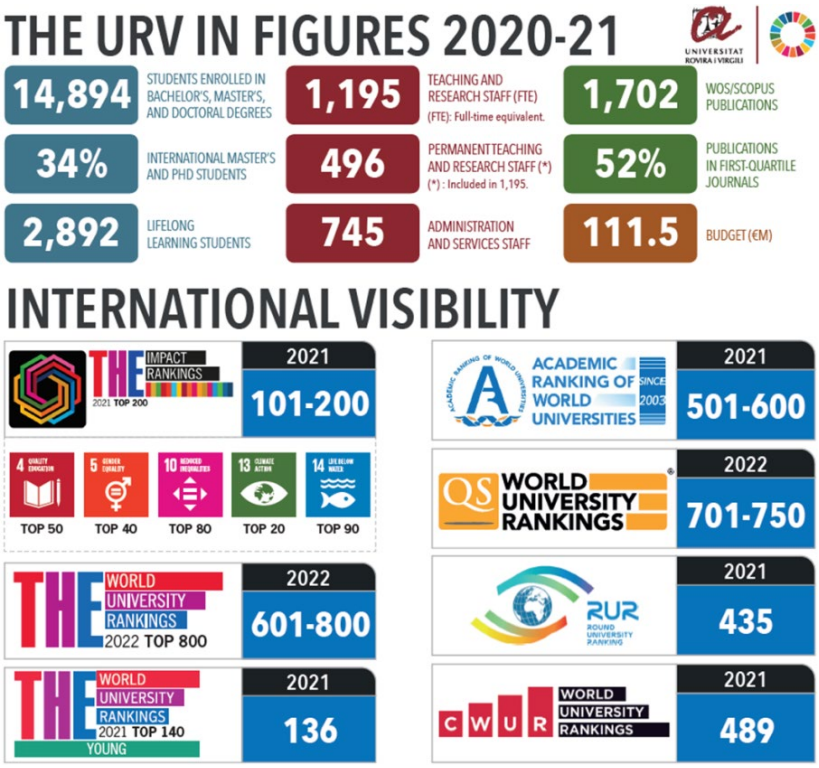
This edition focuses on the importance of food bioactives for disease prevention. It comprises four sessions that will cover different topics including new insights in the activity of these bioactive compounds, the potential of precision nutrition in health managing, the use of omics data in nutrition research and the impact of chrononutrition in metabolism and physiology. Hence, we have an exciting scientific programme ahead involving plenaries from experienced investigators and presentations from young researchers. One more time, the NuGO week brings the chance to young talented researchers to meet senior scientists to discuss about the latest findings on food and nutrition sciences. In addition to the scientific programme, we will enjoy different social events such as a guided tour around Tarragona or the volleyball tournament organized by the Early Career Network (ECN).

We would like to take this opportunity to thank all our speakers, sponsors and everyone who has collaborated to made this event possible.

On behalf of the Organizing Committee of the 18th Edition of the NuGO week

Universitat Rovira I Virgili (URV)

The URV was created in 1991 from the already existing university faculties and schools located in the area of Tarragona. From the very first day its aim has been clear: to place knowledge at the service of society so as to contribute to the social and economic development of its environment.



Since its creation, social and cultural changes have driven our way to face new frameworks and challenges. Hence, at the URV we train professionals under the precepts of European harmonization, a key factor for opening the doors to a world of work without frontiers. And we do so by providing a full range of educational possibilities with more than 40 undergraduate courses and 50 master's degrees (many of which are interuniversity), an extensive doctoral programme and a flexible lifelong learning programme so that professionals can constantly update their knowledge and improve their skills. Altogether, our courses are being enjoyed by over 15,000 students.

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https://www.urv.cat/media/upload/arxius/gabinet-comunicacio/visio-global/urv-overview-2022.pdf

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Scientific programme

Prof. Henrik Oster, Institute of Neurobiology, University of Lübeck, DE
A time to fast, a time to feast - on the circadian regulation of energy intake and metabolism

Prof. Carsten Carlberg, Institute of Animal Reproduction and Food Research, Polish Academy of Sciences, PL
Precision nutrition by vitamin D

Session 1: New insights in the activity of food bioactive compounds

(Chairs: Dr. Manuel Suarez, Prof. Rosita Gabbianelli)

Prof. Yves Desjardins, Institute of Nutrition and Functional Food, Laval University, CA
The (poly)phenol/gut microbiota conundrum: Towards new insights on (poly)phenols mode of action

Florijan Jalsevac, MoBioFood Research Group, Departament Bioquímica i Biotecnologia, Universitat Rovira i Virgili, SP
Protective Effect of Grape-Seed Derived Procyanidin (GSPE) Against Ageing and Cafeteria Diet on the Expression of Bitter Taste Receptors in Rat Intestine

Dr. Annalisa Terranegra, Laboratory of Precision Nutrition - Mother and Child Health Division, Sidra Medicine, QA
Modulation of Gut Microbiota: the effects of a Fruits and Vegetables Supplement

Prof. Timothy (Ted) Dinan, University College Cork, IR
The Psychobiotic Revolution: Mood, Food, and the New Science of the Gut-Brain Connection

Francesca Accardo, University of Parma, Department of Food and Drug, IT
Molecular composition of protein fraction of almond, beef and lesser mealworm after in vitro simulated gastrointestinal digestion and correlation with the hormone-stimulating properties of the digesta

Prof. Joan Ribot, Universitat de les Illes Balears, SP
Combined beta-carotene and metformin treatment against obesity and obesity co-morbidities in mice

Dr. Christine Feillet-Coudray, Muscular Dynamics and Metabolism Unit, INRAE, FR *Health effects of uncommon fatty acids in the diet: focus on FAHFAs and FuFAs*

POSTERS of Session 1

Session 2: Precision Nutrition

(Chairs: Prof. Lorraine Brennan, Dr. Lydia Afman)

Dr. Lydia Afman, Human Nutrition and Health, Wageningen University & Research, NL
Precision Nutrition for Metabolic Health

Anouk Gijbels, Human Nutrition and Health, Wageningen University & Research, NL
Precision Nutrition By Modulating Diets According To Tissue-Specific Insulin Resistance Phenotypes Improves Cardiometabolic Health: The PERSON Study

Dr. Elaine Hillesheim, University College Dublin, IR
Personalised Nutrition Delivered Using a Metabotype Approach Improves Diet Quality and Lipid Profile: A Randomized Controlled Trial

Prof. Bruce Y. Lee, Health Policy and Management at the City University of New York, USA *Role of systems modelling approaches in Precision Nutrition*

Dr. Josep M del Bas, EURECAT — Technology Centre of Catalonia, SP
PREVENTOMICS: Empowering consumers to prevent diet-related diseases through omics sciences.

Dr. Federico Bernuzzi, Quadram Institute BioSciences, UK
The Effect of Dietary Bloactives on Gut Microbiome DivErstiy (DIME)- A pilot study

Lisa Smeehuijzen, Human Nutrition and Health, Wageningen University and Research, NL
Exploring immune cell metabolism to identify hallmarks of healthy versus unhealthy obesity

POSTERS of Session 2

Session 3: Biomarkers and disease — strategies, discoveries and new trends from omics data

(Chairs: Prof. Lorraine Brennan, Dr. Lydia Afman)

Dr. Jean-Charles Martin, Centre for CardioVascular and Nutrition, INRAE, FR
Multiplexed biomarkers as a powerful tool to integrate heterogenous data: application in disease and nutritional status prediction

Dr. Ana María Rodríguez Guerrero, University of the Balearic Islands, SP
Liver metabolomics reflects the ability of leptin supplementation during lactation to counteract metabolic malprogramming

Dr. Atanaska Doncheva, University of Oslo, NO
Perilipin 2 regulates hepatic lipid content and lipid droplet size during fasting

Prof. Paula Oliver, Laboratory of Molecular Biology, Nutrition and Biotechnology, University of the Balearic Islands, SP
Blood cell transcriptomic biomarkers for obesity prevention

Dr. Xavier Domingo-Almenara, Omics Sciences Unit, EURECAT — Technology Centre of Catalonia, SP
Driving biological discovery with computational metabolomics and systems biology

Vera Plekhova, Ghent University, BE
Customized Sampler for Direct Non-invasive Metabotyping of Biofluids in Pediatric ObesitySelected presentation-BD-1

Dr. Stefania Noerman, Chalmers University of Technology, SE
Discovery of metabolite biomarkers of meat consumption and their association with incident type 2 diabetes in a Swedish population-based cohort

POSTERS of Session 3

Session 4: Chrononutrition: giving rhythm to the metabolism

(Chairs: Dr. Begoña Muguerza, Prof. Michael Müller)

Dr. Anna Arola Arnal, Nutrigenomics Research Group, Universitat Rovira i Virgili, SP
Interaction of biological rhythms and dietary phenolic compounds

Iván Escobar-Martínez, Universitat Rovira i Virgili, SP
Biological rhythms affect the bioavailability of phenolic compounds from grape seed proanthocyanidins extract in healthy and obese fischer 344 rats

Francesca Manocchio, Universitat Rovira i Virgili, SP
Effect of Seasonal Phenolic-rich Fruit Extracts on the Regulation of Metabolic Homeostasis

Dr. Lu Li, Simula Metropolitan Center for Digital Engineering, NO
Analyzing postprandial metabolomics data using multiway models: A simulation study

Dr. Olga Ramich, German Institute of Human Nutrition Potsdam-Rehbrücke (Dife), DE
Meal timing: what to eat and when to eat

POSTERS of Session 4

	Poster Number index for Poster Presentation 1			
1. New insights in the activity of food bioactive compounds				
NR	**POSTER-Title**	**Surname**	**Last name**	**Page Nr**
1	Associations Of Maternal And Infant Metabolomes With Immune Maturation And Allergy Development At 12 Months In The Swedish NICE-Cohort Title	Malin	Barman	Page 97
2 + ORAL	Molecular Composition Of Protein Fraction Of Almond, Beef And Lesser Mealworm After In Vitro Simulated Gastrointestinal Digestion And Correlation With The Hormone-Stimulating Properties Of The Digesta	Francesca	Accardo	Page 23
3	Consumption of salmon fishmeal increases hepatic cholesterol content in obese C57BL/6J mice	Knut Tomas	Dalen	Page 50
4 + ORAL	Protective Effect of Grape-Seed Derived Procyanidin (GSPE) Against Ageing and Cafeteria Diet on the Expression of Bitter Taste Receptors in Rat Intestine	Florijan	Jalsevac	Page 20
5	Immunomodulatory Effects Of Probiotic Strains On The Regulatory Mechanisms Of Inflammation In Chickens	Muzahir	Hussain	Page 51
6	Grape-Seed Proanthocyanidin Extract Modulates Intestinal Inflammatory Parameters In Aged Wistar Rats	Adrià	Vilalta	Page 52
7	Blood Pressure Management And Cardioprotective Effect Of Long-Term Comsumption Of Wine Lees In Hypertensive Rats	Raúl	López Fernández	Page 53
8	Maintenance of intestinal barrier function in aged rats fed with a grape seed proanthocyanidin extract-supplemented cafeteria diet	Zacharia Waithaka	Ng'ang'a	Page 54
9	AHR AND ERA ACTIVATION VIA COMBINED E2 PLUS TCDD OR 3,3´DIINDOLYLMETHANE DIFFERENTIALLY ACTIVATE ARYL HYDROCARBON RECEPTOR AND ESTROGEN RECEPTOR ALPHA TO REGULATE DIVERSE SIGNALING PATHWAYS IN MCF-7 HUMAN BREAST CANCER CELLS.	Siddhartha	Das	Page 56
10	Combined supplementation with hesperidin, phytosterols and curcumin improve body composition and decrease adiposity and LDL-cholesterol in ovariectomized rats	Julio Carlos	Baudin Luque	Page 57
11	Cultivation Conditions of Red Grape Modulate the Seasonal Regulation of Energy Metabolism and the Phenotype of White and Brown Adipose Tissues in Fisher 344 Rats	Èlia	Navarro Masip	Page 58
12	Impact of seasonal consumption of local tomatoes on (poly)phenols absorption in Fischer rats	Manuel	Suárez Recio	Page 59
13	Anti-Obesity And Insulin-Sensitizing Effects Of Glycosaminoglycan Supplementation As Dermatan Sulfate	Joan	Ribot	Page 60
14	Untargeted Metabolomics to Explore the Interindividual Variation in the Metabolism of Flavan-3-ols after Standardized Acute Intake of Cocoa	Claudine	Manach	Page 61
2. Precision Nutrition				
NR	**POSTER-Title**	**Surname**	**Last name**	**Page Nr**
15 + ORAL	Diet Interaction With Gut Microbiome And Serum Lipidome Profiling In A Pilot Study On The Obese Qatari Female Population	Annalisa	Terranegra	Page 64
16	Transcriptomic Differences Between Monozygotic Adolescent Twins Discordant for Metabolic Syndrome Following Weight Loss: A Case Study	Kaitlin	Day	Page 65
17	AI4FOOD: a nutritional intervention to integrate digital tools in nutritional advice	Gala	Freixer	Page 66
18	Precision Nutrition Strategies To Enhance The Decline Of The Immune System	Cristina María	Fernández Díaz	Page 67

5. Other

	Poster Number index for Poster Presentation 2			
2. Precision Nutrition				
NR	**POSTER-Title**	**Surname**	**Last name**	**Page Nr**
36 + ORAL	Precision Nutrition By Modulating Diets According To Tissue-Specific Insulin Resistance Phenotypes Improves Cardiometabolic Health: The PERSON Study	Anouk	Gijbels	Page 28
37 + ORAL	The Effect of Dietary BIoactives on Gut Micrbiome DivErstiy (DIME)- A pilot study	Dr Federico	Bernuzzi	Page 32
38 + ORAL	Exploring immune cell metabolism to identify hallmarks of healthy versus unhealthy obesity	Lisa	Smeehuijzen	Page 34
39	A novel Gut-Brain Axis Model towards Precision Nutrition	Julia	Julia Rode	Page 75
3. Biomarkers and disease — strategies, discoveries and new trends from omics data				
NR	**POSTER-Title**	**Surname**	**Last name**	**Page Nr**
40	Discovery of metabolite biomarkers of meat consumption and their association with incident type 2 diabetes in a Swedish population-based cohort	Stefania	Noerman	Page 42
41	Mitochondrial-Nuclear Homeostasis And One-Carbon Metabolism In Obesity	Irene	Petracci	Page 81
42	High fat and high glucose mixed meal affect distinct lipid metabolism gene expression pathways in adipose tissue from abdominal obese subjects with high liver fat and low liver fat	Yan	Fang	Page 82
43	Dash-In: Facilitating Cross-Study Research With Truly Fair And Open Data	Jan	Stanstrup	Page 83
44	Pre-Diagnostic Saliva Microbiota Of School-Aged Children Who Developed Type 1 Diabetes	Nitin	Agrawal	Page 84
45	Relationship Between Free and Bioavailable Vitamin D and Sperm Quality	Bogdan	Roussev	Page 85
46	Brain N-glycosylation and Lipidomic profile changes induced by a High Fat Diet in dyslipideamic Hamsters	Beatrix	Paton	Page 86
47	Proinflammatory Saliva Microbiome Associated with Central Obesity	Heli	Viljakainen	Page 87
48 + ORAL	Customized Sampler for Direct Non-invasive Metabotyping of Biofluids in Pediatric Obesity	Vera	Plekhova	Page 41
49	Machine Learning-Based Retention Time Prediction of Trimethylsilyl Derivatives of Metabolites	Sara	Martinez de Cripan	Page 88
50	A semi-automated workflow for functional analysis of transcriptomic and metabolomic data	Duygu	Dede Sener	Page 89
51	Salivary levels of some pro-inflammatory cytokines in children with plaque-induced gingivitis	Ayshe	Salim	Page 90
52	Plasma Adiponectin And Leptin Mrna Levels In Colorectal Cancer Patients	Yoana	Kiselova	Page 91
53	Expression Of Microrna Associated With Insulin Resistance Is Not Related To Glycaemic Index And Glycaemic Load	Paula	Nascimento Brandao Lima	Page 92
54	Multi-Omics based machine learning prediction of metabolite levels for knowledge discovery	Trisha	Arora	Page 93
55	Digital resilience biomarkers of heart rate variability to evaluate a personalized combined lifestyle intervention	Willem	van den Brink	Page 94
56	Pbmc Transcriptomic Biomarkers Of Increased Metabolic Risk In Apparently Healthy Subjects With Normal-Weight Or With Overweight-Obesity	Andrea	Costa	Page 95
57	Maternal Diet During Gestation And Lactation Affects Brown Adipose Tissue Thermogenesis Capacity Of The Offspring In A Sex-Dependent Manner	Rocío Agustina	Martín Chamorro	Page 96

4. Chrononutrition: giving rhythm to the metabolism				
NR	**POSTER-Title**	**Surname**	**Last name**	**Page Nr**
58	Analyzing postprandial metabolomics data using multiway models: A simulation study	Lu	Li	Page 47
59	Postprandial Transcriptomic Response of Peripheral Blood Mononuclear Cells to a High Fat Meal: A Systematic Review	Natalie	McPhee	Page 99
60	Postprandial expression levels of circadian rhythm related genes in adipose tissue and immune cells from men with and without metabolic syndrome	Aimee	Dordevic	Page 102
61	Biological Rhythms Affect The Bioavailability Of Phenolic Compounds From Grape Seed Proanthocyanidins Extract In Healthy And Obese Fischer 344 Rats	Iván	Escobar-Martínez	Page 45
62	Effect of Seasonal Phenolic-rich Fruit Extracts on the Regulation of Metabolic Homeostasis	Francesca	Manocchio	Page 46
63	Time-of-day dependent effect of Grape seed proanthocyanidin extract (GSPE) for the treatment of non-alcoholic fatty liver disease in obese rats	Antonio Jesús	Cortés Espinar	Page 100
64	Body mass index from late childhood to adolescence and associations with lifestyle behaviours	Marja	Leppänen	Page 101
65	Protocol of Personalized Nutritional Advice To Improve Short-term Fitness and Long-term Health In Shift Workers	Joelle	Oosterman	Page 103
66	Proanthocyanidins modulate central clock, restore circadian rhythmicity, and improve cardiometabolic risk factors in CAF diet-induced obese rats in a time-of-day-dependent manner	Jorge Ricardo	Soliz Rueda	Page 104
5. Other				
NR	**POSTER-Title**	**Surname**	**Last name**	**Page Nr**
67	On-line Breath Analysis following a Nutritional Intervention Challenge	Stamatios	Giannoukos	Page 106
68	Immune Modulation By Sambucus Ebulus Fruit Tea As Revealed By Changes In Inflammation And Phagocytosis Related Genes Expression In Pbmc	Danail	Pavlov	Page 108
69	Dietary fatty acids increase intestinal L cell numbers independent of the development of obesity	Eva	Rath	Page 109
70	Intestinal Morphometric Changes Induced by a Western-Style Diet in Wistar Rats and GSPE counter-regulatory effect	Helena	Segú	Page 110

Oral Presentations

Day 1

A time to fast, a time to feast - on the circadian regulation of energy intake and metabolism

Henrik Oster [1]

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To adapt to environmental changes caused by the Earth's rotation on its axis, most species have evolved genetically encoded timing systems—called circadian clocks—that adjust physiology and behavior to the time of day. In mammals, these clock genes are expressed in all body cells. The cellular clocks are coordinated by a central pacemaker in the hypothalamus, the SCN, which in turn is set by the external light-dark cycle. Clock genes modulate biological functions at all organizational levels - from cell cycle regulation to the sleep-wake cycle. Numerous endocrine parameters also show pronounced circadian rhythms, including important regulators of appetite and energy metabolism.
Conversely, the timing of food intake itself is a synchronizer for circadian clocks in peripheral tissues. Circadian disorders, whether genetic or caused by external manipulation - for example in night shift workers - have far-reaching effects on energy homeostasis. The manipulation of clock genes and circadian rhythms therefore represents a promising approach for dietary interventions and for the prevention and treatment of common metabolic diseases such as obesity and type 2 diabetes.

Precision nutrition by vitamin D

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The micronutrient vitamin D is important for both cellular metabolism and immunity, as it controls calcium homeostasis and modulates the response of the innate and adaptive immune system. The latter also affects signal transduction pathways that result in the inhibition of cellular proliferation and the induction of differentiation and apoptosis through which vitamin D has also an impact on cancer. Vitamin D directly affects *via* its metabolite 1α,25-dihydroxyvitamin D_3 and the transcription factor vitamin D receptor the human epigenome at thousands of genomic loci. This results in the modulation of the expression of hundreds of vitamin D target genes in diverse target tissues and cells and is mechanistically understood by our chromatin model of vitamin D signaling based on *in vitro* investigations in human monocytic cells (THP-1) and peripheral blood mononuclear cells (PBMCs). In context of our vitamin D intervention trials VitDmet (prediabetic elderly, NCT01479933), VitDbol (young healthy, NCT02063334) and VitDHiD (young and mid-age healthy, NCT03537027) we found that individuals differ *in vivo* in their epigenomic and transcriptomic response to vitamin D_3 supplementation, such as the accessibility of chromatin and the regulation of target genes. A genomic region of particular interest is the human leukocyte antigen (HLA) cluster in chromosome 6. This allowed the determination of a vitamin D response index suggesting that about 25% of the study participants are low vitamin D responders. Thus, these individuals need a higher doses of daily vitamin D_3 supplementation, in order to obtain optimal clinical benefits from the micronutrient. This precision nutrition by vitamin D is based both on variations of the genome and the epigenome of the individual, such as single nucleotide variants in genes encoding for enzymes of vitamin D metabolism as well as epigenetic variations in vitamin D target genes. For example, critical physiological functions, such as effective epigenetic programming of innate immune cells like monocytes, are regulated by personalized vitamin D signaling. In conclusion, personalized responses to the mechanistically well appreciated micronutrient vitamin D may serve as master example for understanding and applying precision nutrition.

Oral Presentations

Session 1: New insights in the activity of food bioactive compounds

The (poly)phenol/gut microbiota conundrum: Towards new insights on (poly)phenols mode of action

Yves Desjardins, Prof., PhD.

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It is widely recognized that diet is an essential determinant of health, yet the contribution of its individual components is intricate and complex. For instance, the Western diet, characterized by high fat, high sugar, and low fiber content, is one of the major factors contributing to the etiology of societal chronic diseases. It is now clear that this unhealthy diet impacts metabolic responses and causes perturbations in the host–microbiota community structure, i.e., dysbiosis. Such an imbalance of the gut microbiota has harmful consequences on the intestinal barrier function and immune function. Certain dietary constituents can specifically shape the gut microbiota through a prebiotic action. To this effect, polyphenols are now considered having a prebiotics action, that is they are selectively used by the gut microbiota as substrates conferring health benefits to the host. Indeed, 90%–95% of dietary polyphenols reach the colon intact where they modulate the composition of the gut microbiota and are degraded to potential bioactive microbial metabolites conferring health benefits. We have previously shown that the consumption of proanthocyanidin rich cranberry extracts modulate the gut microbiota and promote the growth of commensal bacteria, like Barnesiella, Akkermansia muciniphila, Lactobacillus, and Coriobacteriales, while repressing others, like Oscillibacter, Romboutsia, Ruminiclostridium, and Roseburia. We have also shown that the modulation of the microbial community following cranberry consumption reduced metabolic disorders, improving obesity-induced dysbiosis. This response results from a bacterial ecological shift and favor syntrophic relationships that further modulate microbiota's composition and function. Indeed, collaterally to (poly)phenols antimicrobial effect, (poly)phenol resistant bacteria, such as Akkermansia muciniphila, are boosted after dietary (poly)phenol intake, highlighting the capacity of this bacteria to withstand the (poly)phenol's antimicrobial action and its ability to opportunistically occupy freed ecological niches. In this context, polyphenols microbial metabolites are recognized topically by the host gut epithelium and induce the production of mucin and other antibacterial protein (i.e., ecological niche engineering) leading to the growth of keystone bacteria like A. muciniphila. We will stress during this presentation the topical role of polyphenols on gut barrier function improvement and elude to the importance of the gut innate immune response to explain this phenomenon.

POSTER 4

Protective Effect of Grape-Seed Derived Procyanidin (GSPE) Against Ageing and Cafeteria Diet on the Expression of Bitter Taste Receptors in Rat Intestine

Maria Descamps, Florijan Jalševac, Helena Segú, Esther Rodríguez-Gallego, Raul Beltrán-Debón, Ximena Terra, Mayte Blay, Anna Ardévol, Montserrat Pinent

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Abstract:

To keep our health during ageing is a challenge nowadays, a situation that would be aggravated by an unhealthy diet. A deficient health outcome is associated with a deterred intestinal function such as altered incretin profile or increased inflammation. Both systems are under the control, among others, of bitter taste receptors (TAS2Rs). Grape-seed derived procyanidin (GSPE) has been linked to antioxidant effects, inhibition of adipogenesis, and promotion of lipolysis in adipocytes. Furthermore, it has been proved that GSPE can improve glucose homeostasis and insulin resistance, and importantly, has been proved effective in preventing cafeteria diet associated damages. However, this has been tested only in younger animals, so the effectiveness of GSPE in ageing situations has yet to be precisely defined. Since some flavonoid components of GSPE have been described as ligands for some of TAS2R, we tested their ability to act on main TAS2R in different intestinal locations where they can be useful to combat diabetes, obesity, and other metabolic disorders.

