Regulation of Liver and Adipose Tissue
Lipogenesis in Human Obesity

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De Novo Lipogenesis (DNL) Pathway

- **FASN**: fatty acid synthase
- **SCD**: stearoyl CoA desaturase
- **ELOVL6**: fatty acid elongase-6

**Malonyl-CoA**
- **FASN** → **14:0** myristic
- **SCD** → **14:1n-5** myristoleic

**16:1n-7 palmitoleic**
- **SCD** → **16:0** palmitic
- **ELOVL6** → **18:1n-7 vaccenic**
- **SCD** → **18:0** stearic
- **SCD** → **18:1n-9 oleic**

**Very long-chain FA (VLCFA)**
De Novo Lipogenesis (DNL) in Mice

- Mice efficiently convert dietary carbohydrates to fatty acids
- **Liver DNL** is up-regulated in obese mice; mechanisms:
  - Hyperinsulinemia (SREBP1c)
  - Increased glucose flux (ChREBP)
  
- DNL-linked fatty acid elongase ELOVL6 has adverse metabolic effects
  (Matsuzaka et al. 2007, Nat Med 13:1193)

- **Adipose Tissue** DNL is down-regulated in obesity
- DNL-derived palmitoleic acid (C16:1) counteracts insulin resistance (Cao et al. 2008, Cell 134:933)
De Novo Lipogenesis (DNL) in Humans

- Dietary carbohydrates is converted to fatty acids by fatty acid synthase (FASN)
- Obese subjects have a higher rate of hepatic DNL than lean subjects
- FASN mRNA is down-regulated in adipose tissue in obesity
- Common polymorphisms in FASN gene are associated with BMI
Aim of the Study

Characterize the regulation of DNL in human obesity

- Expression of biosynthetic enzymes
- DNL-derived fatty acids
- Link to metabolic disease parameters
Study Cohort

• Tissue bank, Dept. of Surgery, University of Ulm (Anna Wolf, Uwe Knippschild)

• Surgery patients: morbid obesity > non-metastatic cancer > other cases (no liver disease)

• Patients with liver and adipose tissue samples: n=165
Study Cohort: HOMA-IR

R = 0.56
Liver FASN Expression versus BMI
Liver FASN Expression versus BMI

![Graph showing Liver FASN Expression versus BMI](image-url)
Liver FASN Expression versus HOMA-IR, Liver TG, CRP

HOMA-IR

\[ R = 0.58 \]
\[ P < 10^{-10} \]
Liver FASN Expression versus HOMA-IR, Liver TG, CRP

HOMA-IR

Liver TG

log FASN (rel expression)

log HOMA-IR

log liver TG content

R = 0.58
P < 10^-10

R = 0.42
P < 10^-7
Liver FASN Expression versus HOMA-IR, Liver TG, CRP

HOMA-IR

Liver TG

CRP

$log$ FASN (rel expression) vs $log$ HOMA-IR: $R = 0.58$, $P < 10^{-10}$

$log$ FASN (rel expression) vs $log$ liver TG content: $R = 0.42$, $P < 10^{-7}$

$log$ FASN (rel expression) vs $log$ CRP: $R = 0.32$, $P < 10^{-4}$
Experimental Subgroups

- Gender-matched, (partially) age-matched, n=20, controls (lean and overweight), obese, obese+T2D (type 2 diabetes)

![Graph showing BMI comparison between control, obese, and obese+T2D groups with statistical significance indicated by * p< 0.05, ** p< 0.001]
Experimental Subgroups

- Gender-matched, (partially) age-matched, n=20, controls (lean and overweight), obese, obese+T2D (type 2 diabetes)

T-Test vs. controls, * p< 0.05, ** p< 0.001
Experimental Subgroups

- Gender-matched, (partially) age-matched, n=20, controls (lean and overweight), obese, obese+T2D (type 2 diabetes)

T-Test vs. controls, * p< 0.05, ** p< 0.001
Liver DNL Gene Expression

FASN

T-Test vs. controls, * p < 0.05, ** p < 0.001
Liver DNL Gene Expression

**Liver DNL Gene Expression**

![Bar charts showing gene expression levels of FASN and ELOVL6 in control, obese, and obese + T2D groups.](chart.png)

T-Test vs. controls, * p< 0.05, ** p< 0.001
Liver DNL Gene Expression

**Liver DNL Gene Expression**

- **FASN**
- **ELOVL6**
- **SCD**

T-Test vs. controls, * p< 0.05, ** p< 0.001
Visceral Adipose Tissue (VAT) Lipogenic Gene Expression

FASN

T-Test vs. controls, * p< 0.05, ** p< 0.001
Visceral Adipose Tissue (VAT) Lipogenic Gene Expression

