Intestinal microbiota and energy balance – pro’s and con’s

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Worldwide prevalence of obesity in populations age above 20 in 2008

Prevalence of obesity (%)
- <10
- 10–19.9
- 20–29.9
- ≥30
- Data not available
- Not applicable

* BMI ≥30kg/m²

WHO 2011
What are the common mechanisms of chronic immune-mediated and metabolic disorders … role of microbes?

Renz, …, Haller 2012 Nature Immunology
Community structure and activity of the intestinal microbiota is tightly linked to immune and metabolic functions

**Gut as central organ**
- Control of barrier integrity
- Control of immune and inflammatory processes
- Energy extraction and control of metabolism

**Gut microbiota**
- Altered composition
- Altered fermentation
- Increased energy harvest

**Diversity and Density**
- Stomach: $10^1 - 10^3$ CFU/ml
- Duodenum: $10^2 - 10^3$ CFU/ml
- Jejunum: $10^4 - 10^5$ CFU/ml
- Ileum: $< 10^8$ CFU/ml
- Colon: $10^{12}$ CFU/ml
Functional interactions between the gut microbiota and host metabolism

Body Mass Index (BMI)
Obesity > 30 kg/m²

- **Epithelium**
  - ↑ Permeability of the epithelium
  - ↓ PYY/GLP-1 from L-cells

- **Liver**
  - ↑ Short-chain fatty acids
  - ↑ Inflammation

- **Brain**
  - ↓ Satiety

- **Muscle**
  - ↓ Fatty-acid oxidation

- **Gut microbiota**
  - Altered composition
  - Altered fermentation
  - Increased energy harvest

- **Adipose tissue**
  - ↑ Triglyceride incorporation
  - ↑ Inflammation

Tremaroli and Bäckhed 2012 Nature
Putative mechanisms for the effect of the intestinal microbiota on metabolic functions of the host

Cox and Blaser 2013 Cell Metabolism
Weight changes affect microbial composition … the first steps

Diversity and Density

- Stomach: $10^1 - 10^3$ CFU/ml
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- Colon: $10^{12}$ CFU/ml

Ley, …, Gordon 2006 Nature
Caloric load changes microbial composition and contributes to increased energy harvest in obese volunteers

- Weight maintaining diet (WMD) calculated as (kg) X 0.5 + 1973
- Experimental diet 1/2 (EXD1) representing either 2400 or 3400 kcal/d with similar macronutrient composition (24% protein, 16% fat, 60% carbohydrates)
- Volunteers include 12 lean (BMI<25; Average 23) and 9 obese (BMI>30; Average 40)

Jumpertz, ..., Krakoff 2011 Am J Clin Nutr
Caloric load changes microbial composition and contributes to increased energy harvest in obese volunteers

Reduced energy loss in feces associated with 20% changes in *Firmicutes* and *Bacteroidetes* ~150 kcal per day

Jumpertz, …, Krakoff 2011 Am J Clin Nutr
Transfer of stool microbiota from twins discordent for obesity into germfree mice mirror human weight gain

<table>
<thead>
<tr>
<th>Twin Pair</th>
<th>1 (DZ)</th>
<th>2 (DZ)</th>
<th>3 (DZ)</th>
<th>4 (MZ)</th>
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</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>23</td>
<td>32</td>
<td>25.5</td>
<td>31</td>
</tr>
</tbody>
</table>

C

% Change in body composition

D

% Change in fat mass

Ridaura, …, Gordon 2013 Science
Early life exposure to low dose concentrations of antibiotics are associated changes in body composition

Age 4 w + 7 w Abx

Associated with induction of lipogenesis in liver

Cho, …, Blaser 2012 Nature
High fat diet is associated with increased LPS plasma concentration and loss of glucose tolerance …

Weight gain positively associated endotoxin in blood

Glucose tolerance negatively associated endotoxin in blood

Inflammation mediators positively associated endotoxin in blood

Cani et al. 2007 Diabetologia (Cani et al. 2007 Diabetes)
… however these effects are not reproducible and thus question the role of the hypothesis „Metabolic endotoxemia“

Collaborative project with Profs Klingenspor and Daniel (in preparation)
... however these effects are not reproducible and thus question the role of the hypothesis „Metabolic endotoxemia”
Does high fat diet and obesity contribute to gut associated inflammation?