The study was designed the following way: 2-month-old and 21-month-old female Wistar rats received either an oral dose of 500 mg/kg BW of GSPE or the vehicle (tap water), for 5 consecutive days, once per month. For 11 weeks, animals were fed either standard or a cafeteria diet. At sacrifice, different intestinal segments were collected, and quantitative PCR was used to quantify the relative abundance of rat TAS2Rs (rTas2r) 108, 119, 139 and 140. As a reference gene, PPIA was used. Student's t-test has been used for statistical analysis.

In aged rats, there was a notable reduction in the expression of bitter taste receptors. More precisely, we observed a reduction of expression of rTas2r108 and rTas2r119 in the small intestine, as well as a reduction of expression of rTasS2r119 and rTas2r139 in the colon. Additionally, we observed that cafeteria diet reduced the expression of only rTas2r108 in the jejunum.
GSPE counteracted these challenges significantly by increasing the expression of rTas2r108 in the jejunum, while in the colon we observed a tendency to increase expression of rTas2r139. However, in other parts of the intestine, we observed no significant changes in the expression.

These results indicate that ageing reduces the expression of TAS2R, and so does the cafeteria diet. This reduction could be ameliorated by the synchronic treatment with GSPE, however, more studies are needed to obtain a more definitive answer.

Funding: This work was supported by the Proyecto AGL2017-83477-R funded by MCIN/AEI/10.13039/501100011033/FEDER "Una manera de hacer Europa". This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska Curie grant agreement No 945413 and from the Universitat Rovira i Virgili (URV).

POSTER 15

MODULATION OF GUT MICROBIOTA: THE EFFECTS OF A FRUITS AND VEGETABLES SUPPLEMENT

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Abstract

The consumption of an optimal amount of fruits and vegetables is known to improve the physical fitness and physiological body functions. Healthy eating habits, including the intake of fruits and vegetables, can modify the gut microbiota. This study aimed to demonstrate the effectiveness of a formulated fruits and vegetables supplement (FVS) in modulating the antioxidant capacity and the gut microbiota composition. We enrolled 30 healthy volunteer subjects, matched for age, gender, BMI, and smoking habits, and randomized into the FVS group and the placebo (PLA) group. We measured the serum level of vitamins A, B2, B6, E, K, folic acid and antioxidant capacity by the ORAC method. The folic acid level resulted significantly higher (p=0.001) and the ORAC level slightly higher, but not reaching the statistical significance, in the FVS group compared to PLA. Interestingly, the vitamin B2 level was significantly higher in the PLA group versus FVS (p=0.028). There was no significant difference in the level of other vitamins. The dietary intake, assessed by24hrs dietary recalls, didn't show any significant changes after the supplementation in both groups. The gut microbiome composition was measured by 16S rDNA sequencing. No difference was identified in both alpha and beta diversity, whether the taxonomic composition analysis revealed a microbial shift in both groups after the treatment: increased relative abundance of the genus *Faecalibacterium* and unclassified genus and family from the order Lactobacillales (UC31) in the FVS group compared to PLA (p=0.0474, p=0.0352, respectively); increased abundance of the genus *Ruminoccocus*, *Lachnobacterium* and unclassified genus from the family Erysipelotrichaceae (UC36) in the PLA vs FVS (p=0.0003, p=0.0010, p=0.0059, respectively). SCFAs measurement by gas chromatography-mass spectrometry showed an increased level of 2-methyl butyrate in the FVS group vs PLA (p=0.0385). Finally, the correlation analysis showed that, in the FVS group, the genus Faecalibacterium positively correlated with the 2-methyl butyrate (p=0.040) and negatively correlated with the serum level of vitamin B6 (p=0.022). In the PLA group, none of the significant bacteria correlated with either SCFA or serum biomarkers. We can conclude that FVS supplementation in healthy individuals modified the gut microbiota composition and metabolites, and it can potentially contribute to improve the antioxidant capacity and vitamins metabolism.

The Psychobiotic Revolution: Mood, Food, and the New Science of the Gut-Brain Connection

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The brain-gut-microbiota axis provides a bidirectional route of communication between gut microbes and the brain. The axis involves the vagus nerve, short-chain fatty acids, tryptophan, cytokines and the hypothalamic-pituitary-adrenal axis. Evidence is accumulating to suggest that gut microbes are involved in neural development and function, both peripherally in the enteric nervous system and centrally in the brain. Studies indicate that the gut microbiota is altered in disorders such as depression and Parkinson's disease.

There are marked differences in the gut microbiota between patients with major depression and healthy controls. Patients with major depression show decreased microbial diversity. We conducted a faecal microbiota transplant in rats with faeces from depressed patients or healthy controls. Those rats receiving a transplant from depressed patients developed a depressive phenotype with alteration in corticosterone release and tryptophan metabolism. They also developed a pro-inflammatory phenotype. Preliminary studies in Parkinson's disease show that a microbiota transplant from healthy subjects to patients with Parkinson's disease may help alleviate symptoms.

That bacteria might have a positive mental health benefit is now becoming clear. Such bacteria may influence the capacity to deal with stress, reducing anxiety, perhaps positively impacting mood and are now called psychobiotics. Whether they are capable of acting like and in some circumstances, replacing antidepressants remains to be seen. Overall, for patients suffering from depression, the recommended diet should be high in fruit, vegetables, nuts, fermented foods and fish.

POSTER 2

MOLECULAR COMPOSITION OF PROTEIN FRACTION OF ALMOND, BEEF AND LESSER MEALWORM AFTER *IN VITRO* SIMULATED GASTROINTESTINAL DIGESTION AND CORRELATION WITH THE HORMONE-STIMULATING PROPERTIES OF THE DIGESTA

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Abstract

The rapid growth of the global population is reflected in an increasing demand for alternative protein sources to conventional animal-based food. Insects, due to the fast life cycle, sustainability and high nutritional value, seem to be good candidates as new protein sources for the human diet. However, the information on the molecular composition of gastrointestinal digestate of insect proteins, in comparison with other common protein sources, is still poorly known. Therefore, investigations on the chemical and biological properties of insect gastrointestinal digesta, also in comparison with other more common foods, is needed in order to overcome this gap.
In this work, a comparative study on three different protein sources, namely lesser mealworm larvae (*Alphitobius diaperinus*), almond (*Prunus dulcis*) and lean beef (*Bos taurus*) was performed before and after simulated gastrointestinal digestion.
The characterization of the chemical composition was done using different analytical techniques, including chromatographic methods coupled to mass spectrometry. The degree of hydrolysis of proteins was also measured and related to the solubilisation after the digestion process. Then, the biological activity of the digestate was investigated focusing on its effect on enterohormone secretion of GLP-1, by in vitro cell tests, also focusing on the possible correlation between the food digestate composition and the hormones released.
The results showed high similarities in terms of amino acid composition, solubilized protein and peptide composition between lesser mealworm larvae and lean beef after digestion, outlining the similarity in terms of nutritional value.
A correlation was observed between the biological activity on enterohormone secretion and the amino acid composition of the solubilized protein fraction. Both beef and insect digesta seemed to stimulate GLP-1 secretion, whereas almond digesta, with a complete different composition of the nitrogen fraction, was much less efficient.
In conclusion, from a nutritional point of view, lesser mealworm larvae can be seen as meat equivalent. Besides the nutritional value, insect protein also seems to have specific effects on enterohormone release which might even increase their value as a new source of food.

COMBINED BETA-CAROTENE AND METFORMIN TREATMENT AGAINST OBESITY AND OBESITY COMORBIDITIES IN MICE

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The combination of natural bioactive compounds with pharma drugs is a potential strategy to simultaneously tackling the same or different health/therapeutic targets in cumulative, complementary or synergistic manners, resulting in more effective treatments, decreased drug doses or an improved patient's response to treatment. Anti-obesity activity has been reported for beta-carotene (BC) supplementation at high doses and metformin (MET). Here, we aimed to investigate if BC treatment at a more physiological (closer to dietary) dose and MET treatment at a lower than a therapeutic dose are effective in ameliorating the development of diet-induced obesity, and whether their combination can counteract unwanted effects of an obesogenic diet more effectively than the individual treatments alone. Obesity-prone mice were challenged with a high-fat diet (HFD, 45% energy as fat) for 4 weeks while receiving a placebo (control HF group) or being treated orally with BC (3 mg/kg/day; corresponding to ~14 mg/day for a 60-kg human), MET (100 mg/kg/day; corresponding to ~500 mg/day for a 60-kg human)), or their combination (BC+MET); a fifth group received a placebo and was kept on a normal-fat diet (10% energy as fat; control NF group). Biometric and glucose control-related parameters were monitored, and tissues were collected for gene and protein expression and morphology/ immunohistochemistry analyses. Cumulative energy intake was unaffected, yet results suggested increased systemic energy expenditure in the HFD-fed treated groups compared with the control HF group. HFD-induced increases in body weight gain and inguinal white adipose tissue (WAT) adipocyte size were attenuated maximally or selectively in the BC+MET group, in which a redistribution towards smaller adipocytes on the HFD was noted. Unwanted effects of HFD on glucose control and insulin sensitivity were attenuated in the treated groups, especially the BC and BC+MET, in which hepatic lipid content was also decreased. Microscopical examination of UCP1-immumnostained tissue sections revealed a more active brown adipose tissue in the treated HFD-fed groups, especially those receiving BC, compared with the control HF group. Transcriptional analyses suggested effects on skeletal muscle and WAT metabolism could contribute to better responses to the HFD, especially in the MET and BC+MET groups. The results support the benefits of relatively low dose BC and MET treatments against the development of HFD-induced obesity and its metabolic burden, and specific benefits of the BC+MET cotreatment.

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Health effects of uncommon fatty acids in the diet: focus on FAHFAs and FuFAs

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Our diet contains many bioactive fatty acids such as n-3 docosapentaenoic acid (n-3 DPA), natural trans fatty acids, conjugated fatty acids (CLAs), furan fatty acids (FuFAs), branched chain fatty acids (BCFAs) and fatty acid esters of hydroxyl fatty acids (FAHFAs). Many of them may have beneficial health effects, particularly in the prevention of cardiovascular diseases, inflammation and metabolic disorders such as diabetes. This presentation aims to give a brief overview of the current knowledge on these lipids. More particularly, information about biosynthesis, food and tissue content, daily intake, biological and potential health effects of FAHFAs and FuFAs will be provided.

Oral Presentations

Session 2: Precision Nutrition

Metabolic Phenotyping and Precision Nutrition

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Obesity is a fast growing problem that is reaching epidemic proportions worldwide. We know that a western type of diet combined with an energy overload and reduced physical activity leads to increased fat mass and obesity. Obesity increases the risk for an array of health problems, including type II diabetes (T2D), cardiovascular diseases (CVD), and several forms of cancers. A common feature of these obesity-related diseases is the dysregulation of several metabolic active organs such as adipose tissue and liver, and the concomitant development of chronic low grade inflammation. It is unclear how nutrition can modulate relevant biological pathways in metabolically active organs such as adipose tissue, liver and immune cells involved in the development of T2D and CVD? It is known that the variation in response to diet can be large. The question is whether this is partly dictated by the metabolic health status of a person. These questions will be addressed within already performed and newly planned human dietary intervention studies.

POSTER 36

Precision Nutrition By Modulating Diets According To Tissue-Specific Insulin Resistance Phenotypes Improves Cardiometabolic Health: The PERSON Study

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Background: Precision nutrition based on markers of glucose metabolism may increase the effectiveness of and adherence to dietary intervention, but evidence from well-designed, prospective trials is lacking. Recent findings indicate that individuals with distinct tissue-specific insulin resistance (IR) phenotypes (muscle IR [MIR] or liver IR [LIR]) respond differentially to diet manipulation.
Aim: We performed a proof-of-concept study to investigate the effect of modulating dietary macronutrient composition according to the tissue-specific insulin resistant phenotypes MIR or LIR on cardiometabolic health.
Methods: In this two-center, randomized, double-blind, 12-week trial, 242 individuals with MIR or LIR ((age 40–75 years, BMI 25–40 kg/m^2) were randomized to Phenotype Diet (PhenoDiet) group A or B. PhenoDiet group A included individuals with MIR following a high-monounsaturated fatty acid (HMUFA) and individuals with LIR following a low-fat, high-protein, high-fiber (LFHP) diet. PhenoDiet group B included individuals with LIR on a HMUFA and with MIR on a LFHP diet. Extensive metabolic phenotyping was performed in a controlled laboratory setting as well as in daily life before and after the intervention.
Results: MIR and LIR individuals in PhenoDiet group B had greater improvements in insulin sensitivity (Matsuda index, HOMA-IR, Muscle Insulin Sensitivity Index) fasting insulin, 2-hr glucose, 2-hr insulin, serum triglyceride levels, and C-reactive protein compared to PhenoDiet group A. Favourable changes in body composition and ectopic fat were found in both groups, with a trend for greater reduction in body fat in PhenoDiet group B, but no difference in weight change between groups.

Personalised Nutrition Delivered Using a Metabotype Approach Improves Diet Quality and Lipid Profile: A Randomized Controlled Trial

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Background: Metabotyping is the grouping of individuals with similar metabolic profiles; metabotypes have differential responses to dietary interventions and thus are a potential tool to provide personalised nutrition. We previously developed a framework to deliver personalised nutrition based on metabotypes defined by four markers (triacylglycerol, HDL, total cholesterol, glucose) and decision trees with individual characteristics. Therefore, the objective of this study is to examine the effectiveness of this metabotype framework compared to population-level dietary advice at improving diet quality and metabolic health markers.

Methods: A 12-week randomized single-blind controlled trial was performed with 107 healthy adults (ethics approval LS-19-98-Brennan). Participants received personalised dietary advice based on the metabotype approach or generic advice based on healthy eating guidelines. All measurements were performed pre and post-intervention and included dietary intake assessed by a 4-day food record, blood collection, anthropometry and blood pressure. Diet quality was computed using the Alternate Mediterranean Diet Score. Targeted metabolomic analysis of plasma was performed using UHPLC-MS/MS. One-way analysis of variance was performed on metabolomic data at baseline to assess differences across metabotypes (FDR≤0.05). Comparison between study groups post-intervention was performed on an intention-to-treat basis using linear mixed models with time, study group and their interaction as fixed factors (p≤0.05).

Results: Following the intervention, individuals receiving personalised advice based on their metabotype had a significantly higher diet quality (mean±SD, 4.77±1.81 vs 4.60±1.94; effect size [95%CI], 0.77 [0.07, 1.48]), higher intake of protein and fibre and a lower intake of saturated fat compared to the control group. Metabolic parameters were also improved in the personalised group with significantly lower concentrations of triacylglycerol (0.5±0.4 vs 0.7±0.6 mmol/L), total cholesterol (4.9±1.0 vs 5.5±1.3 mmol/L) and LDL-cholesterol (3.8±1.1 vs 4.2±1.3 mmol/L) and lower triglyceride-glucose index (7.16±0.89 vs 7.50±0.79). No significance was observed for anthropometry, blood pressure and glucose. Examination of metabotypes as baseline revealed a distinct metabolic profile. Metabotype 3 was characterised by the highest mean total cholesterol (5.7±1.0 mmol/L), triacylglycerol (1.2±0.5 mmol/L) and glucose (4.9±0.5 mmol/L) and the highest levels of leucine, isoleucine and alpha-aminoadipic acid. Metabotype 1 had the highest mean HDL (2.2±0.4 mmol/L). Metabotype 2 had the lowest mean total cholesterol (4.4±0.9 mmol/L) and the lowest levels of phosphatidylcholines and sphingomyelins.

Conclusions: Our metabotype framework classifies individuals into distinct and meaningful metabolic profiles. Personalised nutrition delivered using a metabotype approach is more effective than population-level dietary advice at improving diet quality and metabolic health biomarkers.

Role of systems modelling approaches in Precision Nutrition

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Nutrition and health involve a complex system of interconnected factors (e.g., genetic, biological, behavioral, social, environmental). Precision nutrition is an emerging field that aims to provide targeted dietary and nutritional recommendations for individuals with different characteristics and circumstances in order to prevent and treat diseases, and improve overall health and wellbeing. Computer-aided approaches like Artificial Intelligence (AI) and computer modeling can transform precision nutrition by elucidating the complex factors and processes between an individual's genetics, biology, behavior, social structure and environment and their short and longer-term health outcomes. We are at a key inflection point in society with technology, such as wearables and smartphones allowing for much more information and data to be collected. With AI, we can utilize this data and information to inform precision nutrition efforts. However, in order to fully leverage AI for precision nutrition there is a need for both iterative “top down” data-driven approaches and “bottom up” systems modeling approaches. The National Institutes of Health (NIH)’s Nutrition for Precision Health Consortium is an opportunity to utilize AI to better achieve precision nutrition.

PREVENTOMICS: Empowering Consumers to Prevent Diet-related Diseases through -OMICS Sciences

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The PREVENTOMICS project (H2020) aims to develop a new system for personalised nutrition based on the integration of metabolic modelling and new digital technologies to induce positive changes towards more healthy dietary habits. To do that, PREVENTOMICS apply -omics technologies for characterising the metabolic state of the user and their genetic background. Results are integrated with nutritional and psychological information in order to generate personalised recommendations and induce a behavioural change towards more healthy dietary habits, levering on information and communication technologies. The final goal is to prevent development of highly prevalent diseases linked to unhealthy dietary habits. This approach has been validated in 3 different case scenarios, performing relevant interventional studies with healthy and obese volunteers, to demonstrate its potential for personalization of nutrition at the 3 levels of the food value chain (processing and distribution, marketing and consuming), those closest to the end-users/consumers.

POSTER 37

The Effect of Dietary BIoactives on Gut Micrbiome DivErstiy (DIME)- A pilot study

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Happy to present and give an oral presentation or poster session in session 2 Precision Nutrition depending on what the judges feel the best candidate.

Introduction:

The gut microbiome refers to the complex community of microorganisms (bacteria, fungi, archaea and viruses) present within our gut. The composition and complexity of gut microbiota communities are crucial for maintaining human health. Humans depend on gut microbiota to undertake essential metabolic functions and for effective immune system operations, such as protection against pathogens and maintaining gut integrity. Richer diversity in these microbiota communities has been associated with better health. A key modulator of intestinal microbial colonies is food. Dietary bioactives, also referred to as phytochemicals (non-nutrient food components) present in fruit and vegetables, can modulate metabolic processes, promoting better health; however, the interaction of bioactives with microbial communities is not yet fully understood.

We have conducted a 2x2 randomised crossover study to estimate the effect of diets rich in dietary bioactives on gut microbial diversity and health markers in 20 healthy participants. Participants consumed a diet of high bioactive (HB) rich foods (containing polyphenols, Sulphur (S) metabolites and carotenoids) vs a low bioactive (LB) diet for two weeks, with an in-between washout period of four weeks. The primary aim was to examine the effect of a two-week diet high in bioactives rich foods on gut microbial diversity compared to a low bioactive diet. The secondary aim was to assess a high vs low bioactive diet on markers of cardiovascular health, inflammation, and post-prandial glucose. We hypothesised that consuming a high bioactive diet would increase microbial diversity compared to a low bioactive diet.

Methods:

Each volunteer completed four study visit days, one at the start and one at the end of each intervention phase. Dietary intake, including bioactives, was recorded through the Libro app linked to Nutritics. We recorded diets during a 7-day period (baseline habitual diet) followed by a 14-day intervention period per arm. On each study day, volunteers provided a 24 h urine sample collected in the 24 h preceding their visit and a stool sample. Microbial composition was assessed through whole-genome shotgun sequencing carried out by GeneWiz, performed using Illumina HiSeq 2500 platform with paired-end read length 2 x 125 bp. For vascular health, total HDL/LDL cholesterol and triglycerides, along with inflammatory markers such as hs-CRP, were analysed with an at-home finger-prick blood sample collection kit (Medichecks). Participants also carried out an oral glucose tolerance test; glucose measurements were provided through the Freestyle Libre continuous glucose monitor (Abbott Laboratories) over a 2 h period following ingestion of 113 mL of polycal (75 g anhydrous glucose).

Results:

We identified that the participants adhered well to the different intervention arms. Total energy intake was not changed. We identified that the LB arm consumed more fat ($p < 0.001$), especially more mono- ($p = 2.283e-05$) and poly-unsaturated fat ($p = 0.004$) and omega-6 fatty acids ($p < 0.001$), likely due to increased nuts consumption. Both intervention arms successfully increased fibre intake, with the HB arm slightly consuming more fibre (baseline =21 g vs HB =29 g and LB= 26 g, $p = 0.01$). We identified that consumption of certain minerals such as zinc, copper and manganese along with vitamins B1, B2, B5, B6 and B9 were significantly higher in the LB arm. The HB arm participants consumed 3.3 mg more carotene ($p = 1.907e-06$) and 106 mg more vitamin C (HB = 172 mg vs LB = 66 mg $p < 0.0001$), reflecting their higher vegetable intake. The remaining bioactive group analysis is pending. Initial metagenomics analysis revealed that the different time points only account for 2% of individual variation whilst most (60%) variation came from individual variation.

POSTER 38

Exploring immune cell metabolism to identify hallmarks of healthy versus unhealthy obesity

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The abstract contains preliminary results

Heterogeneity of obesity has resulted in the crude classification of healthy versus unhealthy obesity, the latter being associated with a higher prevalence of metabolic complications. Obesity-associated metabolic complications are driven by systemic inflammation. Immune cells drive systemic inflammation through alterations in intracellular metabolism, but the exact immunometabolic responses are unknown. Therefore, we set out to explore immune cell metabolism in obese individuals before metabolic complications evolve.

We included 185 obese individuals and measured systemic insulin sensitivity together with metabolic and functional signatures of circulating monocytes using seahorse-assays and stimulation assays using Pam3Cys, respectively.

Monocyte metabolic responses, including glycolytic and oxidative metabolism, were highly variable within our study population and positively associated with cytokine production. The rate of oxidative metabolic responses was positively associated with age ($P<0.03$) and higher in males ($P<0.02$). A high ratio between glycolytic versus oxidative rates was associated with higher insulin sensitivity ($p<0.03$).

We identified four types of monocytes with distinct metabolic signatures based on the magnitude of the glycolytic rate upon exposure to glucose or Pam3Cys. Interestingly, these metabolic signatures also presented unique functional profiles by means of cytokine production. However, we were unable to relate our metabolic signatures to the clinical characteristics of our study population. Nevertheless, linear models between systemic insulin sensitivity and monocyte metabolism revealed significant associations within some of the four groups of monocytes, but no clear pattern could be observed.

Our data show that heterogeneity of obesity also exists on the immunometabolic level. The highly variable metabolic responses of monocytes are associated with several clinical characteristics of obese individuals. The four distinctive metabolic signatures we identified in monocytes present discrete signature-specific functional responses of monocytes, indicating that metabolic signatures represent biological relevant differences. These four groups of monocytes present distinct associations between systemic insulin sensitivity and monocyte metabolic features. This high level of variation might indicate the relevance of the immune system in developing personalized preventive strategies against metabolic complications of obesity.

Even though we were unable to connect the metabolic signatures to the clinical characteristics of our population, we suggest that these metabolic signatures could be a new level of characterization of healthy versus unhealthy obesity before metabolic complications evolve. We hypothesize that these metabolic signatures reflect monocyte functional

Oral Presentations

Session 3: Biomarkers and disease — strategies, discoveries and new trends from omics data

Multiplexed Biomarkers as a Powerfull Tool to Integrate Heterogenous Data: Application in Disease and Nutritional Status Prediction

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Abstract

Anticipating the deviation of health towards pathological outcomes before they happened is a long standing and continuous matter of investigation in medical research. Such strategy is believed to allow reversal of the pathological trajectory prior it becomes irreversible. Also, in epidemiology evaluating the role of nutrition in the development of diseases requires to accurately assess the intake of specific food or nutrients over the long term. This is really challenging with current methods based on food intake questionnaires that can be biased and inaccurate. Hence in either situation, disease outcome prediction or food intake evaluation, accurate biomarkers are needed to adjust interventions or to provide nutritional recommendations. Current methods are usually based on the expectation that one biomarker would fulfill the prediction need. In fact, examples of some single biomarker use do exist in health and disease or in nutrition. One of the most famous one is cholesterol in cardiovascular disease, or the use of heptadecanoate or pentadecanoate as surrogate markers of dairy fat over the long term. Nevertheless, high blood cholesterol is only indicative of the severity of the disease that is already set up, and hepta- and pentadecanoate are not only markers of dairy fat intakes and lack specificity. Omics technologies and especially metabolomics (with lipidomics) are described as highly sensitive, and are now used to find new biomarkers of disease development or in nutritional epidemiology (the food metabolome). However, they can also suffer of a lack of specificity since the fluctuation of one single indicator can be influenced by other factor than the main outcome sighted. Aggregating several indicators into a composite score can resolve the problem, by balancing the weakness of one or several indicators by the others. Several methods can be used to aggregate a selection of bioindicator into a multiplexed score, such as Partial Least Square regression, or logistic regression. Heterogenous data can be thus assembled, either from “omics” or from conventional biochemistry. A successful example is the development of the insulin resistance test “Quantose®” now release in the market and based on the assembling of metabolomics and clinical test in a logistic regression equation.
However, many issues still remains to be resolved for using such “multiplexed” strategy, such as the validation of new composite biomarkers, their accuracy over ageing and at various period of lifetime. Several examples will be presented and discussed during the conference, with their advantages and limitations.

