Role of the gut microbiota in over- and undernutrition

Laure Bindels, PhD
Copenhagen
September 7, 2016
Diet
Nondigestible carbohydrates
Fat

Changes in microbial metabolism
Saccharolytic activity
Production of bile acids
...
Changes in composition (phylogenic)
Phyla: Bacteroidetes and Firmicutes
Class: Mollicutes
Species or genera:
Bifidobacteria
Faecalibacterium prausnitzii
Lactobacilli
...

Adapted from Delzenne et al., Nat Rev Endocrinol 2011
Outline

1. Gut microbiota as a nutritional target
2. Metabolic disorders associated with obesity
3. Metabolic disorders associated with cancer
4. Gut microbiota in alcohol-dependent patients
The gut microbiota

40 000 000 000 000 microbes
30 000 000 000 000 human cells

for a 'reference man' (70 kilograms, 20–30 years old and 1.7 meters tall)
Gut microbiota-host crosstalk

**Host**
- Genetic background
- Sex
- Age
- Immune system
- Gut motility

**Diet**
- Nondigestible carbohydrates
- Fat
- Prebiotics or probiotics

**Treatment**
- Antibiotics
- Gastric bypass

**Gut microbiota**

**Changes in microbial metabolism**
- Saccharolytic activity
- Production of bile acids
- ...

**Changes in composition (phylogenetic)**
- Phyla: Bacteroidetes and Firmicutes
- Class: Mollicutes
- Species or genera:
  - *Bifidobacteria*
  - *Faecalibacterium prausnitzii*
  - *Lactobacilli*
  - ...

**Host**
- Changes in phenotype
  - Fat mass development
  - Glucose tolerance
  - Insulin sensitivity
  - Inflammation
  - Steatosis
  - Satiety and energy efficiency
Experimental tools to study our microbial partners

Adapted from Bindels & Delzenne, Int J Biochem Cell Biol 2013
Prebiotics

Dietary Modulation of the Human Colonic Microbiota: Introducing the Concept of Prebiotics

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Gibson & Roberfroid, J Nutr 1995
## Future research on prebiotics

<table>
<thead>
<tr>
<th>Year</th>
<th>Definition</th>
<th>Substantiation of prebiotic effect</th>
<th>Compounds</th>
</tr>
</thead>
</table>
| 2010 | A selectively* fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health⁵² | Selectivity of effect on gut microbiota should be established *in vivo* using most up-to-date technology  
Health effects, or at least physiological effects, should be established in controlled trials and correlated with selective changes in gut microbiota composition or activity | Inulin  
FOS  
tGOS  
Lactulose |
| 2015 | A nondigestible compound that, through its metabolism by microorganisms in the gut, modulates composition and/or activity of the gut microbiota, thus conferring a beneficial physiological effect on the host | The degree to which the effect of the prebiotic on composition and/or activity is "selective" is not a criterion  
The burden of proof for health claims does not change  
Definition places more focus on the causal link between the microbial metabolization of the compound, the resulting modulation of the gut microbiota, and the beneficial physiological effects | Inulin  
FOS  
tGOS  
Human milk oligosaccharides  
**Candidate prebiotics?‡**  
- Resistant starch  
- Pectin  
- Arabinoxylan  
- Whole grains  
- Various dietary fibres  
- Noncarbohydrates that exert their action through a modulation of the gut microbiota |

**Figure 1** Current and proposed definitions for the concept of prebiotics

Bindels et al, Nat Rev Gastroenterol Hepatol 2015
Resistant starches (RS) include all starch and starch degradation products not absorbed in the small intestine of healthy individuals.