**FASN**

**ELOVL6**

T-Test vs. controls, * p< 0.05, ** p< 0.001
Visceral Adipose Tissue (VAT) Lipogenic Gene Expression

**Visceral Adipose Tissue (VAT) Lipogenic Gene Expression**

- **FASN**
  - Control
  - Obese
  - Obese + T2D

- **ELOVL6**
  - Control
  - Obese
  - Obese + T2D

- **SCD**
  - Control
  - Obese
  - Obese + T2D

T-Test vs. controls, * p< 0.05, ** p< 0.001
VAT Westernblots

- FASN, upstream DNL proteins

![Westernblots Image]
**VAT Westernblots**

1-way ANOVA: Repeated T-TEST
Tukey-Kramer test to correct for multiple comparison
VAT Westernblots

1-way ANOVA: Repeated T-TEST
Tukey-Kramer test to correct for multiple comparison
Palmitoleate (C16:1) in Mouse Adipose Tissue

- Biosynthetic capacity DNL severely impaired in obese adipose tissue => is this reflected in fatty acid patterns?
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- Biosynthetic capacity DNL severely impaired in obese adipose tissue => is this reflected in fatty acid patterns?

T-Test vs. controls, * p < 0.05, ** p < 0.001
DNL-Derived Fatty Acids in Human VAT

Palmitic Acid
C16:0

Palmitoleic Acid
C16:1n-7

Vaccenic Acid
C18:1n-7

T-Test vs. controls, * p< 0.05
Summary and Conclusions – Human Liver

- The DNL pathway is profoundly induced in liver of (morbidly) obese humans
Summary and Conclusions – Human Liver

• The DNL pathway is profoundly induced in livers of (morbidly) obese humans

• Liver FASN expression correlates strongly with HOMA-IR, indicating a link to liver insulin resistance/hyperinsulinemia
Summary and Conclusions – Human Liver

• The DNL pathway is profoundly induced in livers of (morbidly) obese humans

• Liver FASN expression correlates strongly with HOMA-IR, indicating a link to liver insulin resistance/hyperinsulinemia

• The induction of liver ELOVL6 may support insulin resistance by increasing synthesis of stearic acid (C18:0), as described in mice (Matsuzaka et al. 2007, Nat Med 13:1193)
Summary and Conclusions: Human VAT

• Except for SCD, the DNL pathway is strongly suppressed in (diabetic) obese humans
Summary and Conclusions: Human VAT

- Except for SCD, the DNL pathway is strongly suppressed in (diabetic) obese humans

- Down-regulation of GLUT4 protein in insulin resistant subjects is consistent with a crucial role of GLUT4 for whole body insulin sensitivity (Abel et al., 2001, Nature 409:729)
Summary and Conclusions: Human VAT

• Except for SCD, the DNL pathway is strongly suppressed in (diabetic) obese humans

• Down-regulation of GLUT4 protein in insulin resistant subjects is consistent with a crucial role of GLUT4 for whole body insulin sensitivity (Abel et al., 2001, Nature 409:729)

• Palmitoleate (C16:1) does not drop in obesity (compensation by liver)
Ongoing/Future Work

• Fatty acid profiling in liver and plasma

• Gene expression changes in adipose tissue after weight loss

• Study liver pathology

• Lipidomics (DNL biomarker)
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Appendix
Study Cohort: Liver Steatosis

BMI

liver steatosis (%)
Study Cohort: CRP

R = 0.47
Liver FASN Westernblot

n > 8, T-Test vs. controls, * p < 0.05, ** p < 0.001
Correlation VAT GLUT4 - HOMA-IR

\[ R = -0.68 \]
\[ P < 10^{-5} \]
Mouse Adipose Tissue Macrophage Infiltration

- In mice, obesity is accompanied by massive macrophage infiltration in white adipose tissue

Scheja et al., 2011, BBRC 407:288
Expression of Macrophage Markers in Human VAT

F4/80

CD11b

CD68

T-Test vs. controls, * p < 0.05, ** p < 0.001
Inflammatory Cytokine Expression in Human VAT

**IL-1β**
- Control
- Obese
- Obese + T2D

**TNFα**
- Control
- Obese
- Obese + T2D

**IFNγ**
- Control
- Obese
- Obese + T2D

T-Test vs. controls, * p< 0.05, ** p< 0.001
Adipose Tissue Gene Expression After Weight Loss

- Bariatric surgery, performed at Maastricht University Hospital
- Subcutaneous adipose tissue samples before and after intervention
Liver Transcription Factor Expression

SREBP1

ChREBP

PPARγ

Liver SREBF1 (rel expr)

Liver ChREBP (rel expr)

Liver PPARγ (rel expr)

control  obese  obese + T2D

control  obese  obese + T2D

control  obese  obese + T2D

control  obese  obese + T2D
Title