LIVER METABOLOMICS REFLECTS THE ABILITY OF LEPTIN SUPPLEMENTATION DURING LACTATION TO COUNTERACT METABOLIC MALPROGRAMMING

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Abstract:
Introduction: The adipose-derived hormone leptin is present in milk and, when supplemented at physiological doses, has been described to protect against obesity and metabolic associated disorders in rodents. Perinatal nutritional factors can program offspring's metabolic phenotype and risk of obesity, as happens with gestational undernutrition, which increases metabolic disturbances and obesity risk later in life. This study investigates the potential role of leptin supplementation (during lactation) in ameliorating the malprogrammed effects caused by mild maternal calorie restriction during gestation on young rat offspring's liver metabolic response.
Methods and results: Pregnant rats were 20% calorie-restricted during the first half of pregnancy, and we studied their female and male offspring compared to the offspring of control (non-restricted) rats. Half of the animals in each group were supplemented with Leptin (5x the daily intake received from milk) during lactation. The animals were sacrificed at 25-27 days of life, and liver and blood samples were collected. Untargeted and targeted metabolomics studies on liver samples were performed by NMR and GC-MS, respectively. We also studied global DNA methylation, the expression by RT-PCR of critical genes involved in different pathways, and circulating and biometrical parameters. By NMR, 15 liver metabolites were altered in the offspring of gestational calorie-restricted dams (CR group) at days 25-27 of life. Physiological leptin supplementation during lactation partially reverted the effects of the gestational calorie restriction for most of these metabolites. Moreover, targeted fatty acid analysis by GC-MS showed a significant decrease in the hepatic concentration of certain very long-chain fatty acids (VLCFA) in the gestational calorie-restricted offspring, partially or totally reversed by leptin supplementation. No remarkable changes were found in global DNA methylation or mRNA expression.
Conclusion: This study brings new insights into offspring metabolic maladaptation when challenged with maternal undernutrition during foetal life and shows how physiological leptin supplementation during lactation reverses the detrimental changes caused by maternal mild calorie restriction on the liver metabolome. This agrees with the putative role of leptin supplementation in preventing or reversing metabolic disturbances caused by gestational metabolic malprogramming. Therefore, leptin supplementation during lactation is a putative agent to consider in preventing or reversing metabolic alterations malprogrammed during early life.

Perilipin 2 regulates hepatic lipid content and lipid droplet size during fasting

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Abstract

A strong association between deposition of lipids in liver and metabolic disease is well acknowledge. Lipid droplets (LD) consist of a core of mainly triglycerides (TG) or cholesterol esters (CE), surrounded by a phospholipid monolayer with proteins. The perilipin 2 protein, encoded by the Plin2 gene, is abundant at the LD surface in liver. Plin2 may facilitate storage of lipids by interfering with lipolytic enzymes and autophagy. Plin2 expression is upregulated in response to increased intracellular fatty-acid levels with high-fat diet and Plin2-/- mice have decreased TG content in liver and alleviated hepatic steatosis.

We generated Plin2 knockout mouse to explore the contribution of Plin2 to hepatic lipid homeostasis during substantial lipid loading in liver such as fasting. Plasma TG and total cholesterol were the same between *Plin2*$^{+/+}$ and *Plin2*$^{-/-}$ mice in fed and fasted state. However, after 24 hours of fasting hepatic TG levels were less in Plin2-/- compared to Plin2+/+ mice. Hepatic total cholesterol levels remained the same. Furthermore, staining of liver cryosections showed that lipid droplets with Plin2 deletion have increased size when challenged with lipids during fasting. Liver lipidomics showed that almost all TG with different fatty acid content, as well as the CE are affected by the Plin2 deletion in mice when challenged with fasting. In line with previous high-fat diet studies, we showed that Plin2 deficiency reduces hepatic TG during fasting. However, in this study we show that LD size is strongly affected by the absence of Plin2 and this also increases hepatic CE levels. Discrepancy in storage of lipids in the absence of Plin2 may be caused by distinct changes in protein coating of TAG-rich versus CE-rich LDs, autophagy or destabilization. Future experiment will be directed to examining LD surface proteome, cholesterol uptake, fatty acid oxidation and autophagy.

BLOOD CELL TRANSCRIPTOMIC BIOMARKERS FOR OBESITY PREVENTION

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Obesity and associated comorbidities constitute nowadays a major health concern. Therefore, it is important to identify biomarkers to detect early metabolic alterations associated with unbalanced nutrition and obesity before the appearance of more relevant clinical signs. In this way, proper prevention strategies could be implemented to avoid the development of future pathologies. Omics technologies provide a powerful tool to search for molecular biomarkers of disease, including transcriptomic (gene expression) biomarkers. Blood cells, and in particular the fraction of peripheral blood mononuclear cells (PBMC), basically composed of lymphocytes and monocytes, constitute an ideal, easily obtainable source of transcriptomic biomarkers. This is because, in addition to their immunological function, PBMC express practically the entire human genome and can be used as surrogate tissue since they are capable of reflecting gene expression profiles that occur in internal tissues, including altered gene expression patterns in different pathological situations, such as obesity. The 'Nutrigenomics, Biomarkers and Risk Evaluation' group at the UIB has widely contributed to characterizing the usefulness of PBMC gene expression analysis in obesity research. On the one hand, PBMC transcriptomic profiling allows for determining metabolic health status, identifying those apparently healthy individuals with a higher metabolic risk associated with increased adiposity, even in the absence of obesity (metabolically obese, normal-weight phenotype). PBMC transcriptomic biomarkers also allow performing personalized follow-up of the efficacy of weight loss therapies, by analyzing if body weight loss is associated with metabolic recovery. In addition, the UIB group has demonstrated the usefulness of "ex vivo" human PBMC systems to quickly and easily test the safety/efficacy of bioactive compounds in the diet, which is of interest to promote functional food research. Moreover, these "ex vivo" tests make it possible to identify individualized responses to the compounds analyzed, which is of special interest to select bioactive compounds with positive effects on health to be included in personalized nutrition plans. In short, PBMC transcriptomic biomarkers provide a tool for the early identification of metabolic risk and for the establishment of personalized nutritional interventions aimed at improving metabolic health by preventing obesity and related complications.

Driving biological discovery with computational metabolomics and systems biology

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Metabolomics, the -omics discipline that analyzes small molecules known as metabolites, provides a metabolic readout that is considered the closest to the phenotype. Specifically, untargeted (or global) metabolomics based on mass spectrometry is used to measure as many metabolites as possible without bias. However, the analysis of untargeted metabolomics data, including the identification of metabolites, is one of the most important challenges in the field. Current metabolite data analysis workflows lack enough throughput and accuracy to confidently identify a large number of metabolites. While genomics and proteomics can provide a massive amount of measured identities (thousands of proteins and genes), metabolomics studies typically report less than one hundred robustly identified metabolite identities. And due to the complexity of mass spectrometry data, the total number of metabolites that can be observed - including both identified and unidentified - is unknown, even in broadly analyzed fluids like serum.

In my presentation, I will overview the current challenges of metabolomics and discuss how we use bioinformatics to tackle these challenges. In particular, I will describe our efforts to increase the identification ratio in untargeted metabolomics by developing new analytical and computational strategies, including the use of machine learning for multi-omics integration. Finally, I will show examples of the application of untargeted metabolomics for bioactive metabolite discovery.

POSTER 48

Customized Sampler for Direct Non-invasive Metabotyping of Biofluids in Pediatric Obesity

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Of today's striking health issues faced by children, especially obesity has witnessed a substantial increase. Hence, the identification and stratification of high-risk states are very urgent in terms of timely intervention (as still reversible at this point). While currently rapid analysis of the biofluid metabolome has been made possible, these methods often are associated with a variety of (pre)analytical and instrumental issues, like sampling inconvenience (e.g. stool), turnaround times (i.e. preservation), and matrix effects, impeding metabolome coverage, and thus not fit for *in situ* analysis. To address those limitations, we invented a sampling device (MetaSAMP®, WO2021/191467). The purpose of this MetaSAMP® is to configure it as a sampling kit for urine and in combination with a medical swab for rectal usage in children, in that it captures a broad, physicochemical diverse range of metabolites and is directly applicable as a substrate for ambient mass spectrometric (MS) analysis such as laser-assisted rapid evaporative MS (LA-REIMS). The optimized MetaSAMP® comprises a biofluid-specific electrospun nanofibrous sheet of polyvinylpyrrolidone and polystyrene with a biocompatible polyacrylonitrile cover layer. The *ex vivo* performance of the MetaSAMP® was biologically validated in the context of pediatric obesity (MetaBEAse study, n=234; n=57 IOTF ≥2 (obese), n=36 IOTF 1 (overweight) versus n=141 IOTF≤ 0 (healthy weight and underweight), TS≤1(9±2 year), 45% girls). LA-REIMS-MetaSAMP® analysis led to similar (urinary) and superior (rectal) OPLS-DA models as compared to crude biofluid analysis, i.e. rectal MetaSAMP®: Q^2Y=0.63, R^2Y= 0.96 and p-value=1.15e^{-13}. In parallel, targeted metabolomics was pursued by spiking the rectal MetaSAMP® with analytical standards spanning a broad mass (m/z 100 – 800 Da) and polarity (logP -4 to 13) range. Next, linkage of discriminating markers to metabolic pertubations and dysbiosis in childhood obesity was pursued. Hereto, correlations between normalized metabolic features, anthropometrics (waist, BMI-z, IOTF a.o.), microbial abundances (OTUs) and metabolic/clinical blood measurements (i.e. ALT, AST, urea, creatinine, CRP, uric acid, LDL, HDL, triglycerides, cholesterol, glucose, insulin, IGF-1, SHBG, DHEAS, cortisol, vitamin D (Spearman's ρ-value up to 0.55) were determined. The top-ranked metabolic features were subjected to univariate statistical analysis and based on significance and contribution to the OPLS-DA models, metabolite annotation and predictive potential (e.g. ROC analysis) will be presented.

To summarize, the MetaSAMP® has proven adequate ab-, ad- and desorption capacities and thereby provisions a holistic bioanalytical approach toward *in situ* robust mapping of the human biofluid metabolome as a first-line rapid screening strategy (in <1 min) to timely decision-making in healthcare.

POSTER 40

Discovery of metabolite biomarkers of meat consumption and their association with incident type 2 diabetes in a Swedish population-based cohort

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Background and objectives: Biomarkers of different meat intakes, complemented with self-reported intake, could clarify their yet inconsistent associations with incident type 2 diabetes (T2D). We aim to discover potential plasma metabolite biomarkers for intake of various meat food groups, and to investigate their associations with the risk of developing T2D.

Methods: Self-reported meat intake, covariates, and fasting plasma samples were from a case-control study nested within the prospective Västerbotten Intervention Program (VIP), including 403 randomly selected participants who developed T2D (median 7 years to diagnosis) and matching controls. We used random forest on untargeted LCMS metabolomics data (24758 features) to discover biomarker candidates to reflect the intakes of total-, processed-, and unprocessed meat, as well as poultry. Selected features were adjusted for age, sex, and total energy intake using partial Spearman correlation with meat intake. These selected features were further associated to T2D risk using conditional logistic regression, adjusting for age, sex, physical activity, smoking, total energy and alcohol intake.

Results: Features associated with total- (n=18), processed- (n=67), unprocessed meat (n=29), and poultry (n=53) were identified. Processed meat intake was associated with octenoylcarnitine (r = 0.32, FDR = 1.28 x 10^{-8}), decatrienoylcarnitine (r = 0.24, FDR = 3.40 x 10^{-5}), and inversely with methylproline (r = -0,18, FDR = 0.002). Poultry intake was associated with hydroxyvaleric acid (r = 0.16, FDR = 5.70 x 10^{-3}) and inversely with LPC(17:1) (r = -0.20, FDR = 1.93 x 10^{-3}) and PC(15:0/18:2) (r = 0.18, FDR = 4.09 x 10^{-3}). Interestingly, they were also associated with T2D risk. Octenoylcarnitine (OR 1.41, 95% CI 1.21-1.65, FDR = 1.05 x 10-4), decatrienoylcarnitine (OR 1.37, 95% CI 1.17-1.61, FDR = 4.86 x 10-4), and hydroxyvaleric acid (OR 1.60, 95% CI 1.34-1.92, FDR = 3.45 x 10-6) were associated with higher T2D risk, whereas methylproline (OR 0.77, 95% CI 0.66-0.90, FDR = 4.21 x 10-3), LPC(17:1) (OR 0.71, 95% CI 0.61-0.83, FDR = 1.47 x 10-4), and PC(15:0/18:2) (OR 0.73, 95%CI 0.62-0.85, FDR = 4.86 x 10-4) with lower risk. These associations disappeared after an additonal adjustment for BMI, except for hydroxyvaleric acid (OR 1.47, 95% CI 1.19-1.82, FDR = 0.015).

Conclusion: We discovered several biomarker candidates of meat intake which were also associated with T2D risk.

Keywords: food intake biomarker, blood metabolites, untargeted metabolomics, meat, type 2 diabetes

Oral Presentations

Session 4: Chrononutrition:

giving rhythm to the metabolism

Interaction of biological rhythms and dietary phenolic compounds

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Phenolic compounds are plant secondary metabolite produced under stress conditions as a defense mechanism against unfavorable environmental conditions. Epidemiological studies demonstrated the health effects of the consumption of phenolic-rich foods. Otherwise, animals evolved to adapt their metabolism, physiological and behavior to the environmental changes of light, allowing a temporal distribution of these processes that optimize health. In this sense, results showed that the proanthocyanidins (PAs) bioactivities and bioavailability in cafeteria diet-induced obese rats depends on the time of the day and the photoperiod conditions. In addition, in a disturbance state, PAs could act as synchronizers of biological rhythms interacting with the clock system and facilitating the adaptation to the environment to improve health. Moreover, results with phenol-rich fruits administered to rats exposed to different photoperiod conditions to simulate the specific seasons, showed that the seasonality and the geographical origin of fruits gives a phenolic hallmark from the environment that influences their health effects depending on the photoperiod conditions. In conclusion, there is a bidirectional interaction between dietary phenolic compounds and biological rhythms: the time of consumption of phenolic compounds influences their effects in obesity and these effects can also be mediated by the interaction of these compounds with the clock system acting as synchronizers.

POSTER 61

BIOLOGICAL RHYTHMS AFFECT THE BIOAVAILABILITY OF PHENOLIC COMPOUNDS FROM GRAPE SEED PROANTHOCYANIDINS EXTRACT IN HEALTHY AND OBESE FISCHER 344 RATS

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Phenolic compounds are bioactive molecules that are associated with several health benefits. Once absorbed, they undergo extensive metabolization leading to the production of a great variety of metabolites that may exert different bioactivities. Thus, the study of the factors that modulate this metabolization and bioavailability is essential. Recently, it has been shown that circadian and seasonal rhythms, characterised by different light/dark cycles or day lengths (photoperiod) respectively, significantly impact phenolic compounds bioactivities indicating that they may also affect their bioavailability. Hence, the objective of this study was to evaluate if the bioavailability of a grape seed proanthocyanidins extract (GSPE) is affected by biological rhythms in healthy and obese rats. To this aim, we evaluated how different administration time (8:00 am (ZT-0) or at 8:00 pm (ZT-12)) and different photoperiod conditions (L6: 6 h of light, L12: 12 h of light and L18:18 h of light) impacted the serum phenolic compounds profile in Fischer 344 rats. In both studies, rats were fed either a standard (ST) or a cafeteria diet (CAF) for 9 weeks and administered a daily oral dose of GSPE (25 mg/kg) for the last 4 weeks. Serum phenolic metabolites were quantified by HPLC-ESI-MS/MS. We observed that phase-II and gut microbiota-derived phenolic metabolites were affected by ZT and photoperiod conditions in both healthy and obese rats. These findings demonstrate that circadian and seasonal rhythms are key factors influencing phenolic compounds bioavailability.

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POSTER 62

Effect of Seasonal Phenolic-rich Fruit Extracts on the Regulation of Metabolic Homeostasis

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A broad range of essential nutrients can be found in fruits and vegetables, as well as non-essential such as phenolic compounds. Phenolic compounds, which are produced by plants in response to stress, play a relevant role in preventing chronic metabolic disorders. There is growing evidence that phenolic compounds act as signals in the regulation of biological rhythm, however, it remains to be elucidated if the consumption of phenolic compounds from different seasonal fruits regulate differentially the homeostasis alteration depending on the photoperiod in which they are consumed. Our goal was to evaluate the effects of phenolic-rich extracts from eight seasonal fruits on lipid metabolism and inflammation in short and long photoperiod, which simulate winter and summer season, respectively. To accomplish this, the metabolic effects and the interaction with seasonal rhythm of the eight individual extracts were studied in male Fischer 344 rats, housed in two different photoperiods: short (L6, 6h of light/day) and long (L18, 18h of light/day. Standard diet-fed animals were orally supplemented with vehicle or with 100 mg/kg of body weight of each extracts for 15 days. Different metabolic challenge tests were designed to temporarily incite a degree of disturbance in the homeostasis and to evaluate the benefit of each extract depending on the photoperiod consumption. Specifically, after 12 hours of fasting, oral triglycerides tolerance test (OTTT) was conducted. Moreover, lipopolysaccharide (LPS)-induced inflammatory challenge was performed to assess the modulation of inflammation depending on photoperiod exposure and the administration of different extracts. Results from OTTT showed differences in the area under the curve depending on the fruit phenolic extract and the photoperiod. Additionally, inflammation markers (interleukin 6, IL-6; tumor necrosis factor alpha, TNFα) were significantly affected by the photoperiod exposure and the type of phenolic-rich fruit extract supplementation. Through this screening, we can distinguish which type of phenolic-rich fruit extract might be more effective at preventing or treating metabolic disorders by restoring the disturbed homeostasis, depending on the photoperiod. The results highlight the fact that beneficial effects of phenolic compounds depend not only on phenolic profile but also on the season they are consumed.

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POSTER 58

Analyzing postprandial metabolomics data using multiway models: A simulation study

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Abstract. Analysis of time-resolved postprandial metabolomics data can improve our understanding of metabolic processes and reveal deficiencies or aberrations in metabolism. Traditional analysis approaches for such data focus on clustering temporal profiles relying on summaries of the data across subjects or univariate analysis studying one metabolite at a time. However, such methods fail to reveal which subgroups of subjects differ due to which subsets of metabolites and what type of temporal response. Considering that we can arrange such data as a three-way array, i.e., *subjects* by *metabolites* by *time points* array, we aim to explore the structure of the dynamic information using multiway data analysis methods (also referred to as tensor factorizations), in particular, using the CANDECOMP/PARAFAC(CP) model.

While CP models are effective tools revealing variation patterns from complex data, interpretation in terms of the underlying metabolic processes is not straightforward due to the lack of ground-truth in real datasets. Therefore, in this study, we simulate postprandial metabolomics data using a comprehensive human whole-body model. We generate datasets with known individual and induced variation (the latter mimics metabolic deficiencies) and demonstrate how realistic the simulations are by comparing the simulated data and its analysis with a real dynamic metabolomics dataset collected during a meal challenge test. Furthermore, to understand the metabolic differences between the (pure) dynamic and the fasting-state information, we assess the performance of analysis of full postprandial data as well as the data corrected by subtracting the fasting state.

Our numerical experiments show that CP models can capture the underlying metabolic mechanisms and reveal patterns corresponding to subject groups, related metabolites, and their temporal profiles. In particular, we demonstrate that while the analysis of postprandial data reveals a mixture of information from the fasting state and (pure) dynamic responses, the analysis of the corrected data may better capture the mechanisms, and the changes in metabolism corresponding to metabolic deficiencies.

Meal timing: what to eat and when to eat

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A growing body of evidence suggests that meal timing is an important factor for metabolic regulation and that the circadian clock tightly interacts with metabolic functions. The proper functioning of the circadian clock is critical for maintaining metabolic health. Therefore, chrononutrition, a novel discipline which investigates the relation between circadian rhythms, nutrition, and metabolism, has attracted increasing attention in recent years. Circadian rhythms are strongly affected by obesity, type 2 diabetes, and other dietary-induced metabolic diseases. With increasing age, the circadian system also undergoes significant changes which contribute to the dysregulation of metabolic rhythms. Metabolic diseases are a major health concern, particularly in light of a growing aging population, and effective approaches for their prevention and treatment are urgently needed. Recently, animal studies have impressively shown beneficial effects of several dietary patterns (e.g., caloric restriction or time-restricted feeding) on circadian rhythms and metabolic outcomes upon nutritional challenges. Whether these dietary patterns show the same beneficial effects in humans is, however, less well studied. As indicated by recent studies, dietary approaches might represent a promising, attractive, and easy-to-adapt strategy for the prevention and therapy of circadian and metabolic disturbances in humans of different age.

Posters

Session 1: New insights in the activity of food bioactive compounds

Consumption of salmon fishmeal increases hepatic cholesterol content in obese C57BL/6J mice

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Abstract:
Purpose: By-products from farmed fish contain large amounts of proteins and may be used for human consumption. The purpose of this study was to investigate cardiometabolic effects and metabolic tolerance in mice consuming fishmeal from salmon by-products, salmon filet, or beef.

Methods: Female C57BL/6J mice were fed chow, as a healthy reference group, or a high-fat diet for 10 weeks to induce obesity and glucose intolerance. Obese mice were subsequently given isocaloric diets containing 50% of the dietary protein from salmon fishmeal, salmon filet, or beef for 10 weeks. Mice were subjected to metabolic phenotyping, which included measurements of body composition, energy metabolism in metabolic cages and glucose tolerance. Lipid content and markers of hepatic toxicity were determined in plasma and liver. Hepatic gene expression was determined with RNA sequencing and immunoblotting.

Results: Mice fed fishmeal, salmon filet, or beef had similar food intake, energy consumption, body weight gain, adiposity, glucose tolerance, and circulating levels of lipids and hepatic toxicity markers such as p-ALT and p-AST. Fishmeal increased hepatic cholesterol levels by 35-36% as compared to salmon filet ($p=0.0001$) and beef ($p=0.005$). This was accompanied by repressed expression of genes involved in steroid and cholesterol metabolism and reduced levels of circulating Pcsk9.

Conclusion: Salmon fishmeal was well-tolerated, but increased hepatic cholesterol content. The high cholesterol content in fishmeal may be responsible for the effects on hepatic cholesterol metabolism. Before introducing fishmeal from salmon by-products as a dietary component, it may be advantageous to reduce the cholesterol content in fishmeal.

IMMUNOMODULATORY EFFECTS OF PROBIOTIC STRAINS ON THE REGULATORY MECHANISMS OF INFLAMMATION IN CHICKENS

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Poultry is the main animal protein source for human nutrition. However, due to an overuse of antibiotics, animal production is considered one of the most important sources of multidrug resistant bacteria becoming an enormous risk for the public health, especially for the acquired resistances in zoonotic pathogens. In fact, in-feed antibiotics play a crucial role in the economic effectiveness of the livestock production reducing the chronic inflammation caused by foreign antigens, diet or environment, improving growth rate, reducing mortality, and modulating the immune response. Therefore, the reduction of antibiotics use is essential, but more research is needed to find alternatives with a similar mode of action (reduction of inflammation, modification of the microbiota, and direct effect on pathogens). Probiotics are considered promising alternatives due to their immunomodulation (promoting homeostasis), and antimicrobial capacities (competitive exclusion of pathogens) improving the efficiency and animal health. In this regard, this study focused on the analysis of beneficial effects of 3 selected probiotic strains (for their antimicrobial activity against pathogens) on the performance and immune parameters of poultry when they are challenged with a proinflammatory diet (rich in non-starch polysaccharides).
An *in vivo* trial was carried out (4 treatments, 6 pens/trt, 36 animals/pen). Each treatment was based on the basal diet + $5x10^7$ CFU probiotic/animal per day (Probiotic 1, 2, or 3), except the negative control group (only basal diet). Performance indicators (BW, ADG, ADFI, FCR, EPEF, mortality and morbidity) were monitored throughout the experiment while samples were collected on day 7, 14, 21 and 35 to analyse the immunomodulatory effects of probiotics on intestinal inflammatory biomarkers (pro- and anti-inflammatory cytokines [IL-1β and IL-10, respectively), and mucus production (epithelial protection)].
The results demonstrated an increase of performance traits (BW, ADG, ADFI, FCR, and EPEF) in animals consuming Probiotic 1, and a conversion improvement in chickens fed the Probiotic 3, compared with the negative control group. Moreover, Probiotics 1 and 2 showed an immunomodulatory capacity on cytokine expression, promoting an anti-inflammatory status in the intestine. In contrast, Probiotic 3 demonstrated an antimicrobial capacity improving the intestinal barrier through the increase of mucus expression.
In conclusion, the probiotics characterised in this study are promising candidate strains to become alternatives to antibiotics use, with demonstrated immunomodulatory and antimicrobial capacities. More research is needed to know if a blend of them could generate a synergistic effect, improving the efficiency and reducing the infection and spread of zoonotic pathogens.

Grape-Seed Proanthocyanidin Extract Modulates Intestinal Inflammatory Parameters In Aged Wistar Rats

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Obesity and ageing are current health issues of global concern. Adaptive homeostasis is compromised in the elderly, who are more likely to suffer age-related disorders, such as obesity, metabolic syndrome, and cardiovascular diseases. The current worldwide prevalence of obesity and higher life expectancy call for new strategies for treating metabolic disorders. Grape-seed proanthocyanidin extract (GSPE) is effective in reducing the intestinal inflammation associated to obesity, especially in young animal models. In this study, we aimed to test the effectiveness of GSPE in modulating obesity-induced local inflammation in the jejunum of aged rats receiving an obesogenic diet. 21-month-old rats were fed a high-fat/high-sucrose diet (cafeteria diet) for 11 weeks. GSPE was administered at a pharmacological dose of 500 mg/kg body weight at two different time points: preventively, during 10 days prior to cafeteria diet intervention, and synchronically once per month with the cafeteria diet. Inflammation markers as MPO activity and relative gene expression, ROS levels and TNF-α, IL-1β, IL-10, IL-6 and iNOS were analysed in the jejunum of the rats. GSPE administration was effective in reducing MPO activity and ROS levels. Generally, aging tended to decrease cytokine gene expression levels in comparison with young rats. Moreover, GSPE treatment was effective in reverting the effects of age in some of these biomarkers. All in all, our results confirm that the administration of GSPE improves some of the inflammatory disruptions caused by age in rats.