**TABLE 1** Types of resistant starches

<table>
<thead>
<tr>
<th>Designation</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS I</td>
<td>Physically inaccessible starch</td>
<td>Coarsely ground or whole-kernel grains</td>
</tr>
<tr>
<td>RS II</td>
<td>Granular starch with the</td>
<td>High-amylose maize starch, raw potato, raw banana starch</td>
</tr>
<tr>
<td></td>
<td>B- or C-polymorph</td>
<td></td>
</tr>
<tr>
<td>RS III</td>
<td>Retrograded starch</td>
<td>Cooked and cooled starchy foods</td>
</tr>
<tr>
<td>RS IV</td>
<td>Chemically modified starches</td>
<td>Cross-linked starch and octenyl succinate starch</td>
</tr>
<tr>
<td>RS V</td>
<td>Amylose-lipid complex</td>
<td>Stearic acid-complexed high-amylose starch</td>
</tr>
</tbody>
</table>

1 RS I, type I resistant starch; (RS); RS II, type II resistant starch; RS III, type III resistant starch; RS IV, type IV resistant starch; RS V, type V resistant starch.
Outline

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Cancer cachexia

- Fat Mass Loss
- Inflammation
- Insulin Resistance
- Physical Activity
- Food Intake
- Muscle Wasting
- Gut

Bindels & Thissen, Clin Nutr Exp 2015
Cancer cachexia

• Up to 80% of cancer patients, depending of the tumor site
• Reduces quality and length of life
• May be a cause of cancer therapy discontinuation
• No valid treatment

A microbial signature in cancer cachexia

Community-wide approach to characterize the gut microbiota in two mouse models of cancer cachexia

Bindels et al, The ISME J 2016
A microbial signature in cancer cachexia

16S rRNA genes from the caecal microbiota analysed by Illumina MiSeq. Logarithmic LDA score.

**↑ Enterobacteriaceae**

**↑ Parabacteroides goldsteinii**

**↓ Lactobacilli**

With Inès Martinez and Jens Walter
... independent of the food intake
Acetate
Propionate
Butyrate

Acetate
Propionate
Butyrate

Acetate
Propionate
Butyrate

Acetate
Propionate
Butyrate

Bindels et al, Br J Cancer 2012; Bindels*, Neyrinck* et al, Plos ONE 2015.
Selected synbiotic approach

D0

D1

D13

Bcr-Abl-expressing BaF3 cells

L. reuteri 100-23

ITF

Bindels et al, The ISME J 2016

With Bruno Pot & Corinnee Grangette
16S rRNA genes from the caecal microbiota analysed by Illumina MiSeq. LEfSe cladogram.
Benefits of the synbiotic approach

**Bcr-Abl**

- mRNA levels (relative expression)
  - CT
  - BaF
  - BaF-LrI
  - ND

**Organ weight (% body weight)**

- tibialis
- gastrocnemius

**Morbidity score**

- Score
  - BaF
  - BaF-LrI

**Survival**

- Fraction survival
  - Days after BaF injection
  - Days after BaF injection
  - p = 0.007
  - median survival + 2 days

*Bindels et al, The ISME J 2016*
Hypothetical role of the gut barrier

- Tumor
- Anorexia
- Fat mass loss
- Muscle atrophy

↑ bacterial compounds

Gut barrier function

Bindels & Thissen, Clin Nutr Exp 2015
Hypothetical role of the gut barrier

- Decreased in leukemic mice
- Increased by synbiotics

Gut permeability

- Decreased in leukemic mice
- Increased by synbiotics

Immune system

Antimicrobial peptides

Decreased in leukemic mice
Increased by synbiotics

Bindels et al, The ISME J 2016
Current working model

Gut barrier function

Cancer cachexia

Propionate

New metabolites?

Prebiotics

Probiotics
Outline

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A role for the gut permeability?

A role for the gut permeability?

Leclercq et al, PNAS 2014
Dysbiosis

Leclercq et al, PNAS 2014
Altered fecal metabolite profile

Analysis of Volatile organic compounds by gas-chromatography-mass spectrometry (K. Verbeke, Kuleuven B)
Bi-plot analysis reveals ADT1 HP versus LP are differentiated (14 metabolites)
Conclusions

• Importance of the prebiotic concept.
• Microbiota-dependent and independent effects of functional foods: strategies to demonstrate causality exist.
• Underexplored areas could benefit from targeted prebiotic or synbiotic approaches.
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