BLOOD PRESSURE MANAGEMENT AND CARDIOPROTECTIVE EFFECT OF LONG-TERM COMSUMPTION OF WINE LEES IN HYPERTENSIVE RATS

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Hypertension (HTN) is the leading cause of premature death in the worldwide and increases the risk to suffer other cardiovascular diseases (CVD). In many patients, antihypertensive drugs are able to manage HTN stage; however, they can produce some side effects. Therefore, other alternatives to prevent and manage HTN are searched, mainly compounds obtained from natural products. We have previously demonstrated that the acute dose of a wine lees extract (WLE) exerted a potent antihypertensive effect in spontaneously hypertensive rats (SHR). Its effect was associated to its content in flavanols and anthocyanins. The aim of the present study was to evaluate the antihypertensive and cardioprotective effect of WLE after a long-term administration to hypertensive animals as HTN is a chronic disease. SHR were orally administered WLE at a dosage of 125 mg/kg bw/day or vehicle (VH) for five weeks. Body weight, water and food intake were measured once a week. Systolic and diastolic blood pressure (SBP and DBP), heart rate (HR), maximum and minimum derivative of change in pressure (max and min dP/dt), end diastolic pressure (EDP), contractility index, body temperature and activity were monitored in the aorta by a telemetry system before, during and after treatment (24 h, twice a week). SBP and DBP of VH-group increased during the experiment; however, this increase was avoided when animals consumed WLE. Similar effect was observed for EDP and contractility index, where contractility index is reduced along the experiment in VH-rats. Moreover, WLE consumption reduced the marker of cardiac status HR respect to VH-group, being specific of the light period. Furthemore, WLE-rats kept the dipper pattern in HR at the end of the study in contrast to control animals, whose lose this HR pattern. WLE also maintained max and min dP/dt levels of SHR respect to control group, in which a reduction of these parameters was observed. Finally, WLE increased the locomotor activity levels in SHR, being specific of the darkness period. All these results suggest that WLE could be a potential functional food ingredient with many benefits in the treatment of CVD, attenuating the development of HTN and exerting a cardioprotective effect.

This work has been supported by Grant number: RETOS COLABORACIÓN: RTC-2017-6044-2 from the Spanish Ministry of Economy and Competitiveness and European Regional Development Fund.

Maintenance of intestinal barrier function in aged rats fed with a grape seed proanthocyanidin extract-supplemented cafeteria diet

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Abstract

Cafeteria diet (CAF diet) has been found to induce intestinal alterations and metabolic endotoxemia in young obese rats. In this work, we explore the intestinal barrier function in aged, obese rats and evaluate the possible beneficial effects of a grape seed proanthocyanidin extract (GSPE) on 21-month-old female Wistar rats. Animals were either fed an obesogenic diet, fed a standard diet, treated with 500 mg/kg body weight of the extract for 10 days before the onset of the CAF diet or treated with the extract synchronically to the obesogenic challenge. We determined the plasma lipopolysaccharide (LPS) and the mRNA levels of gut integrity-related genes and performed an ex vivo gut barrier integrity assay of different intestinal sections. This study provides evidence that the intestinal barrier function is maintained in the elderly under both healthy and obesogenic conditions and that GSPE could be useful as a complement for a healthy aging process.

Keywords: intestinal permeability, tight-junctions, obesity, aging, proanthocyanidins.

BLOOMING FRESHWATER EFFECTS ON VIABILITY OF HUMAN INTESTINAL EPITHELIAL CELLS

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Abstract

Cyanobacterial blooms of freshwaters have highly increased worldwide in recent years. This is linked to the climate changes and growing effects of anthropogenic factors. Cyanobacteria generate many highly toxic to animals and humans metabolites. Gastrointestinal epithelial cell layer is the main barrier for their absorption into the circulation system of mammals, including humans.

We analyzed the effect of blooming freshwater samples on viability and proliferation of HIEC-6 human intestinal epithelial cell line using MTT test. The phytoplankton species composition was proved by light microscopic observations.

In 13 out of 16 analyzed samples, we observed gradual dose-dependent decrease in cell viability by 58.9%, $p<0.001$ vs.untreated cells. Different cyanobacteria species known to produce cylindrospermopsin toxin (CYN) were found in the tested samples. Among these, *Microcystis pseudofilamentosa*, *Microcystis smithii*, *Microcystis wesenbergii* were established in four of the analyzed freshwater samples. When tested on the same HIEC-6 cells pure CYN solely in concentrations of 1 μM and 11μM in the culture media, decreased cell viability by 13.4%, $p<0.001$ and by 21.8%, $p<0.001$, respectively. The effect was similar to that of the tested samples. Interestingly, other three samples highly stimulated cell proliferation by 194%, $p<0.001$ at lower doses and by 159.3% $p<0.001$ at the higher ones.

We assume that the toxicity of the majority of the samples could be attributed to the cocktail of toxins expressed by cyanobacteria species, including presence of CYN. The cytoproliferative effect of the other three samples may be related to possible tumor initiation effects, as a step of cancerogenesis, linking consumption of blooming freshwaters to the increased rate of cancers established for regions where these environmental events are regularly observed.

Acknowledgements: This study was financed by the Bulgarian National Science Fund projects NSF-KP-06-OPR03/18 and NSF-DN-13/9.

AHR AND ERA ACTIVATION VIA COMBINED E2 PLUS TCDD OR 3,3´DIINDOLYLMETHANE DIFFERENTIALLY ACTIVATE ARYL HYDROCARBON RECEPTOR AND ESTROGEN RECEPTOR ALPHA TO REGULATE DIVERSE SIGNALING PATHWAYS IN MCF-7 HUMAN BREAST CANCER CELLS.

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Abstract:
Crosstalk between estrogen receptor alpha (ERa) and aryl hydrocarbon receptor (AHR) is proposed to influence breast cancer growth. AHR is best known for mediating the toxicity of 2,3,7,8-terachlorodibenzo-p-dioxin (TCDD), but it is activated by many dietary ligands some of which also target ERa. Here we used next generating sequencing to identify gene-wide targets of AHR and ERa in MCF7 breast cancer cells after treatment with 17b-estradiol (E2) and TCDD, E2+TCDD, 3,3'diindolmethane (DIM), which activates AHR and ERa, or resveratrol (RES), which activates ERa but inhibits AHR. We identified approximately 61000 ERa bound regions that were greater than DMSO (vehicle) after treatment with E2, E2+TCDD, or DIM and compared with 1409 by TCDD using ChIP-sequencing. Treatment with E2+TCDD or DIM induced approximately 18000 AHR bound regions, while E2 induced 1153 and RES only 39. Only 2% of the E2 ERa bound peaks overlapped with AHR bound peaks, while 9.6% of the TCDD AHR bound peaks overlapped with ERa bound peaks. Conversely, 89% and 75% of the AHR-bound peaks overlapped with ERa bound peaks for E2+TCDD and DIM, respectively. De novo motif analysis for ERa after treatment with E2, E2+TCDD, DIM and RES resulted in the identification of an ERE as the top ranked site, while an AHRE site was the second top ranked site for E2+TCDD and DIM treatments. Similarly, AHRE and ERE were the top two sites for AHR-bond regions after E2+TCDD and DIM, while an ERE was not among those motifs found after TCDD treatment. Integration of the ChIP-sequencing data with RNA-sequencing revealed that AHR and ERa coregulated the absolute changes in 1153 and 1145 genes after E2+TCDD and DIM treatment, respectively. However, AHR and ERa only coregulated changes in 248 and 90 genes after E2 and TCDD treatment, respectively. Among unique GO terms for AHR and ERa genes after E2+TCDD treatment were genes enriched for xenobiotic transport process, cell adhesion and GTPase mediated signal transduction, while after DIM treatment processes involved in regulation of cell adhesion, in enzyme linked receptor signalling and negative regulation for cell differentiation were enriched. Overall, this study shows that the dietary ligand, DIM, activates both AHR and ERa but targets different molecular pathways compared with cotreatment with E2+TCDD. These findings highlight that some dietary ligands can activate multiple cellular pathways and provide better insight into the crosstalk between ERa and AHR in breast cancer.

Combined supplementation with hesperidin, phytosterols and curcumin improve body composition and decrease adiposity and LDL-cholesterol in ovariectomized rats

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Abstract

During menopause, women begin to experience different physiological changes that lead to an increase in several risk factors for women's health, including osteoporosis, abdominal obesity, hypercholesterolemia, insulin resistance, diabetes, metabolic syndrome and cardiovascular disease (CVD).

Ovariectomized (OVX) rats, which mimic the metabolic alterations related to estrogen deficiency, are a well-established preclinical model of menopause because they develop osteoporosis, abdominal/visceral obesity and different risk factors for CVD.

Different *in vivo* and human studies have shown beneficial effects of bioactive compounds, such as genistein, against metabolic alterations that appear with menopause. However, some studies strongly suggested that better responses are obtained when treatments are carried out under a multifaceted approach, using different bioactive compounds that act against complementary targets.

The aim of this study was to evaluate, in an ovariectomized rat model, whether the supplementation for 8 weeks with a multi-ingredient (MI) including hesperidin, phytosterols and curcumin exerted beneficial effects against fat mass accretion and metabolic alterations associated with menopause. For this purpose, 20 ovariectomized rats were orally supplemented with either the MI (OVX-MI) or the vehicle (OVX). In addition, 10 OVX rats received orally the vehicle and a biweekly estrogen treatment by subcutaneous injections of 17β estradiol (OVX-E2), whereas an extra group of 10 rats used as a control group was sham operated and supplemented with the vehicle (SHAM).

The supplementation with the MI partly counteracted the fat mass accretion observed in the OVX animals, which was evidenced by a decreased total fat mass (%), adiposity index and the weight of all the white adipose tissue depots studied (retroperitoneal –RWAT-, mesenteric –MWAT- and inguinal –IWAT-). Furthermore, MI supplementation significantly increased the lean/fat mass ratio compared to OVX rats suggesting a healthier body composition. The lower adiposity observed in MI-treated rats was accompanied by lower circulating levels of c-LDL compared to OVX rats. These effects were of a similar order of magnitude to those observed in rats treated with estradiol. Our findings highlight the anti-adiposity and anti-hypercholesterolomic effect of the MI, which could contribute to a decreased risk for CVD and Metabolic Syndrome associated to menopause and shed more light on the use of alternative or complementary therapies to tackle obesity and metabolic disorders occurring in menopause. Nevertheless, further research is needed to shed more light on the mechanisms involved in the observed results.

Cultivation Conditions of Red Grape Modulate the Seasonal Regulation of Energy Metabolism and the Phenotype of White and Brown Adipose Tissues in Fisher 344 Rats

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It is well known that the effects of polyphenols in metabolism are seasonal-dependent, but also, in polyphenol-rich fruits as red grapes, their composition and bioavailability is influenced by the cultivation conditions. In our study, we examined the effects of red grape consumption on energy metabolism and adipose tissue functionality, considering photoperiod and cultivation conditions. For this purpose, Fisher 344 rats were exposed into 3 different photoperiods and supplemented with 100mg/kg of either conventional or organic red grapes for 10 weeks (n=6). Results showed a clear influence of both cultivation conditions and seasonality on the effects of grape consumption in energy expenditure and BAT functionality, as well as in the gene expression pattern of WAT. Moreover, these data partly support the xenohormesis theory, as rats showed a BAT-independent increase in energy expenditure after grape consumption during summer-like conditions. Additionally, our findings suggest a beneficial effect of grape consumption on the metabolism of WAT and a differential fat storage pattern between experimental groups.

Impact of seasonal consumption of local tomatoes on (poly)phenols absorption in Fischer rats

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Abstract

Consuming phenol-rich fruits and vegetables, such as tomato, is associated with beneficial health outcomes. The health effects of phenolics compounds have been attributed to their metabolism products. The bioavailability of these compounds can be modulated by several factors. This study aims to evaluate the effect of a seasonal consumption of local tomatoes on their (poly)phenols absorption. For this, (poly)phenolic bioavailability was analyzed by uHPLC-MS^n in Fischer rats exposed to three photoperiods to mimic the seasonal daylight schedule after chronic consumption of tomatoes from two locations in Spain (LT, local tomatoes from Tarragona and NLT, non-local tomatoes from Almería). The bioavailability of tomato (poly)phenols depended on the photoperiod to which the rats were exposed, significantly varying the metabolite concentrations between seasons. Some metabolites were even not detected in winter. In-season consumption of tomato allowed obtaining the highest amounts of total circulating metabolites. In addition, the origin of the tomato administered generated marked differences in metabolic profiles, being higher amounts after NLT ingestion. We conclude that in-season consumption of tomato increases their (poly)phenols ad in Fischer rats, whereas local tomatoes consumption showed lower circulating metabolites than non-local tomatoes. Thus, the tomato cultivar and the seasonal daylight schedule affect the bioavailability of tomato (poly)phenols that could also affect to their bioactivity.

Keywords
Metabolites, phenolic compounds, photoperiod, seasonal consumption, Solanum lycopersicum.

ANTI-OBESITY AND INSULIN-SENSITIZING EFFECTS OF GLYCOSAMINOGLYCAN SUPPLEMENTATION AS DERMATAN SULFATE

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Glycosaminoglycans (GAGs) are a special group of carbohydrates found in food that exert biological effects beyond basic nutrition. Previous studies showed that a mixture of GAGs favors the loss of fat mass in obese mice associated with enhanced capacities for oxidative metabolism in visceral adipose tissue (AT) depots, in an effect attributable specifically to the dermatan sulfate component (DS). We here studied whether oral supplementation with DS can counteract the development of dietary obesity. C57BL/6J mice were fed with a high-fat diet (HFD-45) for 4 weeks while supplemented with DS (30 mg/kg/day, DS group) or vehicle (water, HF control group); a third group of animals was kept on a standard normal-fat diet and received the vehicle. Body weight, body composition, food intake and functional tests were monitored/ conducted in live animals, and biochemical, morphological, metabolomic and gene expression analyses on tissues at end-point. HFD feeding induced as expected an increase in body weight, adipocyte size, and adiposity, together with a relative loss in lean body mass. These effects were attenuated in the DS group, despite their energy intake was higher than that of the HF group. Resistance to the development of obesity was associated with a greater energy expenditure and activation of brown adipose tissue in the DS group as compared to the HF control group. Undesirable effects of HFD on blood glucose and insulin sensitivity were also attenuated in the DS group, which had lower levels of proinflammatory eicosanoids in the liver. Gene expression analysis in skeletal muscle and adipose tissues suggested that metabolic changes including a preferential channeling of excess fuel substrates towards skeletal muscle might contribute to the better response to the HFD observed in the DS group. The results support a possible use of DS as an active component in functional foods/supplements for the management of obesity and associated metabolic diseases.

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Untargeted Metabolomics to Explore the Interindividual Variation in the Metabolism of Flavan-3-ols after Standardized Acute Intake of Cocoa

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Flavan-3-ols are considered the most important flavonoids in terms of level of intake and cardiometabolic health effects. Their metabolism has been extensively described. However, the exploration of the interindividual variation in their bioavailability has been fairly limited, since studies enrolled small numbers of subjects, or did not quantify all relevant metabolites. Our objective was to explore the interindividual variation in the metabolism of cocoa flavan-3-ols using untargeted metabolomics in a large controlled intervention study. We leveraged the COB study that enrolled 128 healthy volunteers (half young (18-30y), half older (65-77 y), 50% male, 50% female). Volunteers collected urine in different fractions over 48h after consuming in controlled conditions a polyphenol-rich breakfast composed of cocoa, orange juice, and blackberry and providing 640 mg of flavan-3-ols. Urine samples were analyzed by untargeted metabolomics (UPLC-QToF-MS, pos&neg). A target-screening approach allowed to identify 29 flavan-3-ol specific metabolites, namely epicatechin, phenyl-γ-valerolactones, phenylvaleric acids and their methylated, sulfated and glucuronidated derivatives. Thirteen ions highly correlated with these flavan-3-ol metabolites were identified as small phenolics or metabolites of cocoa compounds. Clustering analysis revealed a high interindividual variation in the excretion of both host and microbial metabolites. Subjects were classified by K-Means in 4 metabotypes, which were further characterized by applying V-test on the whole metabolomic profiles to pinpoint the metabolites that were specifically associated with each metabotypes. Age, gender and BMI did not significantly differ between metabotypes. Analyses are ongoing to identify possible associations with microbiota data (16S) and genotype (SNPs for 112 selected genes involved in polyphenol bioavailability) The relevance of the observed metabotypes regarding the health effects of flavan-3-ols will deserve further investigation.

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Antihypertensive potential of food industry by-products: inhibition of the angiotensin converting enzyme and modulation of gut bacteria populations

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Abstract

Hypertension (HTN) is one of the major risk factors for cardiovascular diseases (CVD) and its prevalence is increasing worldwide. Current pharmacological treatments have side effects and new alternatives are needed. In this regard, protein-rich food by-products are attracting attention as they have shown to inhibit the angiotensin converting enzyme (ACE), which is a key enzyme in the blood pressure regulation within of the Renin-Angiotensin-Aldosterone system, and to exert antihypertensive properties. Moreover, it is well known that gut bacteria play an important role in host health and disease and its modulation has recently been eluded as a therapeutic target for CVD and HTN. Considering all these facts, the objective of this study was to investigate the in vitro potential of hydrolysates from industrial by-products to exert ACE inhibitory activity and to modulate fecal bacterial populations from prehypertensive patients.
To this aim, several hydrolysates were obtained from a food industry by-product using different food-grade enzymes and hydrolysis conditions. Firstly, these hydrolysates were tested for their ability to inhibit ACE in vitro. Then, the hydrolysates were fermented with fecal microbiota during 24 h and different bacterial taxa were analyzed by quantitative polymerase chain reaction using specific primers. Many of the hydrolysates had a good ACE inhibitory capacity, which depended on the enzyme and the hydrolysis conditions. In addition, fecal fermentations with some of these hydrolysates led to changes in different bacterial populations compared to the control, increasing the levels of bacteria associated to beneficial health effects and decreasing those related to disease.
Results are relevant as they may facilitate the valorization of food industry by-products, contributing to the circular economy model by reducing the waste of these by-products and increasing the use of raw materials to improve human health. However, additional studies are needed to evaluate the blood-pressure lowering effects of the bioactive hydrolysates in animals.

Posters

Session 2: Precision Nutrition

DIET INTERACTION WITH GUT MICROBIOME AND SERUM LIPIDOME PROFILING IN A PILOT STUDY ON THE OBESE QATARI FEMALE POPULATION

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Abstract

Obesity is a complex disease with underlying genetic, environmental, and epigenetic factors, etc. Obesity is a risk factor for various disorders in women, including cardiovascular diseases, diabetes, infertility, pregnancy complications, that are among the most prevalent chronic conditions in Qatar. Also, according to data released by MOPH in Qatar, the obesity prevalence rate is higher in women than men in Qatar. Recent studies have highlighted the significant roles of the gut microbiome and serum lipid metabolites in contributing to the pathology of obesity. Thus, in this study, we aimed to identify the interaction of diet with microbial and lipidomic biomarkers in an obese Qatari female population.

We enrolled 35 adult female subjects (18-65 years), and they were classified based on their BMI, in Obesity-I group (<35 kg/m^2, n=18), and Obesity-II and -III group (>35 kg/m^2, n=17). For each subject, we measured anthropometric data, body composition, biochemical profile, dietary intake using 24hrs dietary recalls, gut microbial composition by 16s rDNA sequencing method that targeted the v3-v4 region using Illumina Miseq and serum lipid metabolites using liquid chromatography - high resolution mass spectrometry (LC-HRMS). Bacterial diversity index, microbial markers, and correlation analysis were performed.

The results were analyzed by comparing 2 groups: Obesity-I vs Obesity-II and III together. The dietary data showed a positive correlation of vitamin D and total sugars intake with basal metabolic rate (R=0.488, p=0.007, R=0.382, p=0.037, respectively) and multiple body composition parameters. The taxonomic and lipidomic profiling showed that Obesity-II & -III group had a higher abundance of genera *Streptococcus* (8.90% vs 24.09%, p=0.04.) and unclassified bacteria from the class of TM7-3 (0.35% vs 0.86, p=0.02), a higher level of a mono-hexosylceramide metabolite - Hex1Cer(t18:0_24:1) (3.04x10^7 vs 2.49x10^7, area under the pick, p=0.005) and lower levels of different phosphatidylcholines, lysophosphatidylcholines and phosphatidylethanolamine metabolites. Also, correlation analysis revealed that the genera *Streptococcus* and unclassified bacteria from the class of TM7-3 were positively correlated with body weight (BWT, R=0.487, p=0.04 (*Streptococcus*), R=0.367, p=0.004 (Unclassified bacteria from the class of TM7-3), muscle mass (MM, R=0.416, p=0.016 (*Streptococcus*), dietary MuFA (R=0.641, p<0.0001), PuFA (R=0.415, p=0.0035), galactose (R=0.428, p=0.029), sucrose (R=0.448, p=0.022), and available carbohydrates R=0.548, p=0.004).

Controlling the dietary intake, particularly the intake of fats and sugars, can contribute to modulate the genus *Streptococcus* and the ceramide metabolite Hex1Cer(t18:0_24:1) playing an unprecedented role in the management of severe obesity in the Obese Qatari female population

Transcriptomic Differences Between Monozygotic Adolescent Twins Discordant for Metabolic Syndrome Following Weight Loss: A Case Study

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Background: Much attention has been paid towards how different genotypes influence obesity development and treatment response despite genetic models explaining relatively little of the variation in BMI. Gene expression levels may be a good indicator of the influence of both exogenous and endogenous factors on obesity treatment. The present study describes a pair of monozygotic paediatric twins with obesity and Metabolic Syndrome (MetS) who underwent a 16-week weight reduction program.

Methods: RNA was extracted from peripheral blood mononuclear cells (PBMCs) at baseline and week 16 and whole genome expression assessed via RNA sequencing (Illumina NextSeq 500) and counts generated using the "RNAsiq" pipeline by Monash Bioinformatics. Body composition was analysed via dual x-ray absorptiometry and cardio-metabolic outcomes from a fasted blood sample. Due to the case study design, only transcripts with a log fold change < -0.26 or > 0.26 were considered to be differentially expressed between baseline and week 16. Gene ontology (GO) analysis on differentially expressed genes was conducted using Cytoscape software with GO terms considered enriched with an adjusted p value < 0.05 and at least five genes were mapped to the GO term. GO terms were grouped using a connectivity kappa threshold of 0.4.

Results: Despite a 14 kg weight reduction in both participants, only Twin A saw an amelioration of MetS. This was due to a larger reduction in triglycerides (-2 mmol/L vs 0.4 mmol/L) in Twin A. Considerably more transcripts were down regulated in Twin A (12,850) compared to Twin B (2,557) with little overlap between transcripts (12.2%). Contrastingly, 48.1% (2,280 genes) of genes down-regulated following weight loss in Twin A were up-regulated in Twin B. These genes mapped to 90 GO terms and nine out of the top ten enriched terms related to immune cell activation, in particular, neutrophil functions.
Conclusion: Opposite gene expression regulation in twins despite the same degree of weight loss and similar reductions in central obesity is puzzling. Alterations in the transcriptome may precede the development of more traditional markers of pro-inflammation. In the current case report it appears that genetics have little influence on the response to weight loss treatment and that the transcriptome may be reflective of these other influential factors.

AI4FOOD: A NUTRITIONAL INTERVENTION TO INTEGRATE DIGITAL TOOLS IN NUTRITIONAL ADVICE

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Abstract:

Artificial Intelligence for the prevention of chronic diseases through personalized nutrition (AI4Food) project will develop a series of enabling technologies to process, analyze and exploit a large number of biometric signals indicative of individuals' habits, phenotypic and molecular data. The main objective of AI4Food is to integrate all this information and develop new machine learning algorithms to generate a paradigm shift in the field of nutritional counselling. Our project seeks to develop a new generation of digital tools to assist in personalized decision making in the field of nutrition. These tools will allow a more objective and effective assessment of individuals' nutritional status, helping experts to propose changes towards healthier eating habits from general to personalized recommendations that will be more effective and sustained over time for the prevention of chronic diseases.
For this purpose, we designed an interventional study with cross-over design that will include nearly 100 overweight and obese individuals, which will be monitored for a month while following an hypocaloric diet for healthy weight-loss. Participants are going to be randomized in two groups. The first group will start collecting data via questionnaires (traditional method) for the first two weeks, and switch to the digital data-collection method for the last two weeks. The digital data-collection includes: 1) automatic image processing of the diet using computer vision approaches (pictures acquired with their smartphone); 2) glycemic curve obtained by a interstitial fluid sensor, and several biometric/behavioral data acquired with a smartwatch (skin temperature, breathing rate, blood oxygen saturation, heart rate, sleep cycles, inertial sensors for physical activity patterns, among others). Conversely, the second group will perform the data-collection on the opposite order. The intervention consists of three follow-up visits in which clinical, anthropometric, lifestyle, biochemical, metabolomic, lipidomic, genetic and metagenomic data will be obtained.
This project will allow us to gain knowledge on 1) which are the sensor-dependent and sensor-independent biomarkers that work best for nutritional modelling of human behaviour and habits 2) when, that is, under what circumstances (e.g., user habits, signal quality, context, phenotypic and molecular data), and 3) how can we best leverage those signals and context information to improve nutritional recommendations.
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PRECISION NUTRITION STRATEGIES TO ENHANCE THE DECLINE OF THE IMMUNE SYSTEM

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Abstract

Deterioration of the immune system is responsible of an increased susceptibility to autoimmune diseases, infections, and cancer, as well as a decreased vaccination efficacy. In addition to age, there are some environmental factors that accelerate the decline of the immune system and compromise its function: exposure to chemotherapy, chronic infections, or obesity play a predominant role among these factors. Thus, elderly, obese individuals, cancer patients, and people suffering from severe and persistent covid are highly vulnerable groups.

To face these challenges, our project "NutriSION" propose to design Precision Nutrition strategies to slow down the decline of the immune system, focused on developing new bioactive compounds and nutritional strategies with immunomodulatory activity that can boost the immune system function. To achieve this goal, a clinical study involving volunteers from these vulnerable populations has been initiated. From each volunteer, a large number of anthropometric and lifestyle data, medical records and biological samples have been collected to perform biochemical, genetic, lipidomic, metabolic, and metabolomic analysis, thus obtaining a holistic view of the participant.

This molecular analysis will provide relevant data about molecular marks of the decline of the immune system that will serve as a target to design effective precision nutrition interventions. Revitalization of the immune system could prevent infectious diseases such as COVID19, increase the vaccination efficiency and delay the appearance of cancer, autoimmune or inflammatory diseases.

This work has been supported by Synergy R&D Projects in New and Emerging Scientific Areas (2020) of Regional Government of Community of Madrid (NutriSION-CM Y2020/BIO-6350), and by the REACT EU Program 2021 (FACINGLCOVID-CM project, European Regional Development Fund (ERDF) and Community of Madrid).

Examining individual factors influencing adherence and response to wholegrains and nuts in a series of interventional N-of-1 studies: the MI-DIET study

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Inter-individual variations in response to dietary interventions are common, which can be affected by both physiological and behavioural factors. N-of-1 studies enable examination of response at an individual level, by collecting multiple measurements over time in a single volunteer. The goal of the MI-DIET study was to examine behavioural factors associated with compliance to a Dietary Approaches to Stop Hypertension (DASH)-style intervention with wholegrains (WGs) and nuts, and subsequent blood pressure (BP) response, through a series of N-of-1 interventional studies.
14 volunteers with mildly elevated BP (120/80-140/90mmHg) who were low consumers of WG foods (≦7 portions/wk) were recruited. Each volunteer carried out a 24-week N-of-1 study, composed of three 8-week periods (observation, intervention, and follow-up). Each day, volunteers responded to semi-personalised morning and evening questionnaires using a wrist-worn device (PRO-Diary, CamNtech Ltd.) and measured their BP using a wireless monitor (QardioArm, Qardio Inc.), providing sufficient statistical power for individual N-of-1 dynamic modelling analysis. During the intervention phase, volunteers were provided with 3-4 portions of WGs and a handful of nuts each day, in line with DASH dietary recommendations. Every four weeks, volunteers completed an online 24h diet diary (Intake24) and visited the institute to measure their weight and provide a fasted blood sample for analysis of cholesterol concentrations and WGs intake biomarkers.
12 volunteers completed the study, with 11 collecting enough measurements for N-of-1 analysis. For two volunteers, better self-reported sleep quality was significantly associated with lower systolic BP, and nuts consumption was associated with lower systolic BP in another volunteer (p<0.01). 6 volunteers consumed significantly more WGs in the follow-up phase compared with the start of the study, with weekends or days off associated with significantly lower consumption in 3 volunteers (p<0.05). Consuming nuts was associated with significantly higher motivation to eat well and a higher degree of food restriction in two volunteers (p<0.05). This study provides a proof-of-concept for an interventional N-of-1 study in nutrition. Collecting repeated measurements on an individual level can identify relevant predictors of compliance and response to a dietary intervention for a given person. Further work is ongoing to include objective actigraphy measures in the N-of-1 dynamic regression models.

Developing models to predict change in plasma triglyceride concentrations and long-chain n-3 polyunsaturated fatty acid proportions in healthy participants after fish oil intervention

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Substantial response heterogeneity is commonly seen in dietary intervention trials. Large datasets can be used to identify potential predictors of these differences in physiological response.

Using data from a large, controlled crossover study (the FINGEN study) supplementing with two doses of long chain n-3 polyunsaturated fatty acids (LC n-3 PUFAs), the primary goal of this analysis was to develop models to predict change in concentrations of plasma triglycerides (TG), and in the plasma phosphatidylcholine (PC) LC n-3 PUFAs eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) after fish oil (FO) supplementation. A secondary goal was to establish if clustering of data prior to FO supplementation would lead to identification of groups of participants who responded differentially.

Unsupervised clustering was implemented using k -medoids and hierarchical clustering, with cluster membership compared with changes in plasma TG and plasma PC EPA+DHA. To generate models for the outcomes of interest, variable selection methods (forward and backward stepwise selection, LASSO and the Boruta algorithm) were applied to identify suitable predictors. The final model was chosen based on the lowest validation set root mean squared error (RMSE) after applying each method across multiple imputed datasets. Models for predicting change in plasma PC EPA+DHA showed greater increases with age and female sex. The model for predicting plasma TG change suggested a healthier profile (including lower insulin and LDL-cholesterol levels) was associated with greater TG-lowering after 1.8g/d EPA+DHA. There were no statistically significant differences in the outcomes between clusters.

The analysis procedure generated models and selected relevant variables for predicting change in plasma TG and plasma PC EPA+DHA after FO supplementation. The results demonstrate how application of appropriate statistical methods can provide new insights for precision nutrition, by predicting participants who are most likely to respond beneficially to nutritional interventions.

Gut microbiota histidine catabolism is a key player in the NAFLD disease

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The gut microbiome develops a critical role both in the pathophysiology of non-alcoholic fatty liver disease (NAFLD) and in the histidine metabolism, although their complex interaction remains unclear. Low histidine levels were associated with different metabolic conditions, such as chronic kidney disease, obesity, and heart failure. In turn, it has been described that gut microbiota plays a key role regulating of dietary histidine bioavailability through histidine utilization (*hut*) operon. Thus, histidine supplementation has been proposed as a potential treatment against NAFLD by increasing hepatic histidine levels. An integrative systems medicine approach was applied (faecal metagenomics, plasma metabolomics, and hepatic transcriptomics) in 2 well-characterised human cohorts (discovery n = 49 and validation n = 628) and an independent cohort (n = 130), combined with *in vitro* and *in vivo* models. Serum histidine levels were negatively associated with liver steatosis in parallel with lower gut microbial gene richness, composition, and functionality. In addition, microbial functions of the histidine utilization operon positively correlate with the steatosis degree. Faecal xenotransplantation in mice from low histidine donors, resulted in a higher hepatic triglyceride content together with alterations in genes related to fatty acid metabolism and insulin signalling. Besides, human primary hepatocytes exposed to a high concentration of palmitic acid, were protected to develop a steatosis like phenotype after histidine supplementation, by a reduction in the expression of genes related to lipogenesis and an induction of the expression of genes related to lipid transport. Moreover, *in vivo* treatment with histidine-related amino acids promotes a substantial amelioration of NAFLD features and reducing hepatic insulin resistance in accordance with a reduction of the metagenomic dysbiosis and a decreased microbial histidine catabolism. Together, these data pointed that histidine catabolism is critical in the development of NAFLD and supplementation with histidine related amino acids may be a novel strategy for the treatment of this disease.

The efficacy of genotype-based dietary or physical activity advice on behaviour change in healthy individuals and individuals that are at risk of cardiovascular disease, type II diabetes or obesity: A systematic review and meta-analysis.

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Despite clear evidence that adherence to dietary and physical activity advice can reduce the risk of cardiometabolic disease, a significant proportion of the population do not meet recommendations. Personalised advice based on genetics has been proposed to motivate behaviour change, although research to date has been contradictory. The aim of this systematic review and meta-analysis was to evaluate the efficacy of genotype-based dietary or physical activity advice on behaviour change in the general population and individuals that are 'at risk' of cardiovascular disease, type II diabetes or obesity. The databases searched were MEDLINE, Embase, PsycINFO and the Cochrane Central Register of Controlled Trials (CENTRAL). Searches were from inception to the 7th January 2022. Randomised controlled trials of a genotype-based dietary and/or physical activity advice intervention that aimed to change dietary and/or physical activity behaviour were included. Abstracts of 7899 records were screened, and 14 reports from 11 studies met the inclusion criteria. A random effects model using the inverse variance method was used to pool effect sizes. There was no effect of genotype-based dietary or physical activity advice on dietary behaviour for all studies SMD 0.00 (-0.11 – 0.11) or when analysed by sub-group; 'at risk' SMD 0.00 (-0.16 - 0.16); general population SMD 0.01 (-0.14 – 0.16). Similar findings were identified for physical activity behaviour for all studies SMD - 0.01 (-0.10 – 0.08) or when analysed by sub-group; 'at risk' SMD 0.07 (-0.18-0.31); general population SMD -0.02 (-0.13 – 0.10). There was no effect of being informed of a risk associated genotype compared to a non-risk associated genotype in addition to genotype-based dietary or physical activity advice on dietary behaviour SMD 0.14 (-0.06 – 0.33) or physical activity behaviour SMD 0.01 (-0.24 – 0.25). The quality of evidence for the dietary behaviour outcome was low and for the physical activity behaviour outcome was moderate. This meta-analysis of pooled data from identified studies suggests that genotype-based advice does not affect dietary or physical activity behaviour more than general advice or advice based on lifestyle or phenotypic measures. This finding was consistent in studies that had recruited participants from the general population as well as studies that had recruited participants from populations 'at risk' of CVD, T2DM or obesity.

Metabolic Footprinting of Acidified and Fermented Milk Consumption in Serum and Urine of Healthy Men

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Fermentation of food has been a widely used method of natural preservation for thousands of years, which also has an impact on the nutritional value of the transformed food. Fermented dairy products are increasingly being studied as they have health benefits in addition to their nutritionally valuable properties. In the present study, the influence of cow's milk fermentation on the postprandial response of healthy young men was investigated in serum and urine.

In a randomised crossover study, serum and urine samples were taken from 14 healthy young men after consuming 800 g of acidified milk (AM) or probiotic yoghurt (YO) for a period of six hours. For comparison, the subjects consumed a high fat non dairy meal (53 % energy fat) and again serum samples were collected during a six-hour period.

The metabolome of serum and urine was analysed using two untargeted gas chromatography mass spectrometry (GC-MS) methods. In the first method, double derivatisation was performed to convert as many compounds as possible into a volatile form. The first method was complement with a nutrivolatilomic approach, measuring only volatile compounds using headspace sample preparation.

With the first GC-MS method (semivolatiles), total 30 postprandial active compounds could be identified at level 1 and 2 for AM and YO. With the second GC-MS method (volatiles), total 35 postprandial active compounds could be identified at level 1 for AM and YO. All compounds were finally integrated with targeted analysis. The incremental area under the curve (iAUC) was used to estimate of the postprandial response in serum and the 6 h pool was used to estimate the postprandial response in urine.

The postprandial change in the serum and urine metabolome is strongly influenced by the composition of the consumed dairy product. The fermentation of milk increases many metabolites derived from proteins, fatty acids and carbohydrates in yogurt. Most of these metabolites are then also increased in the serum and urine after consuming yogurt. Many metabolites show a positive postprandial effect even after consumption of a high fat meal (without dairy products) and are not specific biomarkers for dairy consumption.

Nutrivolatilomics of Milk and Yoghurt Intake in Serum from Young and Elderly Men

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Abstract

Dairy products are ubiquitous in the human diet and many studies have addressed their nutritional properties, including their contribution to health. Despite this wealth of information, the impact of milk fermentation, on the product side, as well as the impact of aging, on the consumer side, on these properties are not well characterized. The recent study by Kim et *al.* (*Front. Nutr.,* **2022**) consequently identified the metabolic signatures associated with milk and yogurt intakes in healthy young and elderly men, by means of GC-MS and LC-MS analysis on postprandial serum through a randomised, controlled and crossover study. After a run-in period of three weeks, during which the consumption of dairy products and other fermented products was excluded, the subjects were asked to consume 600ml of milk or yogurt. Their serum was collected over a period of 24h and then analysed..

Building on the aforementioned contribution, the present work adds a nutrivolatilomics analytical strategy by measuring the volatile compounds present in the samples from the intervention study. Untargeted analyses of serum samples were performed by dynamic headspace vacuum transfer in trap gas chromatography mass spectrometry (DHS-VTT-GC-MS) method.

1’669 postprandial metabolites were detected, among which 24 were found to differ in their response in the two age groups. 16 of these compounds could be identified at level 1. The incremental area under the curve (iAUC) showed that elderly men had a higher postprandial response than young men. For six of these metabolites (phenol, octanoic acid, m-cresol, 2-coumaranone, 2-methylbutanal and one unknown compound), an increased iAUC was observed in the elderly group after the intake of both yogurt and milk. In addition to revealing potentially new markers for the intake of dairy products this study indicate that metabolic difference associated with the aging process can be revealed by postprandial challenge tests.

Altered mRNA levels of circulating peripheral blood mononuclear cells in adult and elderly men after the acute intake of milk or yogurt

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We have previously shown that the acute intake of dairy products, fermented can alter the postprandial profiles of circulating metabolites. Interestingly, we noted that the postprandial responses of the clusters of identified metabolites where different when considering the age of the consumers, suggesting a major role of the ageing process on the metabolic response to the dairy intake.
In order to investigate the mechanisms behind these changes, here we explored the mRNA profiles of 44 targeted genes in the circulating peripheral blood mononuclear cells (PBMC) of the *FermentoMilk* study participants, including adult (20-35yr, n=11) and elderly (65-80yr, n=11) men. After a run-in period of three weeks, during which the consumption of dairy products and other fermented products was excluded, the participants were asked to consume 600 ml of milk or yogurt. PBMC were collected before and after the run-in period, as well as before (0h) and after (2h, 4h) the acute dairy intake. Following RNA extraction and retrotranscription, the mRNA levels of 44 genes were simultaneously measured using TaqMan Array Cards. The statistical analyses revealed that the most important alterations observed on the studied genes came from the age factor, either during the restriction or the postprandial period. Thus, 8 genes (mostly related to inflammation), namely CXCR2, Actn4, GPBAR1, IFNG, MRPS33, SVPB, TLR4, TNFRSF1 were up-regulated in the elderly when compared to the adult participants, irrespectively of the dairy product consumed or the period considered. In addition to this, 16 genes showed postprandial changes, with at least one time point being different from the basal value. Interestingly, some of the targets showed changes related to specific interactions. When yogurt was consumed, several genes related to inflammation (IFNG) apoptosis (SH3KBP1), lipid metabolism (NR1H2, NR1H3) and oxidative phosphorylation (NDUFS4) were up-regulated only in the elderly participants.
We conclude that the ageing process has a predominant impact on the targeted mRNA levels in circulating PBMC. In addition, some of the targets studied reacted to the short-term (postprandial) stimulation, especially when yogurt was consumed by the elderly participants, revealing age-related differences that can contribute to explain the population-specific metabolic responses to dairy intake.

A novel Gut-Brain Axis Model towards Precision Nutrition

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The gut-brain axis is a bidirectional communication system that has recently gained increased attention for its importance in health and disease. From a mechanistical point of view, the gut-brain axis includes endocrine, immune and neural pathways. However, as the human body is a complex system, it is difficult to grasp the underlying mechanisms as a whole. The gut microbiota is an important part of this axis and can modulate brain function, for instance via the production of short-chain fatty acids (SCFAs) or via altered systemic levels of the serotonin-precursor amino acid tryptophan.
We recently showed that SCFA butyrate rescued the transport of tryptophan into oxidatively stressed fibroblasts, which serve as a common *in vitro* model for the nervous system. This effect could partly be explained by an increased gene expression of two relevant tryptophan transporters.
Here, we present a study that assessed the effects of microbial metabolites, after passage through intestinal tissue, on fibroblasts *in vitro*. Serosal fluids (SFs) were sampled from Ussing chamber systems containing a freshly harvested distal colonic biopsy mounted between two chamber halves separating the luminal and serosal side. Thereafter, fibroblasts were exposed to a mixture of SFs of n=16 healthy subjects.

SF showed no microbial growth and a pH ~8. Exposure of fibroblasts with a mixture of one part regular medium (RM) and one part SF showed similar cell viability and cytotoxicity measures as RM alone or a mixture of RM and SF's carrier substance (Krebs solution). Exposure to 10 µM H_2O_2 resulted in non-significantly decreased cell viability and increased cytotoxicity. Oxidatively stressed cells treated with RM+SF showed similar viability and cytotoxicity measures as non-stressed cells; whereas application of oxidative stress to pre-treated cells increased cytotoxicity compared to RM+SF exposure.
All conditions showed similar gene expression levels of the main tryptophan transporters, except SF treatment of stressed cells that showed significantly increased gene expression of SLC7A5 and SLC7A8, but not the common subunit SLC3A2, more than 2.5-fold compared to control. SF treatment of oxidatively stressed cells also significantly increased gene expression of SLC7A5 compared to H_2O_2 exposure.

To date, most studies to understand the gut-brain axis have focused on one of its compartments isolated rather than investigating their connection. The presented study is an attempt to build an extended gut-brain axis *ex vivo-in vitro* model based on individually well-established methods to meet the need of standardised mechanistical assessments of personalised dietary and medical interventions.

The design of a crossover trial to study the effects of omega-3 fatty acids on individual postprandial TG response in healthy overweight subjects (Omega-3PT trial)

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Abstract

Cardiovascular diseases (CVDs) are the most common cause of death worldwide. Observational cohort studies and Randomized Crossover Trials (RCTs) have shown that marine omega-3 fatty acids reduce the risk of CVD, although inconsistency exists in the findings. The beneficial effects are predominantly mediated through lowering of fasting triglycerides (TG) levels, however anti-inflammatory effects may also play a role. In addition, non-fasting TG levels are a significant risk factor for CVD, and omega-3 intake has been shown to affect postprandial TG levels. It is well known that there is a large inter-individual variation in the magnitude of fasting plasma TG change after omega-3 fatty acids supplementation. However, little is known about the inter-individual variation in the postprandial TG response after omega-3 fatty acids supplementation, and the mechanisms causing this variation. Thus, this trial aims to elucidate how omega-3 fatty acids supplementation affects postprandial lipid and inflammatory responses after a high-fat meal in healthy overweight subjects.

We will perform a novel clinical trial in which the first phase will be a classical RCT. The participants will either take a control oil or 2g/d of marine omega-3 fatty acids from fish oil for 4 weeks with a 12-week wash-out period before changing to the opposite intervention. Before and after each treatment period, the fasted participants will be served a high-fat mixed meal containing 60 g of butter. Lipids, glucose, insulin and inflammatory markers, and PBMC gene expression, will be measured during the postprandial period, which last for 8 h. After the classical crossover trial, all participants will be supplemented with 2 g/d of marine omega-3 fatty acids for 4 weeks after a 12-week wash-out period. This repeated exposure period offers the opportunity to define omega-3 responders and non-responders to better understand individual variation in post-prandial TG levels.

We aim to recruit 52 healthy overweight male and female participants with fasting TG in the normal range (1-1.7 mmol/L). In order to better understand individual fasting and postprandial TG response age, sex, body composition, genetics, habitual dietary intake, chrono-nutrition, continuous glucose measurements and physical activity will be determined.

In addition, for future analyses, fecal samples will be collected for microbiota analyses and plasma for untargeted metabolomics analyses. This study seeks to generate new knowledge in precision nutrition to understand better why some people respond better to omega-3 fatty acids than others. Details about eligibility criteria, design and measurements will be presented in the poster.

The MetabotypAGE project: exploring the inter-individual variability in response to food in a non-frail living at home older population

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There is a high inter-individual variability in response to food, which is determined by multiple interacting factors, such as age, sex, genotype, intestinal microbiota, eating behaviours, physical activity or socio-demographic factors. Previous studies recently demonstrated the possibility to predict the postprandial glycemic response to food in healthy individuals based on a deep phenotyping exploration. Personalized advices based on these predictions showed a higher benefit than standard dietary recommendations. We hypothesize that inter-individual variability may be amplified at later ages, as a result of different life trajectories and long-life exposures.

The MetabotypAGE project proposes to explore the inter-individual variability in response to food in the elderly using a deep phenotyping approach, and in the context of a participatory research with strong territorial anchoring. MetabotypAGE is structured in three WP: (i) WP1, an interdisciplinary, prospective and participatory task, aiming to establish the best tools and methods to carry out a multi-dimensional phenotyping adapted to the older population living at home; (ii) WP2: an exploratory study on 150 clinically healthy people between 60 and 75 y.o., who will wear a CGM for 2 weeks, during which they will eat 4 standardized test meals. Volunteers will be extensively phenotyped with a battery of functional tests, analyses (biochemical, transcriptomics, metagenomics and metabolomics) and questionnaires to cover many dimensions including their metabolism, physical capacity, cognitive function, oral health, gustative function, vascular health or dietary habits. They will be classified in metabotypes according to their response to test meals; and (iii) WP3: an in-depth exploration of the post-prandial response to a dietary challenge, for selected subjects representing the identified metabotypes and aimed at understanding the mechanisms explaining their differences in response. The consortium of MetabotypAGE combines strong multidisciplinary partners with complementary skills on the nutrition and health of the elderly, as well as several clinical research structures and local actors of social action among seniors. Our ultimate goal is to lay a solid basis for further development of tailor-made strategies and recommendations for seniors. The participatory nature of the project will allow a direct impact on the 150 participants, thanks to personal assessments, recommendations, and targeted educational workshops, with the ambition to be able in the future extend the experience over time for these same volunteers and thus assess the impact of personalized recommendations based on in-depth phenotyping, and on the other hand to apply the same approach to a larger population.

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Genetics of Caffeine and Brain-related Effects - A Systematic Review

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Background: Although the stimulant and anxiogenic properties of caffeine are widely accepted, research on its specific effects on the brain remains controversial. Growing evidence shows that interindividual differences to caffeine response may be partly due to variations in genes such as *CYP1A2* and *ADORA2A* which have been used to identify individuals as 'fast' or 'slow' caffeine metabolisers and as having a 'high' or 'low' caffeine sensitivity, respectively.

Objectives: To identify, evaluate and discuss current evidence on the influence of common genetic variations on caffeine's brain-related effects in humans.

Methods: PubMed and Embase databases were independently searched for relevant reports based on a predetermined search strategy. Included records involved observational and experimental studies on healthy adults who underwent a) genetic analysis for polymorphisms in genes associated with caffeine metabolism and effect and b) measurements of brain-related effects such as mood and anxiety, insomnia and sleep deprivation, as well as indices of cognition such as reaction times, attention and reasoning with the consumption of caffeine (habitual intake or supplementation).

Results: Of the 22 records, 15 were randomised controlled trials, six were cross-sectional studies and one was a genome-wide association study. The main outcomes identified were cognition (n = 9), anxiety (n = 7) and sleep disturbance / insomnia (n = 6). Polymorphisms in *CYP1A2* gene demonstrated effects on cognitive function, while variations in *ADORA2A* gene demonstrated anxiogenic and sleep effects.

Conclusions: The present review has provided evidence that variability in the *CYP1A2* and the *ADORA2A* genes are consistently associated with brain-related effects of caffeine. Nevertheless, it is not yet clear what specific genotypes are implicated in each brain outcome, which functions of cognition are particularly affected (simple vs complex), whether there are gender differences in the anxiogenic effects and how habitual caffeine intake may influence the acute effects of caffeine. Future studies are warranted to investigate the specific polymorphisms implicated in each brain outcome, which cognitive functions are particularly affected (simple vs complex), whether there are gender differences in anxiogenic effects and how habitual caffeine intake may influence the acute effects of caffeine.

Posters

Session 3: Biomarkers and disease — strategies, discoveries and new trends from omics data

Mitochondrial-Nuclear Homeostasis And One-Carbon Metabolism In Obesity

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Abstract

Obesity is a complex disease characterized by the excessive accumulation of dysfunctional adipose tissue that might lead to mitochondrial dysfunctions. Since food provides substrates and cofactors for mitochondrial enzymes, nutrient excess or disequilibrium can deeply alter mitochondrial dynamics. For this reason, mitochondrial DNA copy number (mtDNAcn) and mtDNA methylation might be altered by obesity and unbalanced diet. Moreover, mitochondria provide intermediate metabolites required for epigenetic modifications in the nucleus, which in turn control the expression of mitochondrial proteins. Moreover, the one-carbon cycle (1CC), which is duplicated in the cytoplasm and mitochondria, strictly interconnects nutritional status, epigenetic pathways, and the redox system.
In a cohort of 198 subjects (101 controls and 97 overweight or obese subjects), we investigated the potential association of mtDNAcn and the methylation levels of mitochondrial (D-loop) and nuclear areas (methylenetetrahydrofolate reductase (*MTHFR*) and LINE-1 repeated elements) with body weight, metabolic profile and blood levels of 1CC intermediates (i.e., folate, betaine, choline, vitamin B12, glutathione (GSH), and homocysteine).
From our study it emerged that the overweight/obese group showed reduced levels of GSH compared to controls ($p = 1{,}3 * 10^{-5}$), as well as lower mean LINE-1 methylation levels ($p = 0.004$) and lower mean *MTHFR* methylation levels ($p = 0.047$). Also, mtDNAcn was lower in overweight/obese subjects ($p = 0.004$) and independently correlated with *MTHFR* methylation levels ($p = 0.005$), but not to LINE-1 methylation levels ($p = 0.086$). DNA methylation in the light strand of the mtDNA did not differ between overweight/obese and normal-weight subjects. However, it was nominally correlated with homocysteine levels ($p = 0.035$) and *MTHFR* methylation ($p = 0.033$).
Overall, our findings support the idea that increased body weight might reduce the availability of nutrients acting as intermediates of the one-carbon cycle and perturb the mitochondrial-nuclear homeostasis.

HIGH FAT AND HIGH GLUCOSE MIXED MEAL AFFECT DISTINCT LIPID METABOLISM GENE EXPRESSION PATHWAYS IN ADIPOSE TISSUE FROM ABDOMINAL OBESE SUBJECTS WITH HIGH LIVER FAT AND LOW LIVER FAT

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Abstract

Introduction: Liver is an important organ for lipid metabolism. Excessive liver fat content is often related to some chronic metabolic diseases, such as non-alcoholic fatty liver disease (NAFLD) and type II diabetes. Adipose tissue is an important organ for adequate lipid metabolism and storage. To examine whether lipid metabolism and storage is differently regulated in people with high versus low liver fat, we investigate the differences in post-meal whole genome gene expression response in adipose tissue of people with different liver fat content.
Methods: In this study, which is part of the Belly Fat Study, abdominal obese males and females(BMI>27kg/m^2 or waist circumference>88cm females, >102cm males) received a high fat and high glucose mixed meal(76.3g carbohydrates,17.6g protein,60.0g fat), adipose biopsies were taken before (fasted) and 4 hours after the mixed meal. Intrahepatic lipids values were determined using MRS. Intrahepatic lipid values were known for 66 of the 100 individuals that completed the study. Participants in the first tertile of intrahepatic lipids values (0.14 - 2.05) were classified as low liver fat group (22 participants), and participants in the last tertile of intrahepatic lipids values(7.99 - 32.58) were classified as high liver fat group (22 participants). Results: The postprandial responses of plasma glucose, insulin as well as triglycerides are significant stronger in high liver fat group than in low liver fat group. At baseline, there were 2014 genes significantly differently expressed between the two groups. And 613 genes responded significantly different to the mixed meal between both groups. Preliminary analyzes showed that genes in the network 'non-alcoholic fatty liver disease' were upregulated postprandially in the high liver fat group compared to the low liver fat group. Oxidative phosphorylation was decreased postprandially in the low liver fat group compared to the high liver fat group.
Conclusions: Based on the results of gene expression changes, we conclude that people with different content of liver fat response differently in the adipose tissue to a high fat and glucose mixed meal.

DASH-IN: FACILITATING CROSS-STUDY RESEARCH WITH TRULY FAIR AND OPEN DATA

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Many research fields have established databases for deposition of their data in an effort to promote open and FAIR science. While research policy continues to promote FAIR and open science, there is still a need for structured, yet flexible databases that are able to connect research data of many types while keeping the data both Interoperate and Reusable. GDPR and its local interpretations also creates friction between open science and the need for protection of personal data.

Here we present a new database, DASH-IN, with the aim of being able to store and structure all data that can be represented in a tabular form, including processed 'omics data.

Access control makes it possible to structure the data early while only making the data available to named parties. The study designs and existing datasets can be made public while keeping the data private. The system has also been made to allow for easy local deployment such that data can be kept strictly internal until the data is appropriate for public release.

The study design links all datasets in a study and the use of ontologies makes it possible to annotate the datasets with regards to performed measurements and their associated units. The latter makes it possible to search across studies.

In order to subset data, we have also implemented advanced facilities, making the database appropriate for creating data hubs in ongoing studies, giving access to subsets of data for collaborators.

We believe that this ability to connect data of different types and across studies will increase the value of research data many-folds and will pave the way for important advances by combining data from different studies.

In the context of biomarkers and 'omics in nutrition this database would allow for quicker validation of biomarkers, checking the occurrence of a specific unknown and performing correlation analysis of a biomarker in a selection of other cohorts. Examples will be provided.

PRE-DIAGNOSTIC SALIVA MICROBIOTA OF SCHOOL-AGED CHILDREN WHO DEVELOPED TYPE 1 DIABETES

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Background: Type 1 diabetes mellitus (DM) is a common autoimmune disease in children with a distinct disease course management. Previous studies have reported alterations in saliva microbiota during onset and progression of DM. To investigate whether the altered saliva microbiota composition is a predisposing factor of DM, we compared the saliva microbiota before the onset of DM with healthy controls in a nested case-control setting using data from the Finnish Health in Teens (Fin-HIT) study cohort. By describing the differences in saliva microbiota before diagnosis, we anticipated to identify potential pre-diagnostic biomarkers for DM.

Methods: Using 16S rRNA gene sequencing, we compared the saliva microbiota of children with DM (n= 20) 0-2 years before their diagnosis and their controls. We explored the differences in alpha diversity (Shannon, inverse Simpson, and Chao1 indexes), beta diversity (Bray-Curtis dissimilarity index), and abundance (at the phylum and genus level) in two phases: 0-2 years pre-diagnosis in DM cases vs. (i) a group of controls (n=81) and (ii) vs. age, sex, and residential area matched controls (n=20). We also predicted the altered functional pathways through PICRUSt2.

Results: Alpha diversity indexes for pre-diagnostic DM cases were observed to be higher than in controls. The beta-diversity also differed between DM cases and their disease-specific controls (unadjusted *p*-value=0.04). The abundance of several genera such as *Streptococcus, Fusobacterium, Gemella, Veillonella, Rothia, Abiotrophia* was higher in DM cases compared to the control samples (unadjusted *p*-value < 0.05). Only one microbiome pathway differed between the cases and all controls: a lower proportion of succinate fermentation to butanoate pathway was observed in DM cases compared with controls (corrected *q*-value: 0.034).

Conclusion: Even though our search for a biomarker in pre-diagnostic DM saliva samples proved inconclusive, we demonstrated that saliva microbiota was altered in children 0-2 years before the onset of DM. PICRUSt2 results summarized the functional capacities of microbiome and pointed towards impaired succinate to butanoate fermentation pathway, likely depending on the Firmicutes phylum. Thus, observed functional changes in this pathway may indicate susceptibility to DM in the future, but further studies are needed to verify our findings.

Relationship Between Free and Bioavailable Vitamin D and Sperm Quality

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Vitamin D has many important functions related to bone mineralization and immune response modulation. Recently, it is hypothesized that vitamin D might be involved in semen quality due to the presence of vitamin D receptor (VDR), transient receptor potential vanilloid (TRPV1) cation channels and 1-alpha-hydroxylase enzyme inside spermatozoids. Our goal is to determine whether vitamin D metabolites, including 25-hydroxycholecalciferol (25OHD), free 25OHD, bioavailable 25OHD, and 1,25-dihydroxycholecalciferol (1,25 $(OH)_2$ D) may affect semen quality, such as sperm count, motility, and morphology. Forty healthy patients from Assisted Reproduction Clinic – Varna, aged 25-45, were involved in this study. Two volunteers dropped out due to exclusion criteria. The other 38 participants were classified in two groups: control group with normal seminal parameters, and target group with one or more abnormal seminal parameters. Semen quality was evaluated by spermogram analyses. 25OHD and 1,25 $(OH)_2$ D levels in blood serum were measured by enzyme-linked immunosorbent assay (ELISA). Free 25OHD and bioavailable 25OHD levels were calculated using Vermuelen and Bikle formulae.

A trend of higher mean 25OHD levels for the control group compared with the target group (21.25 ng/mL vs 17.08 ng/Ml; $p>0.05$) was observed. This tendency was maintained for calculated free 25OHD (4.15 pg/mL vs 3.26 pg/mL; $p>0.05$). Interestingly, calculated bioavailable mean 25OHD levels were significantly higher for the control group as compared with the target group (1.89 ng/mL vs 1.39 ng/mL; $p=0.05$). No differences in 1,25 $(OH)_2$ D levels were detected between both groups.

Statistical significant positive correlations between free 25OHD and total sperm motility ($r=0.44$; $p=0.006$) and between free 25OHD and progressive sperm motility ($r=0.44$;$p=0.006$) were detected. Similar positive correlations were observed between bioavailable 25OHD and total sperm motility ($r=0.41$; $p=0.001$), and between bioavailable 25OHD and progressive sperm motility ($r=0.46$; $p=0.004$). A significant relationship between the percentage of normal sperm cells and the levels of free/bioavailable 25OHD were detected, respectively ($r=0.35$; $p=0.003$ and $r=0.37$; $p=0.002$). No associations were observed between 1,25 $(OH)_2$ D levels and semen quality parameters.

These results indicate that 25OHD may have more significant effects on the semen quality, especially on sperm motility, as compared with the active 1,25 $(OH)_2$ D form. These may be contributed to the more sensitive to 25OHD and not to 1,25$(OH)_2$D TRPV1 membrane receptors involved in non-genomic effects related with cation channels and membrane depolarization. Free and bioavailable 25OHD levels in blood may be used as additional biomarkers for the assessment of male fertility.

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Brain N-glycosylation and Lipidomic profile changes induced by a High Fat Diet in dyslipideamic Hamsters

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The consumption of diets rich in saturated fats is known to be associated with higher mortality. The adoption of healthy habits, for instance adhering to a Mediterranean diet, has proved to exert a preventive effect towards cardiovascular diseases and dyslipidaemia. Little is known about how a suboptimal diet can affect brain function, structure and the mechanisms involved. The aims of this study were to examine how a high fat diet can alter the brain N-glycan and lipid profile in male Golden Syrian hamsters and to evaluate the potential of a Mediterranean-like diet including nuts, fish oil and extra virgin olive oil to revert this situation. A total of 67 glycans and 192 lipids were identified in brain samples, from those, 23 *N*-glycans and 53 lipids were found to be statistically significant between experimental groups. Our results suggest that brain N-glycan composition in high fat diet-fed hamsters can produce events comparable to those found in some neurodegenerative diseases and may promote brain ageing process, that were partially restored changing to a Mediterranean-like diet.

Proinflammatory Saliva Microbiome Associated with Central Obesity

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Abstracts

Background
Several differences in saliva microbiota have been described by weight status, but due to dependency on age, sex, and geographical region, these have been conflicting. Focusing on clinically relevant outcomes such as central obesity and using deep sequencing techniques might fill in the gaps of knowledge.

Aims
We aimed to a) compare saliva microbiome between groups of adolescents with (n=14) and without central obesity (n=36) and b) to investigate, if the differences occur due to dietary factors or oral health.

Methods
Data on diet was self-reported with a questionnaire, while oral health variables were collected from register data. Unstimulated saliva samples were collected with Oragene® DNA Self-Collection Kit and subjected to whole-genome shotgun sequencing. Taxonomic profiling was achieved with the METAnnotatorX2 bioinformatics platform. For taxonomic classification, the NCBI database was used. Microbiota-encoded enzymatic potential profiles based on the Metacyc database were analyzed.

Results
Groups showed no differences in oral health, while a tendency for lower consumption of sweet pastry, ice cream, and salty snacks was observed in the group with central obesity. Of the 43 genera, *Pseudomonas* showed lower mean abundance (0.7% vs 1.4%; p=0.041) in the centrally obese group. Species-level analysis revealed that *Pseudonomos guguanensis* had lower abundance among centrally obese (0.69 % vs 1.34%, p=0.046). Group with central obesity showed a complete absence of *Psedomonas unknown* and several *Prevotella* species e.g., *scopos, oulorum*, and *oris*, for each (p<0.05). Oral health or dietary factors did not determine these differences except for *Prevotella oris*, whose presence associated with the consumption of ice cream with OR 2.76 (95% CI 1.13; 6.72), p=0.026. Group with central obesity showed enrichment of microbial pathways involved in amino acids and proteins metabolism releasing lactate and ammonia, which both evoke proinflammatory responses.

Conclusions
A few differences in the abundance of saliva microbiota were observed based on central obesity, but these were hardly determined by current dietary factors or oral health. Interestingly, the enzymatic profiles implied saliva microbiota to have proinflammatory nature in the presence of central obesity, which warrants further investigations.

Machine Learning-Based Retention Time Prediction of Trimethylsilyl Derivatives of Metabolites

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Introduction

In gas chromatography–mass spectrometry-based untargeted metabolomics, metabolites are identified by comparing mass spectra and chromatographic retention time with reference databases or standard materials. In that sense, machine learning has been used to predict the retention time of metabolites lacking reference data. However, the retention time prediction of trimethylsilyl derivatives of metabolites, typically observed in untargeted metabolomics using gas chromatography, has been poorly explored. Here, we provide a rationalized framework for machine learning-based retention time prediction of trimethylsilyl derivatives of metabolites in gas chromatography.

Methods

We compared di
erent machine learning paradigms, in addition to exploring the influence of the computational molecular structure representation to train the prediction models: fingerprint class and fingerprint calculation software.

Results

Fingerprint class and fingerprint calculation software, as well as the molecular structural similarity between the training and test or real case sets, showed to be critical modulators of the prediction performance. Our study challenged predicted retention time when using chemical ionization and electron impact ionization sources in simulated and real cases, demonstrating a good identity ranking capability despite observing a limited false identity filtering power in cases where an spectrum or a monoisotopic mass match to multiple candidates. Specifically, machine learning prediction yielded median absolute and relative retention index (relative retention time) errors of 37.1 retention index units and 2%, respectively. Finally, we propose a novel method to determine the probability that the prediction error is lower than a specific threshold by leveraging the structural similarity between metabolites in the training and test sets.

Conclusion

Our study demonstrates that predicted retention time can provide insights on the true structure of unknown metabolites by ranking from the most to the least plausible molecular identity, and sets the guidelines to assess the confidence in metabolite identification using predicted retention time data.

A semi-automated workflow for functional analysis of transcriptomic and metabolomic data

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Keywords: Semi-automated workflow, functional analysis, transcriptomics, metabolomics, Inflammatory bowel diseases, Crohn's disease, Ulcerative Colitis.

With the exponential growth of omics data generation and storing in different data sources, analyzing these data has become a crucial need for researchers. There are various bioinformatics tools available developed for solving specific problems related to diseases in terms of gaining a deeper understanding of underlying molecular mechanisms and finding a diagnosis or treatment. These workflows contain quality control of raw data, differential expression analysis, enrichment analysis for differentially expressed results, etc. but there is still a need for tools for network analysis and multi-omics visualization.

In this study, a semi-automated workflow for functional analysis of transcriptome and metabolome data was designed. The workflow, developed in R markdown files as well as Jupyter notebook files, includes differential gene expression analysis, statistical analysis of metabolomics data, as well as pathway enrichment analysis for both transcriptomics and metabolomics data followed by integration of this data through network analysis to identify disease-related processes and visualization of multi-omics data. A publicly available gut-transcriptome and stool-metabolome dataset (https://ibdmdb.org/) of the gut microbial ecosystem in inflammatory bowel diseases was used to demonstrate the proposed workflow.

Our study identified the main characteristics of inflammatory bowel diseases by combining and functionally analyzing omics data types in a semi-automated way. In conclusion, this study provides information on the enriched pathways including immune-related pathways which altered both at the gene and metabolite levels, as well as networks in which associated overlapped genes and pathways occur in inflammatory bowel disease patients. These findings could help elucidate the underlying mechanisms behind inflammatory bowel diseases. All workflows were generated using the R environment and automation in Cytoscape and are open-source and accessible on GitHub.

Salivary levels of some pro-inflammatory cytokines in children with plaque-induced gingivitis

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Saliva is rich in biomolecules with local and systemic origin which may serve as promising diagnostic markers, especially for oral-dental diseases. The aim of our study was to identify the diagnostic value of the pro-inflammatory cytokines IL-6, IL-1β and CRP in saliva of children with different degrees of plaque-induced gingivitis. The study included 45 children with no common diseases. Based on the Gingival Index Löe-Silness (GI) the participants were divided into four groups: without gingival inflammation (control group, n=6), with mild (n=12), with moderate (n=18) and with severe (n=8) degree of plaque-induced gingivitis. Clinical indices Plaque Index Silness-Löe (PLI) and GI were determined. ELISA methods for quantification of IL-6, IL-1β, and CRP in unstimulated whole saliva were used. Statistical methods of column statistics, t-test, correlation, and ROC curve analysis were applied.

Mean levels of IL-6, IL-1β, and CRP were higher in children with gingivitis as compared to the control group (ns). The highest mean levels of IL-6, IL-1β, and CRP were recorded in the group with severe gingivitis, respectively: 14.96 pg/ml; 28.94 pg/ml; 490.0 pg/ml, exceeding significantly these in the control group (9.506 pg/ml; 16.93 pg/ml; 254.4 pg/ml) (ns). We did not establish statistical significance between the groups due to the relatively small number of representatives. A positive significant correlation was observed between the investigated salivary cytokines among all the participants with gingivitis: the Spearman's rank correlation coefficients between IL-6 and IL-1β was 0.7758 ($p<0.0001$); between IL-6 and CRP was 0.9231 ($p<0.0001$); between IL-1β and CRP was 0.7753 ($p<0.0001$). Based on the ROC curve analysis we estimated a moderate diagnostic capacity of the investigated cytokines with AUC 0.7083 (95 CI: 0.415-1.00; $p=0.1968$) to distinguish children with a severe degree of gingivitis from those without gingivitis. At the optimal cut-off values based on the largest Youden's index IL-6, IL-1β, and CRP demonstrated sensitivity values ranging from 75% to 87.5 % and specificity values ranging from 66.67 % to 83.33 %. IL-6 and CRP showed the highest sensitivity (87.5 %) and IL-1β showed the highest specificity (83.33 %). The precise diagnosis of the state of gingival inflammation in children is important for disease monitoring and control to prevent progression of gingivitis into periodontitis. All of the investigated salivary cytokines IL-6, IL-1β and CRP showed a good diagnostic capacity to differentiate children with severe degree of plaque-induced gingivitis from healthy subjects and for the evaluation of the disease degree.

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PLASMA ADIPONECTIN AND LEPTIN mRNA LEVELS IN COLORECTAL CANCER PATIENTS

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Abstract

With the discovery of leptin and adiponectin, studies of the link between obesity and colorectal cancer (CRC) have begun to generate data suggesting a link between adipose tissue dysfunction, abnormal regulation of adipokines in obesity, and the initiation and progression of CRC. In addition to the standard matrices, in recent years increasing attention has been paid to liquid biopsies as carriers of information in various diseases. mRNA from tumors is detected in plasma and research is focused on the possibilities to extract useful information from such samples. The aim of this study was to analyze adiponectin and leptin mRNA levels in CRC patients (CRC group) in comparison with individuals with benign neoplasm (Control 1, C1) and with individuals without neoplasm (Control 2, C2). Fifty one patients of the First surgery clinic, St Marina Hospital–Varna were included in this study. mRNA levels of respective gene levels were analyzed using $2^{-\Delta\Delta Ct}$ method. In addition, the relationship between relative mRNA levels and Body mass index (BMI) and gender was analyzed. Adiponectin and leptin mRNA levels were increased both in benign (27%, $p<0.01$ and 59%, $p<0.01$, respectively) and CRC individuals (39%, $p<0.01$ and 33%, $p<0.05$, respectively). CRC patients with moderate obesity (BMI 25-30) had higher adiponectin (by 58%, $p<0.001$) and leptin (by32%, $p<0.05$) mRNA levels. A significant difference depending on gender was established in CRC group only where a lover levels for adiponectin (by 26%, $p<0.05$) and leptin (by 28%, $p<0.05$) was detected for females. In conclusion, plasma mRNA levels of adiponectin and leptin appear to be a promising biomarkers in CRC and it is dependent on BMI and gender. Increasing the number of the samples in the study, which is in progress, is expected to provide more reliable results in this aspect.

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EXPRESSION OF MICRORNA ASSOCIATED WITH INSULIN RESISTANCE IS NOT RELATED TO GLYCAEMIC INDEX AND GLYCAEMIC LOAD

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Abstract

Dietary glycaemic index (GI) and glycaemic load (GL) may modify pathways related to energy balance and insulin metabolism. Low GI/GL dietary patterns are associated with lower insulin secretion, improved glycaemic control, greater satiety, and have been used as strategy to decrease body weight. MicroRNAs, small non-coding RNA, participate in insulin signaling and glucose homeostasis, and many of these microRNAs are dysregulated in diabetes. In a previous analysis, we found increased expression of four microRNAs in plasma in individuals with insulin resistance (HOMA-IR > 2.71, cut-off value for Brazilian adults) (unpublished results), which highlights the role of microRNAs in glucose metabolism. We assessed relationships between GI, GL, and expression of four microRNA in plasma from a sample of 188 adults (aged 20-59 years), from the 2015 ISA-Nutrition survey, a household cross-sectional, population-based survey of residents from the urban area of Sao Paulo, Brazil. Participants did not have major systematic disease including acute inflammatory or thyroid diseases; cancer; use of antibiotics, anti-inflammatory, immunomodulators, antiretrovirals; chronic alcoholism; or were pregnant/lactating women. The expression of miR-let-7c-5p, miR-122-5p, miR-126-3p, and miR-30a-5p in plasma was quantified by RT-qPCR. Spike-in cel-miR-39 and UniSp6 were used as reference controls for normalization. Relative microRNA expression was calculated using the $2^{-\Delta\Delta CT}$ method. GI and GL were calculated using data from two 24-hour food recalls (R24h) on two nonconsecutive days, which were adjusted to remove intrapersonal variance using the Multiple Source Method (MSM). The confidence intervals for Kendall's tau-a were obtained in Stata to estimate correlations between microRNAs and GL and GI values. Differences in microRNAs expression according to GL category (Low <80 | Moderate 80-120 | High > 120) were evaluated by the Adjusted Wald test (Stata, version 17.0, StataCorp).
Women comprised 54% of the participants, 59% were overweight/obese (BMI ≥ 25). Individuals were classified as low (15%), moderate (41%) and high (44%) GL. There were no differences in the GI and GL between individuals with [GI=54.7 (95% CI:54.1-55.3) | GL=119.8 (95% CI:110.1-129.5)] and without insulin resistance [GI=54.8 (95% CI:54.3-55.4) | GL=126.7 (95% CI:116.7-136.7)]. Of the four microRNAs evaluated, only miR-122 showed increased expression in the moderate GL group, compared with the low GL group ($P < 0.05$). There were no significant correlations between microRNAs expression and GI and GL.
In conclusion, there were insufficient evidence that GI and GL influence expression of microRNAs that are associated with insulin resistance in Brazilian adults.

Multi-Omics based machine learning prediction of metabolite levels for knowledge discovery

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ABSTRACT

Discovering molecular interactions in biological pathways is of utmost importance in life sciences. Combining multi-omics data and machine learning paradigms can be used to quantitatively predict changes and reveal associations between different biological layers. Since metabolites constitute the ultimate effector molecules and provide a sensitive measure of the phenotype, their quantification from different omics modalities would help in understanding underlying mechanisms and reveal unknown connections in diseased phenotypes. Building on predicting levels of molecules, machine learning based regression models were used to quantify the metabolome using proteomics and lipidomics data along with their combination as predictors from lymphocyte data. Additionally, feature selection was used to identify proteins responsible for variations in metabolite levels, to enable discovery of relationships between proteins and small molecules. The performance of the models varied depending on the metabolite being predicted which suggests the different levels of regulation that the proteome exerts on the levels of individual metabolites. Addition of lipidomics layer however did not not yield any significant increase in performance despite the known role of lipid species in molecular signaling and their role in mediating different cellular responses. Feature importance applied on the different models yielded some known protein-protein and protein-metabolite interactions upon projection onto pathways and network databases such as KEGG and STITCH which validates the association between the proteins selected via feature selection and the metabolite being predicted. Further investigation of the strong unknown relationships using this approach could in turn lead to discovery of new connections between proteins and the associated small molecule in relation to the phenotype being studied. Application of this methodology to clinical and nutritional studies could eventually lead to better integration of multi - omics data using machine learning and gain information about molecular interactions that can not be easily inferred by a single omics layer.

Digital resilience biomarkers of heart rate variability to evaluate a personalized combined lifestyle intervention

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Abstract

Introduction. Digital biomarkers are biomarkers measured by digital devices such as smartwatches, phones or medical patches. A digital resilience biomarker is a digital biomarker measured as the response to an external challenge to reflect the resilience of the biological system. This allows continuous, non-invasive monitoring of health and disease in the home environment. Over the last decade, digital biomarkers and endpoints have been increasingly developed and applied for, among other applications, the evaluation of therapeutic interventions. Heart rate variability, as a reflection of the autonomous nervous system activity, is expected to decrease upon immune-metabolic challenges. Here we aim to verify metabolically challenged heart rate variability as digital resilience biomarker in response to a lifestyle intervention. **Methods.** In an open label intervention study, participants with obesity were subjected to a combined lifestyle intervention with extended personalization based on environmental, behavioral, mental and biological aspects and additional coaching during the combined lifestyle program. At baseline and after 6 months, the subjects underwent a standardized mixed-meal challenge (PhenFlex challenge, TNO). Over the course of this challenge, single lead electrocardiogram was monitored by a research-grade vital sign patch (Nighthawk 1.0, TNO). The electrocardiogram wa used to calculate heart rate and heart rate variability. Root mean square of successive differences (RMSSD) and the low frequency/high frequency ratio (LF/HF) were calculated as metrics of heart rate variability. Analysis of variance of the parameters against study visit, post-challenge time point, and their interaction during the PhenFlex challenge was used to perform initial statistical exploration. **Results.** Preliminary results shows that RMSSD, but not LF/HF decreased in response to the PhenFlex challenge. Although no differences were found in RMSSD when comparing pre- and post-intervention visits, visual exploration indicates a faster increase in RMSSD to baseline level during the post-intervention visit. In addition, heart rate decreased comparing the post-intervention visit against the pre-intervention visit. **Conclusion.** Pending further verification of these results, lower RMSSD in response to the PhenFlex challenge and lower post-intervention heart rate suggest the feasibility of heart rate and heart rate variability measured with vital sign patch as a digital resilience biomarker to reflect immune-metabolic disturbances and potentially evaluate the effects of a combined lifestyle intervention.

PBMC TRANSCRIPTOMIC BIOMARKERS OF INCREASED METABOLIC RISK IN APPARENTLY HEALTHY SUBJECTS WITH NORMAL-WEIGHT OR WITH OVERWEIGHT-OBESITY

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Peripheral blood mononuclear cells (PBMC) express a significant proportion, around 80%, of the genes encoded by the human genome and act as “sentinels” capable of reflecting gene expression profiles of internal tissues. Therefore, these cells provide a useful source of transcriptome biomarkers for nutrition and obesity research as they reflect diet-related pathologies by changes in their gene expression pattern. Obesity is traditionally linked to a wide range of metabolic complications. However, different obese phenotypes exist and, moreover, obesity-related metabolic risk can be observed even in subjects with normal weight according to BMI classification.

Here, we aimed to identify predictive risk biomarkers of increased metabolic risk regardless of BMI. To do this, we analysed the global PBMC transcriptome in lean subjects according to BMI presenting at least one metabolic syndrome-related complication (i.e. MONW, n=5) and in healthy normoglycemic volunteers with overweight-obesity (OW-OB, n=12) *vs* normal weight (NW, n=12) controls.

We identified 1,072 differentially expressed genes (DEGs) in OW-OB *vs* NW and 992 DEGs in MONW *vs* NW. Hierarchical clustering of the top 100 DEGs clearly distinguished OW-OB and MONW from NW. Remarkably, although the OW-OB and MONW phenotypes differed in anthropometric and biochemical parameters, they shared 257 DEGs that were regulated in the same direction (73.6% down-regulated and 26.4% up-regulated). We studied the top up- and down-regulated common shared genes as potential markers for predicting increased metabolic risk. Notably, transcriptome changes for all the affected genes studied were greater (both up- or down-regulation) for the MONW than for the OW-OB group. Gene expression of the top common shared up-regulated gene *CXCL8*, encoding interleukin 8, a pro-inflammatory cytokine involved in the pathogenesis of obesity-related pathologies, correlated directly with C-reactive protein levels. The down-regulated genes presented an inverse correlation mainly with total cholesterol and LDL-cholesterol.

In conclusion, we provide a set of common genes affected by two metabolic phenotypes (OW-OB and MONW) as potential robust markers for early metabolic risk assessment. The expression of the PBMC *CXCL8* gene expression stands out, so it might be used in clinical practice for preventive and personalized health strategies. All in all, PBMC provide an effective source of early transcriptomic biomarkers for detecting increased risk in apparently healthy people, regardless of their BMI.

MATERNAL DIET DURING GESTATION AND LACTATION AFFECTS BROWN ADIPOSE TISSUE THERMOGENESIS CAPACITY OF THE OFFSPRING IN A SEX-DEPENDENT MANNER

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Gestation and lactation represent a sensible window for the development of brown adipose tissue (BAT). Nutritional and environmental factors during these periods may trigger adaptations that affect long-term health status. Considering the contribution of BAT function to the propensity for fat accumulation and other metabolic alterations, here we aimed to study the effects of implementing a healthy diet during lactation in rat dams exposed to a western diet (from one month prior to gestation to the end of gestation) on BAT metabolism and thermogenesis capacity in the adult offspring, and whether this affects their adaptation to western diet exposure after weaning. The following rat groups were studied: 1) offspring of control dams fed a standard diet (CON); 2) offspring of dams fed a western diet from one month prior to mating and throughout gestation and lactation (WD), and 3) offspring of dams fed as in group 2 but moved to a standard diet for the whole lactation period (REV). After weaning, half of the animals were exposed to a standard diet, and half to a western diet, until 4 months of life. Body composition and weight, and mRNA (RT-PCR) and protein (Western Blot) expression in BAT were analyzed. BAT weight, adiposity and body weight were significantly increased by western diet feeding, with a tendency for a greater fat mass under this dietary challenge in WD-males versus their controls. WD-males, under the western diet, showed increased CPT1 mRNA levels, but levels were normalized in REV-males. Moreover, WD-males, but not REV-males, under a standard diet, showed increased levels of PGC1α mRNA, TH protein (a marker of adrenergic innervation), and CPT1 protein than their controls. WD-females, but not REV-females, displayed lower UCP1 mRNA levels (under standard diet) than controls. They also showed a trend to lower TH protein levels than controls, whereas animals of the REV group showed higher TH levels than those of the WD group, particularly in those exposed to western diet. REV-females also showed higher CPT1 levels than controls, and a positive correlation was found between TH protein levels and both UCP1 and CPT1 protein levels. In conclusion, maternal exposure to an obesogenic diet before and during pregnancy and lactation affects the expression of thermogenesis-related genes in BAT of the adult offspring, with partial normalization by reversion to a standard diet during lactation, in a sex-dependent way.

Associations Of Maternal And Infant Metabolomes With Immune Maturation And Allergy Development At 12 Months In The Swedish NICE-Cohort Title

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Allergy is the most common chronic disease in high-income countries. The aim of this study was to investigate associations between the plasma metabolome of pregnant mothers (third trimester, n = 605; delivery, n = 558) and their newborns (n = 366) measured by untargeted LC-MS and immune maturation (T- and B-cell subpopulations) up to 4 months after delivery and to doctor's diagnosed eczema, food allergy and asthma at 1 year.

Using random forest analysis, we found maternal and cord plasma at delivery to predict the number of memory B-cells. CD27+ memory B-cells correlated negatively with an unidentified phosphatidylserine (r = -0.751) and positively with an unidentified diglyceride (32 carbons, one unsaturation; r = 0.657) in maternal pregnancy plasma. CD24+CD38low memory B-cells correlated negatively with a triglyceride (45 carbon atoms, seven unsaturations) in maternal delivery plasma (r = -0.617) and with phenylacetylglutamine in both maternal and infant delivery plasma (r =-0.635 and -0.579 respectively). Future allergy status could not be distinguished from any of the three measured metabolomes.

We further investigated whether previously reported biomarker candidates of manifest allergic disease could be observed in the metabolic profiles of the present study. Among 182 metabolites that had been associated with manifest allergy in previous studies, five measured in cord plasma associated with future allergy in our study ($p < 0.05$). However, hypoxanthine was the only metabolite where the association was in the same direction (increased) and for the same allergic disease (asthma) as in the literature .

This exploratory study suggests that foetal immune programming occurs during pregnancy as the metabolomic profiles of mothers and infants at delivery related to infants' B-cell maturation. However, the measured metabolomes did not associate strongly to allergy development at 12 m, likely due to a combination of short follow-up (few cases) and potentially weak underlying associations.

Posters

Session 4: Chrononutrition:

giving rhythm to the metabolism

Postprandial Transcriptomic Response of Peripheral Blood Mononuclear Cells to a High Fat Meal: A Systematic Review

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Background: The ability to adequately respond to nutrient stimuli ("metabolic flexibility") is a key feature of metabolic health. Acute meal challenges provide the potential to characterise metabolic stress, and determine participants' state of health. While many studies have explored acute responses to a high-fat (HF) meal challenge, reported results are varied. We aimed to characterize the response to a HF meal challenge in human peripheral blood mononuclear cells (PBMCs) through systematic review and analysis of published postprandial transcriptomic studies.
Method: Four databases were searched (PubMed, Web of Science, Embase and Medline) up to November 2021. Studies that measured the human PBMC transcriptome at fasting and following a HF meal (>30g or >80% fat) were included. Studies that had microarray data publicly available were analysed. All raw data were normalised using the workflow tool ArrayAnalysis. Differential analysis was performed to compare fasting with post-meal gene expression levels using a modified paired *t*-test (*limma* R/Bioconductor package). Genes were differentially expressed if adj-p < 0.05. Genes significantly altered in at least three studies, and with the same direction of change were identified. Gene Ontology analysis was performed on these lists of genes using ClueGo in Cytoscape software. Biological processes were considered significantly regulated with adj-p < 0.01.
Results: Ten studies met the inclusion criteria. The average sample size was n=26 (range: n=5-86). Studies included healthy weight participants (n=5), obese or metabolic syndrome only (n=1), or a mixture of both (n=4). Meal challenges included either predominately saturated fat (SF) (n=5) or unsaturated fat (UF) (n=7). Raw data were available for six studies (including eight study arms). Eight genes were significantly altered across all studies. 52 genes were commonly changed in at least three SF studies, and 54 genes were identified for the UF studies. 'Entrainment of circadian clock' biological process was altered in both SF and UF studies. In SF studies, common biological processes included 'platelet aggregation', 'negative regulation of lipid localization', and 'skeletal muscle differentiation'; whilst the UF list included 'regulation of alpha-beta T cell differentiation', 'PI3K activity', 'response to corticosteroid', and 'neuron recognition'.
Conclusion: Despite variability in the study designs of included studies, biological processes that were commonly impacted were identified. Genes associated with circadian clock processes were similarly altered across all studies, suggesting that this process is highly conserved, and may not be impacted by acute meal challenges. However, SF- and UF-challenge meals differentially impacted gene expression levels and biological processes in PBMCs.

Time-of-day dependent effect of Grape Seed Proanthocyanidin Extract (GSPE) for the treatment of non-alcoholic fatty liver disease in obese rats

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Almost all living organisms have evolved an internal pacemaker, the circadian clock, which synchronizes physiological and behavioral responses to the Earth's 24-hour rotation. Metabolic homeostasis has been linked to the proper circadian rhythmicity of biological processes, as they are driven by core clock genes through multiple signaling pathways in organs. Currently, several human behaviors and activities, such as food excess and sleep deprivation, disrupt the circadian system, leading to metabolic disturbances and the development of the metabolic syndrome (MS), that can manifest in the liver as non-alcoholic fatty liver disease (NAFLD). Polyphenols, which are secondary plant metabolites, such as grape seed proanthocyanidin extract (GSPE), have shown promise as a treatment for MS. Therefore, we wondered whether some of the beneficial effects of GSPE in NAFLD might be mediated by a restorative rhythmic expression of the liver circadian clock and hepatic lipid and glucose metabolic genes, and to assess whether the efficacy of GSPE on liver metabolism is affected by the timing of administration. For this purpose, rats were fed a standard (STD) or cafeteria (CAF) diet for 9 weeks and were treated with vehicle (VH) or 25 mg/kg GSPE during the last 4 weeks at two different times: at the beginning of the light phase (ZT0) or at the beginning of the dark phase (ZT12). Animals were sacrificed one hour after turning on the light (ZT1) and every 6 hours (ZT1, ZT7, ZT13 and ZT19) to assess a diurnal profile. The results showed an altered lipid and carbohydrate metabolism due to CAF-diet intake. GSPE ingestion at ZT12, just before the active phase, restored the oscillations of liver clock genes, liver mass, hepatic lipogenic and hepatic glucogenic genes, and of liver metabolites, demonstrating hepatoprotective properties by reducing triglyceride accumulation and lipid droplet formation in the liver, thus preventing the development of CAF-induced NAFLD. Thus, GSPE may serve as a natural nutritional strategy in the recovery from liver-related metabolic disease by restoring the hepatic circadian machinery and the circadian rhythmicity of liver metabolism.

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Body mass index from late childhood to adolescence and associations with lifestyle behaviours

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Background: Children with overweight or obesity are at an increased risk for diseases in adulthood, such as cardiovascular diseases, type 2 diabetes, and certain types of cancer. Overweight and obesity track from childhood to adulthood highlighting the need for early prevention. Physical activity (PA), sleep, sedentary screen time and dietary habits are modifiable lifestyle behaviours that can influence body weight. We aimed to investigate how these lifestyle behaviors associate with change in body mass index (BMI) from late childhood to adolescence.

Methods: Utilizing the Fin-HIT cohort data (www.finhit.fi), in total 5358 children (girls 53.3%) at 11.2 (SD 0.82) years of age at baseline were included in the analyses. Body weight and height were measured, and furthermore, BMI was calculated as kg/m^2. Leisure-time PA (hours/week), sleep (meeting or not meeting the 9-12h recommendation separately on weekdays and weekends), screen time (hours/day) and dietary habits (Sweet Treat and Plant Consumption) were assessed with a self-administered questionnaire. Linear regression analyses adjusted for age, sex and baseline BMI were conducted.

Results: Children's mean BMI was 17.7 kg/m^2 at baseline and 19.7 kg/m^2 at 3-year follow-up. Sleeping less than recommended on weekends compared to meeting the recommendation was associated with higher increase in BMI over the 3-year follow-up (B=0.21, p=0.028). Likewise, there was a tendency that a higher amount of leisure-time PA was associated with higher increase in BMI (B=0.02, p=0.054). When including all lifestyle behaviours in the same model, sleeping less than recommended on weekends appeared as an independent predictor of change in BMI over the follow-up period (B=0.23, p=0.019). Sleep on weekdays, screen time or dietary habits were not associated with change in BMI.

Conclusion: In conclusion, adequate sleep on weekends supports healthy weight development from late childhood to adolescence. More attention should be paid to promote sleep-related lifestyle behaviours in order to maintain healthy weight. Further studies are needed to clarify the role of leisure-time PA in weight development from childhood to adolescence.

Postprandial expression levels of circadian rhythm related genes in adipose tissue and immune cells from men with and without metabolic syndrome

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Background: Metabolic syndrome (MetS) is a clustering of risk factors that indicate dysregulated metabolism, and increased risk of cardiovascular diseases and type 2 diabetes. Metabolism is regulated across the day, coordinated by circadian rhythms. Nutrient intake contributes to the regulation of peripheral clock mechanisms, but little is known about the impact of nutrient composition on circadian rhythmicity and its association with metabolic disorders. We measured the transcriptome of adipose tissue (AT) and peripheral blood mononuclear cells (PBMCs) in men with MetS and healthy controls after two meals that differed in nutrient composition.
Methods: Twenty men (10 control; 10 MetS) were recruited to participate in a randomised, crossover single meal study. Participants consumed isocaloric soy-based and dairy-based breakfast meals that were matched on % macronutrient contribution but differed in nutrient profile. AT and PBMCs were collected at fasting (0 h), and 4 h following each meal. Global gene expression profiling was performed using Illumina Human WG-6 v3 microarray chips. Differentially expressed genes (+/- 1.2-fold, $p < 0.05$) were used in an overrepresentation using the open-source PathVisio software (v3.3.0) with the WikiPathways pathway collection. Pathways were considered enriched with Z-score > 1.96.
Results: As expected, the AT and PBMCs responded differently to the meal challenges. In AT the MetS participants demonstrated a blunted response in the number of significantly changed genes (control dairy 5295, soy 4998; and MetS dairy 3560, soy 3169). Whereas in PBMCs, differentially expressed genes were similar across groups (control dairy 822, MetS dairy 944, and MetS soy 978), except for the control soy group where 4995 genes were changed after the meal. Pathway analysis showed the 'Circadian Rhythm related Genes' pathway was significantly impacted in AT in both controls and MetS after both meals (Z scores all > 1.96). However, in PBMCs the pathway was only affected in the control groups (Z-score dairy 2.24, soy 2.75), but not the MetS groups (Z-score dairy 0.05, soy 1.64). In PBMCs, several genes from the pathway were changed in opposite directions after the dairy and soy meals including, *DYRK1A*, *EZH2*, and *OPN3*.
Conclusion: Adipose tissue expression levels of circadian rhythm related genes do not appear to be impacted by phenotype or meal composition. However, circadian gene expression in PBMCs may be influenced by the factors associated with MetS. These findings suggest that immune cells may be more sensitive than AT to misalignment associated with metabolic dysregulation, particularly following a meal.

Protocol of Personalized Nutritional Advice To Improve Short-term Fitness and Long-term Health In Shift Workers

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Abstract

Night work is associated with increased risk of cardiovascular diseases and diabetes. A widely supported hypothesis is that eating during the night shift, i.e. out of synchrony with the endogenous biological clock, can lead to metabolic health problems, including tissue specific insulin resistance. Although chrononutrition (i.e. timed nutritional intake) has gained increasing attention, the optimal timing as well as composition of food intake during night shifts has not yet been established.

With this study we aim to assess personalized nutritional advice to improve mental and physical fitness during the night shifts, as well as improving metabolic health as a proxy for long-term health. We aim to diminish blood glucose peaks and troughs, as we hypothesize that stable blood glucose values increase short-term fitness and long-term health.

The design will be a controlled intervention study, in which we aim to recruit 25 male shift workers in both study arms, aged 18 to 60 years, that will undergo a nutritional intervention during 3 months. The intervention will be preceded by a run-in period, during which sleep, physical activity, food intake, and continuous blood glucose values will be measured during a period of night shifts as well as day shifts. At the start of the run-in period, metabolic flexibility will be assessed using the PhenFlex test. This is a mixed meal challenge from which tissue-specific insulin resistance can be determined, which allows for a personalized food intake and physical activity advice. Furthermore, this PhenFlex challenge may serve as proxy to identify how and which tissues are desynchronized. Information from this run-in period will be used for the subsequent personalized intervention period, with advice on food composition as well as food intake timing.
During the intervention, sleep, physical activity, food intake and continuous blood glucose values will be measured. Sleep and physical activity will be measured using actigraphy. Food intake will be monitored with short periods of food logging. Continuous blood glucose will be measured using a continuous glucose monitor three times for a period of 10 days. Short-term fitness during the night shifts will be assessed using psychovigilance tests. After the intervention, the PhenFlex test will be repeated.

Study outcomes will be compared using generalized linear mixed model, comparing within as well as between study groups.

With this study, we aim to increase knowledge on nutritional advice for improving health in shift workers.

Proanthocyanidins modulate central clock, restore circadian rhythmicity, and improve cardiometabolic risk factors in CAF diet-induced obese rats in a time-of-day-dependent manner

Jorge R. Soliz-Rueda [1], Raúl López-Fernández-Sobrino [1], Harriët Schellekens[2, 3], Francisca Isabel Bravo [1], Manuel Suárez [1], Miquel Mulero [1] and Begoña Muguerza [1].

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Circadian rhythms play an important role in the physiological and metabolic adaptation of the organism and their disruption increase the metabolic risk. Proanthocyanidins (PACs) are phenolic compounds which have demonstrated beneficial properties on metabolic disorders, although the bioactivity of these compounds may vary depending on the moment of their administration. Different molecular mechanisms are involved in their healthy properties, including modulation of the circadian system. Therefore, the aim of this study was to evaluate whether the time of PACs administration can modulate their effects in an obesogenic context and if these phenolic compounds can restore the circadian disruption caused by a calorie-dense diet. To do so, sixty-four Fisher rats were fed standard or cafeteria diet (CAF) for 5 weeks. After this, animals were administered a daily dose of 25mg/kg of a grape seed proanthocyanidin-rich extract (GSPE) or vehicle (VH) either at 8 a.m. or 8 p.m., (ZT0 and ZT12, respectively) for 4 weeks. Animals were sacrificed at different times, including ZT1, ZT7, ZT13 and ZT19. Results showed the detrimental effects of CAF diet on circadian rhythmicity of serum biochemical parameters and hormones and hypothalamic clock genes. GSPE administration improve the metabolic health of animals and restored the circadian rhythms of their biochemical parameters, hormones and clock and appetite signaling genes in a time-of-day-dependent manner, showing more effects when administered ZT12. Notably melatonin rhythm, a key marker of the light/dark cycle, was restored by GSPE treatment at ZT12. In conclusion, PACs administration improved metabolic status in CAF-fed rats and restored circadian rhythm of central clock. Although further investigations are needed to elucidate the specific effect of PACs in these conditions, these results suggest that these phenolic compounds may modulate the circadian rhythm of the central clock contributing to the improvement of the metabolic profile, especially, when PACs are administered at night.

Posters

Others

On-line Breath Analysis following a Nutritional Intervention Challenge

Stamatios Giannoukos[1], Cedric Wüthrich[1], Miguel de Figueiredo[1], Kathryn Jane Burton-Pimentel[2], Guy Vergères[2] and Renato Zenobi[1]

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Abstract

On-line breath analysis based on secondary electrospray ionization-high-resolution mass spectrometry (SESI-HRMS) has served as a sensitive method for metabolomics and biomarker discovery. The advantageous characteristics of this technique make it an ideal chemical analysis tool for clinical investigations as well as different health-related fields, including nutritional science.
In our study, eleven subjects underwent a nutritional intervention on three separate days. The nutritional intervention consisted of a shake with 950 kcal contributed to by sunflower oil (57% of the caloric content), dextrose (35%), and whey proteins (8%). Breath was measured before the intervention and up to six hours postprandially at thirty-minute intervals. To analyze breath, a *SuperSESI* ion source (*Fossil Ion Technology*, Spain) was coupled to an Orbitrap *Q-Exactive* mass spectrometer (*Thermo Fischer Scientific*, Germany). After spectra preprocessing, ANOVA-simultaneous component analysis (ASCA) estimated the variation stemming from the individual experimental parameters (subject, day, time).
ASCA analysis of the obtained data revealed the major contribution towards variation stemming from the individual subjects. Experiments to distinguish the effect of the intervention from fasting conditions were also conducted using partial least squares discriminant analysis (PLS-DA). Candidate compound annotation of intervention-related features was performed with pathway analysis and on-line collision-induced dissociation (CID) experiments. Pathway analysis using the mummichog algorithm indicated pathways mostly connected to the macronutrients, such as linoleate, butanoate as well as amino acid metabolism. Tentative compound annotation was performed with on-line CID experiments. The compounds mainly fell into three categories: fatty acids, amino acids, and hydrocarbons. The median kinetic traces were k-means clustered to compare the previously reported postprandial kinetics identified in blood plasma after intake of the shake with the postprandial kinetics obtained in the exhaled breath. Out of the five reported cluster trends, four were detected within the breath data, indicating that on-line SESI-HRMS can follow the postprandial response to a nutritional challenge and eventually deliver new nutritional markers.

EFFECTS OF CYANOBLOOMS OF WATER RESERVOIRS IN BULGARIA ON SKIN CELL VIABILITY

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Abstract

Many shallow waterbodies worldwide are suffering from agricultural and residential pollution and polluted reservoirs often experience blooms of toxic phytoplankton species. Some of them are hazardous to ecosystems and human health as people are exposed while swimming, boating, consuming contaminated water, waterborne food or even dietary supplements. Therefore, our study aimed to test the cytotoxicity of natural waters collected from 13 reservoirs and lakes in the territory of Bulgaria. Reservoir Mandra, Lake Vaya and Lake Uzungeren were with proven by previous investigations blooms of toxin-producing cyanoprokaryotes. The other 10 reservoirs were investigated by the current study. In total 16 surface water samples were collected in August 2021 and evaluated *in vitro* by using the Hs27 human skin cells line. MTT test was performed to measure the cell viability upon exposure to increasing concentrations from 1% to 16% of water samples in culture medium. The phytoplankton species composition was proved by light microscopic observations. Different potentially toxic genera were identified including *Microcystis, Aphanizomenon, Anabaenopsis and Sphaerospermopsis* although present in small quantities and not dominating. At low concentrations (1% and 2%), eight of sixteen water samples showed significant proliferative effect demonstrated as increased cell viability. At concentrations from 120% to 180% the most significant increase was detected in the Uzungeren sample – 280% cell viability elevation. Other samples at the same consentrations exhibited inhibitory effect on cell viability.

Cytotoxicity may be related to the established presence of potentially toxic species of the genera *Peridinium* and *Dolichospermum*, in Dubnica and Ablanitsa waterbodies, respectively. The interpretation of the results allows to suppose the stimulatory effect of certain cyanoprokaryote blooms on skin cell culture, depending on the species of present in the water samples. As is known today, carcinogenesis occurs in stages and the stimulation of cell proliferation may be the result of the action of tumor promoters, subsequent to the mutagenic effects of carcinogens. This proliferative effect of the cocktail of biologically active substances released into the environment during the blooms of the water bodies could be related to various cyanotoxins present in the environment. Although the effect may not be transmitted directly to the human body, it has been remarkably consistent in repeating experiments. It would be interesting to analyze the effect of these samples on other types of selected human cell lines that may get into contact with the phytoplankton species during blooms.

Acknowledgements: This study was funded by the Bulgarian National Science Fund projects NSF-KP-06-OPR03/18 and NSF-DN-13/9.

IMMUNE MODULATION BY *SAMBUCUS EBULUS* FRUIT TEA AS REVEALED BY CHANGES IN INFLAMMATION AND PHAGOCYTOSIS RELATED GENES EXPRESSION IN PBMC

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Abstract

Sambucus ebulus is a traditional herbal remedy and its fruits are used for immune stimulation in the autumn period and for amelioration of gastrointestinal ailments. However, there are no scientific data in support of *S. ebulus* fruits application as a healing remedy. The aim of this study was to check the effect of *S. ebulus* fruit tea intake on expression levels of selected genes in isolated peripheral blood mononuclear cells (PBMC) in humans. A group of 53 healthy individuals enrolled in the intervention study with 200 mL *S. ebulus* tea consumption every day for a period of 4 weeks. Blood samples were collected before and after the intervention for analyses. A model of *ex vivo* stimulation of PBMC with bacterial lipopolysaccharide (LPS) was applied. PBMC fraction was separated from freshly collected blood using gradient centrifugation in Ficoll tubes. Cells were seeded in 6 well flasks and immediately stimulated with 200 ng/mL LPS for 4 hours.In each experiment, there were two groups: Control – non-stimulated cells (C1 and C2, before and after the intervention, respectively) and LPS treated (L1 and L2, before and after the intervention, respectively). Expression levels of inflammation (IL-1β, IL-6 and TNF-α) and phagocytosis (MPO, NOX and SOD-3) related genes were analyzed with $2^{-\Delta\Delta Ct}$ method. LPS treatment before the intervention caused significant increase in MPO and SOD-3 mRNA levels (by 30%, $p<0.01$ and by 29%, $p< 0.05$, respectively). The same genes did not change in their expression upon LPS treatment after the intervention period, revealing a possible immune modulation effect of *S. ebulus* fruit tea intake. A decreased expression of IL-1β, IL-6 and NOX genes was established in C2 PBMC as compared to C1 PBMC (by 34%, $p<0.05$, 38%, $p<0.01$ and 37%, $p<0.001$, respectively). LPS stimulated cells after the intervention (L2) also were with lower mRNA levels as compared to those before the intervention (L1) for IL-1β (by 45%, $p<0.001$), IL-6 (by 39%, $p<0.001$), MPO (by 24%, $p<0.05$) and SOD-3 (by 27%, $p< 0.01$). In conclusion, this is the first evidence about the immune modulation activity of *S. ebulus* fruits as revealed by decreased expression of respective inflammation and phagocytosis related genes after 4 week intervention both in control and LPS stimulated cells. Moreover, the change in the response detected for phagocytic enzymes (SOD-3 and MPO) further confirms the immunomodulatory effect of *S.ebulus* fruit tea.

Acknowledgements: This study was supported by “National Science Fund”, Bulgaria, Grant No KP-06-OPR-03/13/18.12.2018

Dietary fatty acids increase intestinal L cell numbers independent of the development of obesity

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Enteroendocrine cells (EECs), produce various hormones to coordinate optimal absorptive conditions following food intake, ensuring efficient postprandial assimilation of nutrients. EEC are equipped with sensors for the detection of luminal nutrients including free fatty acids, short-chain and long-chain fatty acids. Dietary habits, obesity and microbiome composition are associated with alterations in EEC function and numbers. In particular, glucagon-like peptide 1 (GLP-1)-producing L-cells seem to be affected. Ileal and colonic GLP-1 is suggested to confer location-specific functions, stimulating insulin release and reducing gastrointestinal motility, respectively.
To scrutinize the effect of dietary fat and obesity on L-cell density in the intestinal epithelium, we quantified GLP-1$^+$ cells in the ileum and colon of mice. BL/6J mice were fed high-fat diets (HFD) based on different fat sources (palm oil (P), lard (L)). Effects of the P-HFD were characterized over time (1, 4, 12 weeks) and for 48 and 60 kJ% of fat. Additionally, using mouse strains with different susceptibilities to diet-induced obesity (DIO), AKR/J (high), BL/6J mice (intermediate), and SWR/J (low/none), we investigated P-HFD 48-mediated effects independent of obesity. In accordance with previous reports indicating enhanced L-cell differentiation induced by dietary lipids, P-HFD increased GLP-1$^+$ cell numbers in the ileum and colon of BL/6J mice. In the colon, the effect was already significant after one week (1.98 fold increase (x) of GLP-1$^+$ cells/open crypt over control diet), was enhanced after 4 weeks (2.54x) but stayed stable afterwards (2.43x), without additional impact of fat content. In contrast, 4 weeks on L-HFD caused only a borderline significant increase in ileal GLP-1$^+$ cells (1.27x), but no significant changes in the colon. Corroborating the hypothesis, that dietary fat directly impacts EEC differentiation and not obesity per se, the increase in colonic GLP-1$^+$ cells was similar in all mouse strains, independent of weight gain. In line with a role of colonic GLP-1 in controlling intestinal transit time, numbers of GLP-1$^+$ cells did not correlate with basal blood glucose levels or AUC in SWR/J mice. The main difference in composition between P-HFD and L-HFD is the content of palmitic acid and cholesterol (exclusively present in L-HFD). GLP-1$^+$ cell numbers remained unaltered in L-HFD fed mice, thus palmitic acid or its metabolites might directly foster EEC differentiation. This study highlights potential of precise nutritional interventions in the context of metabolic diseases and underlines the necessity for careful interpretation of data from DIO models due to distinct effects of the fat source.

Intestinal Morphometric Changes Induced by a Western-Style Diet in Wistar Rats and GSPE counter-regulatory effect

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Abstract

The Western diet, known also as Cafeteria diet, is an obesogenic diet for rodents and humans due to its content of saturated fats and refined sugars. This diet has already been reported to cause intestinal alterations in rats, such as increased intestinal permeability and inflammation when consumed over a prolonged period. Grape seed proanthocyanidin extract (GSPE) are natural bioactive compounds which have showed a protective effect against some alterations produced by the diet. The aim of the current work was to analyse the adaptive morphologic and functional changes at intestinal level derived from the components of a cafeteria diet in rats, and to evaluate the effect of different GSPE treatment on diet-induced intestinal dysfunction. Rats were fed a 17-week standard (STD) or a cafeteria diet (CAF) with or without oral-GSPE supplementation: 10-days preventive treatment at 500 mg GSPE/kg body weight (PRE-CAF), simultaneous intermittent GSPE administration (SIT-CAF) or final 10-day GSPE administration at 100 (CORR-100) and 500 mg/kg body weight (CORR-500). As an adaptive response to diet, the rats of CAF group were increased intestinal height of the duodenal epithelium and absorptive surface area. Animals treated with GSPE did not change the absorptive surface area at the current doses and times with respect to cafeteria diet ones and had significantly higher villus heights and M surface than STD, similarly to Cafeteria diet group. The SIT treatment appeared to normalise morphology to levels comparable to those of STD group. Grade of acute and chronic inflammation was increased in the cafeteria fed animals. The Goblet cell content was also modified by the cafeteria intervention and only slightly reversed in SIT-CAF treated rats. In conclusion, CAF diet produced adaptive modifications of the intestine by a mainly increasing the absorptive area *in vivo.* GSPE treatment alleviates intestinal permeability and inflammation *in vivo*, without reversing the morphological intestinal changes induced by fructose/sucrose-rich diet.

Scientific committee 2022

(by chairing order)

Dr. Manuel Suarez *(Universitat Rovira i Virgili, SP)*

Expert in metabolomics, biological rhythms and bioactive compounds, he has developed his scientific career mainly focused in the evaluation of the beneficial effects of phenolic compounds, both in animal models and in humans. He is member of the Nutrigenomics research group, in the URV, which aims to generate general knowledge oriented to the design of functional foods able to prevent, delay or alleviate metabolic diseases such as metabolic syndrome. He has participated in several projects, being the lead researcher of some of them. He is author of more than 60 publications in high SCI journals (h-index 23), 8 book chapters, as well as multiple participations in congresses. He also actively workes in research transfer, being author of 2 patents.

Prof. Rosita Gabbianelli *(University of Camerino, IT*)

Rosita Gabbianelli, is Full Professor of Biochemistry at University of Camerino, Italy. She obtained her PhD in Biology at the University of Camerino in 1997. Her research field includes studies on the interplay between early life exposome and long-term effect on health, and nutrigenomic strategies to counterbalance molecular damage. She is visiting professor in Biochemistry at Jilin Agriculture University-Changchun; visiting Professor in Nutrigenomics at the University of Porto, ISS-ISEP-Porto, University of Cluj-Napoca, University of Pharmacy-Hanoi, and Quy Nhon University. Co-author of over 130 peer-reviewed publications, 4 chapters of books and 138 communications at international meetings. She has supervised more of 90 bachelor/master degree/PhD students. She is Editorial Board Member of several journals on health. She is Italian MC Member of the DEVoTION, PhysAgeNet and HyperChildNET (MC sub), Board of Directors of ISNN, Member of NUGO, SIB and Chair of the Scientific and Organizing Committee of the European Summer School on Nutrigenomics.

Prof. Lorraine Brennan (*University College Dublin, IR*)

Professor Brennan is a full professor and a PI in the UCD Institute of Food & Health and Conway institute. She leads a nutritional metabolomics group that are at the forefront of the application of metabolomics in nutrition research and the development of Personalized nutrition. Her group develop strategies for using metabolomics profiles to aid assessment of food intake and for delivering personalised nutrition. She served as Director of the European Nutrigenomics Organization for 5 years and led a number of important initiatives such as the development of an Early Career Network and expansion of membership of the organization. Recently, she was appointed to the National Academies of Science Engineering and Medicine Standing Committee on Evidence Synthesis and Communications in Diet and Chronic Disease Relationships.

Dr. Lydia Afman (*Wageningen University and Research, NL*)

Lydia Afman is Associate Professor at the Division of Human Nutrition and Health at Wageningen University. She is internationally recognized for her expertise on human nutrigenomics and precision nutrition. She combines omics techniques with human dietary interventions to investigate diet-related underlying mechanism for development of cardiometabolic diseases. She leads a Flagship project of Wageningen University, in which artificial intelligence and computational modeling are used to build a digital twin that will give personalized dietary advice to reduce the personal postprandial triglyceride and glucose response. Dr Afman is executive secretary of NuGO, she is member of the Dutch Health Council and until 2022 she was board member of the Dutch Academy of Nutritional Science. She authored over 65 papers published in leading journals in the field such as Am J Clin Nutr, Prog Lipid Res and Journal of Hepatology.

Prof. Jaap Keijer *(Wageningen University & Research, NL)*

I am full professor in Human and Animal Physiology. I am a molecular/ biochemical physiologist with a strong interest in in vivo metabolic pathways; how these are altered with age and in chronic metabolic diseases and how they are affected by food components. Focusing on mitochondria, substrate metabolism and redox metabolism in humans, model animals and cells, I try to decipher the molecular and biochemical processes underlying physiological functioning, health and disease.

Prof. Catalina Picó (*University of the Balearic Islands, SP*)

Full professor of Biochemistry and Molecular Biology at the University of the Balearic Islands, and member of the Centro de investigación Biomédica en red de Fisiopatología de la obesidad y nutrición (CIBEROBN) and of the Health Research Institute of the Balearic Islands (IdISBa). She is currently the Principal investigator of the Nutrigenomics, Biomarkers and Risk Evaluation (NuBE) group, and Vice-Dean of the Faculty of Medicine. She has been member of the Scientific Committee of the Spanish Agency for Consumer Affairs, Food Safety and Nutrition (AECOSAN), and Coordinator of the Scientific Section of Biochemistry of Nutrition of the Spanish Society of Biochemistry and Biology Molecular. Co-author of over 155 scientific publications in indexed journals and several patents. She has participated in 49 national or European research projects, and is currently the Coordinator of the European project INTEGRActiv (JPI HDHL, 2022-25).

Dr. Begoña Muguerza (Universitat Rovira i Virgili, SP)

Dr. Muguerza is doctor in Biological Sciences and currently she is Associate Professor at the University Rovira I Virgili. She leads the Nutrigenomics Research Group, which focuses in the study of the molecular mechanism by which food components exert health effects on metabolic pathologies. One of her main research lines studies the interaction of biological rhythms with the effectiveness of bioactive compounds. She has participated continuously in competitive projects, being PI of many of them. She is co-author of more than 100 scientific papers and 13 patents and has supervised 8 doctoral theses (7 with International Mention and 5 with extraordinary doctoral prizes). She has also carried out management activities, being Head of the Biochemistry and Biotechnology Department and Coordinator of the Official Master Interuniversity Nutrition and Metabolism. Currently, she is the Coordinator of the Doctoral Programme in Nutrigenomics and Personalized Nutrition and Director of the Uriach Chair of Nutraceutics.

Prof. Michael Müller

Professor Michael Müller is a Professor of Nutrigenomics and Systems Nutrition. He is a renowned expert in the area of molecular nutrition related to lipid homeostasis, nutrigenomics and nutritional systems biology and his work is focussed on the molecular mechanisms underlying genome-wide effects of foods (specific bioactive components or nutrients) on immuno-metabolic health and plasticity of the gut-liver axis.

Professor Muller is a member of the editorial board of the American Journal of Clinical Nutrition. He was a member of the editorial boards of numerous journals, i.e. “BMC Genomics” (associate editor), "European Journal of Nutrition" (section editor "Nutrigenomics") and “PLOS One” (academic editor). He is an visiting professor at Nanjing Agricultural University (China) and (co)author of more than 250 peer-reviewed publications with more than 16000 citations. As promoter, he has supervised 26 PhD students. He has an H-factor of 75. Since September 2019 he is the scientific director (CEO) of NuGO, an association of Universities and Research Institutes with a focus on joint development of research in molecular nutrition, personalised nutrition, nutrigenomics, and nutritional systems biology.

Biosketch of invited speakers

(by presenting order)

Henrik Oster (*Institute of Neurobiology, University of Lübeck, DE*)

Prof. Oster studied biochemistry at the Leibniz University of Hanover from 1993 to 99 and received his doctorate for studies of molecular circadian clocks from the University of Fribourg in 2002. After postdoctoral research at the Max Planck Institute for Experimental Endocrinology Hannover, the University of Oxford and the Max Planck Institute for Biophysical Chemistry in Göttingen, he joined the University of Lübeck as Lichtenberg Professor of Chronophysiology in 2011. Since 2017, he heads the Institute of Neurobiology and in 2018, he was appointed as the first Lichtenberg Endowed Chair of Neurobiology. His research is focused in the interaction between clocks in different tissues and how their time signals influence physiological functions such as sleep and energy metabolism, but also immune functions and cognition.

Yves Desjardins (*Institute of Nutrition and Functional Food, Laval University, Québec, CA*)

Yves Desjardins is full professor at the Plant Science department and he is affiliated with the Institute of Nutrition and Functional Foods at Laval University, Québec Canada. He was recently appointed Dianafood-NSERC Industrial Chair on prebiotic effects of fruits and vegetables (PhenoBio+). Trained in plant physiology, he is conducting research on phytochemistry and functionality of bioactive compounds from plants. He is PI or collaborator on many major preclinical and clinical studies on type-2 diabetes, cognitive decline, low-grade inflammation, urinary tract infection, skin diseases, and oral infections. He is particularly interested in the effects of tannins on the gut microbiota and its interaction with the host mucosal immune and gut barrier function. Over the years, he has accompanied many horticultural and food processing companies in the development and the validation of the health benefits of horticultural commodities (e.g. Urophenol, Glucophenol, Neurophenol). At the international scene, he is recognized for his innovative research program on health effects of fruits and vegetables. He was the Chair first International Symposium on Health Effects of Fruits and Vegetables in Québec City (FAVHEALTH 2005) and the OECD Symposium - "Emerging Topics in Health Effects Fruit and Vegetables" in Lisbon, Portugal (2010). He organized in 2016 the International Strawberry Symposium (750 participants), which made a large place to health effects of this fruit. Recently (October 2017), he also organized the leading International Congress on Polyphenols and Health (www.ICPH2017-Québec.org) (>350 world renowned participants). His leadership in the field is recognized worldwide; he has been invited on numerous occasions to give keynote lectures at international meetings over the last few years (>20). He is the International relation director at INAF. In this function, he is involved in many international research projects in France, Mexico, Italy, Brazil and Belgium.

Prof. Timothy Dinan (*University College Cork, IR*)

Ted Dinan is Emeritus Professor of Psychiatry and a Principal Investigator in the APC Microbiome Institute at University College Cork. He was previously Chair of Clinical Neurosciences and Professor of Psychological Medicine at St. Bartholomew's Hospital, London. Prior to that, he was a Senior Lecturer in Psychiatry at Trinity College Dublin. He has worked in research laboratories on both sides of the Atlantic and has a PhD in Pharmacology from the University of London. He is a Fellow of the Royal Colleges of Physicians and Psychiatrists and a Fellow of the American College of Physicians. His main research interest is in the role of the gut microbiota in stress-related disorders. He has also worked extensively on the regulation of the hypothalamic-pituitary-adrenal axis. In 1995 was awarded the Melvin Ramsey Prize for research into the biology of stress. In 2019 he was ranked by Expertscape as the number 1 global expert on the microbiota. His current research is funded by Science Foundation Ireland, the Health Research Board and European Union FP7. He has published over 500 papers and numerous books on pharmacology and neurobiology. He is on the Editorial Boards of several journals.

Dr. Christine Feillet-Coudray *(Muscular Dynamics and Metabolism Unit, Montpellier (INRAE), FR)*

Christine FEILLET-COUDRAY is research director in the Muscular Dynamics and Metabolism (DMEM) unit at the National Institute for Agronomic, Food and Environmental Research (INRAE), Montpellier, France. She has published over 100 articles/reviews. Her research interests focus on micronutrients, lipids and the pathophysiology of oxidative stress, and more generally, malnutrition and its relationship to the development of metabolic syndrome components. More specifically, her work aims to understand the role and impact of bioactive compounds in the diet in maintaining skeletal muscle mass and strength.

Dr. Lydia Afman *(Human Nutrition and Health, Wageningen University and Research, NL)*

Lydia Afman is Associate Professor at the Division of Human Nutrition and Health at Wageningen University. She is internationally recognized for her expertise on human nutrigenomics and precision nutrition. She combines omics techniques with human dietary interventions to investigate diet-related underlying mechanism for development of cardiometabolic diseases. She leads a Flagship project of Wageningen University, in which artificial intelligence and computational modeling are used to build a digital twin that will give personalized dietary advice to reduce the personal postprandial triglyceride and glucose response. Dr Afman is executive secretary of NuGO, she is member of the Dutch Health Council and until 2022 she was board member of the Dutch Academy of Nutritional Science. She authored over 65 papers published in leading journals in the field such as Am J Clin Nutr, Prog Lipid Res and Journal of Hepatology.

Prof. Bruce Y. Lee *(Health Policy and Management at the City University of New York, USA)*

Prof. Lee received his B.A. from Harvard University, M.D. from Harvard Medical School, and M.B.A. from the Stanford Graduate School of Business. He completed his internal medicine residency training at the University of California, San Diego. He has over two decades of experience in industry and academia developing mathematical and computational modeling, AI, and other computer-aided approaches to assist a wide range of decision makers in health, medicine, and public health. Currently, he is a Professor of Health Policy and Management at the City University of New York (CUNY) School of Public Health where he is the Executive Director of the Center for Advanced Technology and Communication in Health (CATCH) at CUNY, which aims to develop and implement new technologies and approaches to help decision making and communication in health and public health, and Executive Director of the Artificial Intelligence, Modeling, and Informatics for Nutrition Guidance and Systems (AIMINGS) Center. Dr. Lee has been the Principal Investigator for over $59 million in grants/contracts from a variety of organizations and agencies including the National Institutes of Health (NIH), the Agency for Healthcare Quality and Research (AHRQ), the National Science Foundation (NSF), the Centers for Disease Control and Prevention (CDC), UNICEF, the Global Fund, the Bill & Melinda Gates Foundation, and the U.S. Agency for International Development (USAID). He has served as a systems science, AI, and computer modeling expert for a range of different entities including the World Health Organization (WHO), the NIH, and other organizations. Dr. Lee has authored over 255 scientific publications and has also authored three books. Moreover, he is a Senior Contributor for Forbes, covering a wide range of health-related topics including medicine, wellness, digital health, and the business of health and having written over 1,600 articles with many of them selected as Editors Choices.

Dr. Josep M del Bas (*Nutrition and health unit director en Eurecat - Centro Tecnológico de Catalunya, SP*)

Dr Josep del Bas holds a BSc in Chemistry and in Biochemistry and is PhD in nutrition and metabolism by University Rovira I Virgili. During his career, he has worked in the field of dietary polyphenols and health, applying molecular biology and systems biology to understand the mechanisms of action. In the last years, his research activities have been focused on biomarkers of health and their application to personalized nutrition in multidisciplinary environments, integrating -omics technologies, nutritional sciences, digital technologies, and psychology-based programs. In this regard, he is the principal investigator of the European project PREVENTOMICS: Empowering consumers to prevent diet-related diseases through -omics sciences. He has leaded more than 100 R+D+i projects either private or public, including nutritional intervention trials and has participated in more than 10 European projects funded by the European commission. He is co-author of more than 70 peer-reviewed publications and director of two Doctoral thesis in the fields of chrononutrition and biomarkers of health. He is advisor of the Catalan Government's agency for business competitiveness and associate professor in the University Rovira I Virgili.

Dr. Jean-Charles Martin (*Centre for CardioVascular and Nutrition, INRAE, FR*)

Jean-Charles Martin currently works at the Centre for Cardiovascular and Nutrition (C2VN), French National Institute for Agricultural Research. Jean-Charles does research in Biostatistics, Physiology and Systems Biology. He is using the metabolomic approach to understand the environmental influence, including nutrition, on health, disease and well-being.

Prof. Paula Oliver (*Laboratory of Molecular Biology, Nutrition and Biotechnology, University of the Balearic Islands, SP*)

Dr. Paula Oliver is a full professor of Biochemistry and Molecular Biology at the University of the Balearic Islands (UIB), Spain. Co-PI of the research group 'Nutrigenomics, Biomarkers and risk Assessment' of the CIBER of Physiopathology of Obesity and Nutrition (CIBEROBN). Member of the Health Research Institute of the Balearic Islands (IdISBa). Her current research focuses on searching for early molecular biomarkers of metabolic risk associated with increased adiposity/obesity using blood cells (PBMC fraction), to establish personalized preventative strategies. She has (co-) authored >60 peer-review articles and book chapters, and 2 books on nutrition. Guest editor of the journals *Frontiers in Physiology* and *Nutrients*. Author of 4 patents (2 internationally extended) and of a genomic license transfer agreement to Agilent Technologies, Inc. She has participated in >40 research projects. Currently, she is part of the 'coordination office' of the EU project INTEGRactiv ('Identification and validation of integrative biomarkers of physical activity level and health in children and adolescents') in which she is also co-leader of the work package 'Epidemiological platform'.

Dr. Xavier Domingo-Almenara (*Omics Sciences Unit, EURECAT — Technology Centre of Catalonia, SP*)

Dr. Domingo-Almenara received his Ph.D in Bioengineering in 2016 from the University Rovira i Virgili. Between 2017 and 2019, he was a postdoctoral researcher at the Scripps Research's Center for Metabolomics in La Jolla, US. In 2019 he moved to the Omics Sciences Unit at EURECAT in Reus, Spain, as a senior scientist, where he established his independent research program. Since starting his lab, he has received funding from the Spanish Research Agency, "La Caixa" Foundation and from the H2020 program, as PI. His research, at the intersection between engineering, chemistry and biology, combines bioinformatics and analytical chemistry to design new computational methods to understand metabolism using mass spectrometry-based metabolomics.

Anna Arola Arnal (*Universitat Rovira i Virgili, SP*)

Anna Arola is associate professor at the Rovira i Virgili University, Tarragona, Spain, and a member of the Nutrigenomics Research Group. Her research focuses on the study of the bioavailability and beneficial effects of phenolic compounds in metabolic pathologies such as obesity. She has more than 80 publications in international indexed journals and is the co-inventor of 3 patents. She is coordinator of the Interuniversity Master's Degree in Nutrition and Metabolism (URV / UB), she has also been coordinator of the doctoral programs in Nutrition and Metabolism and Nutrigenomics and Personalized Nutrition at the URV.

Dr. Olga Ramich (*German Institute of Human Nutrition Potsdam-Rehbrücke (Dife), DE*)

Olga Ramich completed her master degree in Biology in 2004 at the Institute of Cell Biophysics of the Pushchino State University in Russia, a top-ranking academic center in biological sciences. As a research associate, she joined to the Institute of Molecular Genetics of Russian Academy of Sciences in Moscow, working on genetic risk factors for cardiovascular diseases and diabetes, and proceeded to investigate this topic during her guest scientist visit to Germany in 2005. Awarded with a German Academic Exchange Service (DAAD) scholarship for the PhD program, she moved in 2006 to Germany to join a group of Professor Andreas F.H. Pfeiffer. Under his supervision, she completed her PhD in Medical Science at the Charité-Universitätsmedizin Berlin with a grade summa cum laude. Olga Ramich completed her postdoctoral studies in the Department of Clinical Nutrition, German Institute of Human Nutrition Potsdam-Rehbrücke (DIfE), working on the molecular and pathophysiological mechanisms of metabolic regulation by nutrition. In 2018, she completed a habilitation in Experimental Nutritional Science at the Charité-Universitätsmedizin Berlin and was appointed as a Leader of the Research Group “Molecular Nutritional Medicine” at DIfE. Her current research work focuses on the implication of circadian clock in the nutritional regulation of the human metabolism and in the pathogenesis of metabolic diseases. Her research work has been awarded with prestigious scientific prizes such as Morgagni Prize of the European Association for the Study of Diabetes (EASD) in 2019 and Adam-Heller-Prize of the German Diabetic Society/Abbott in 2020. As a recognized expert, Olga Ramich contribute as a reviewer and editor in a wide range of nutritional and medical journals and funding research organizations and is invited a speaker to scientific and medical conferences in her research field.