**Nutrition as an etiologic risk factor for developing IBD**

- A recent meta-analysis of 19 studies with 1269 CD and 1340 UC patients identified high dietary intake of total fats and meat as a risk factor (Hou et al. Am. J. Gastroenterol. 2011)
- High body mass index (BMI) was not associated with the incidence of UC and CD in prospective cohort (EPIC) of 300,724 participants (Clan et al. Am. J. Gastroenterol. 2013)

**Nutrition in animal models – mechanistic understanding**

- Dietary fat drives pathobiont selection (Bilophila wadsworthia) in experimental colitis (Devkota et al. Nature 2012)
- Changes in gut microbiota control inflammation and gut permeability in obese mice (Cani et al. Diabetes 2007, Gut 2009)
HFD accelerate the development of small intestinal inflammation in a mouse model of Crohn’s disease

Gruber, …, Haller 2013 PLOS ONE
Metabolic fingerprints in response to HFD in plasma and ileal tissue

A  PCA plot plasma

B  PCA plot distal ileum
High-fat diet impairs gut barrier function in normal and the disease-susceptible host

![Western Blot Images]

**Portal vein LPS**

- **WT**
- **TNFΔARE/WT**

<table>
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<th>LPS Concentration [EU/ml]</th>
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<tbody>
<tr>
<td>3.0</td>
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<tr>
<td>2.5</td>
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<tr>
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<tr>
<td>0.5</td>
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<td>0.0</td>
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</table>

- **Control diet**
- **High-fat diet**

- a
- b

Genotype:

<table>
<thead>
<tr>
<th>High-fat diet</th>
<th>WT</th>
<th>ARE</th>
<th>ARE</th>
<th>WT</th>
</tr>
</thead>
</table>

- **β-Actin**
- **E-Cadherin**
- **Occludin**

Gruber, …, Haller 2013 PLOS ONE
High fat diet triggers epithelial chemokine expression and dendritic cell recruitment into the small intestine

CCL20

CD11c+ DC

Gruber, …, Haller 2013 PLOS ONE
High fat diet modulates bacteria-mediated epithelial cell activation and dendritic cell (DC) recruitment

CCL20 secretion
Mode K cell culture

Recruitment of BM-DCs
Towards Mode K conditioned media

Gruber, …, Haller 2013 PLOS ONE
Maternal obesity accelerates disease activity in a mouse model for Crohn’s disease

Hemmerling, …, Haller 2014 PLOS ONE; Hemmerling, …, Haller (in preparation)
Fecal Microbiota Transplantation (FMT) in chronic diseases

- Multiple sclerosis
- Chronic fatigue syndrome

- Non-alcoholic fatty liver disease

- Atherosclerosis
- Idiopathic thrombocytic purpura

- Obesity

- Insulin resistance/ type 2 diabetes mellitus

- C difficile infection
- Irritable bowel syndrome
- Inflammatory bowel disease

Green: beneficial effect FMT in RCT
Blue: beneficial effect FMT in case series
Black: association between gut microbiota and disease from experimental/observational studies

Smits, …, Nieuwdorp 2013 Gastroenterology
Fecal transplantation in type-2 diabetes as a “proof-of-concept” for the clinical relevance of intestinal bacteria

Vriese, …, Nieuwdrop 2012 Gastroenterology
Probiotic intervention to reduce weight in human intervention studies ... a meta-analysis
Conclusion

- Diet affects microbial composition and activity in the gut
- Changes in microbial composition modulate energy homeostasis

The propositions are:

- ✔ Transfer of stool microbiota into germfree mice mimick weight gain in humans
- ✔ Efficiency to extract energy from the diet increases with obesity associated changes in short chain fatty acids
- ✖ Obesity and/or HFD anatgonize intestinal barrier functions and provoke metaolic endotoxemia
- ✔ FMT is effective in modulating systemic insulin resistance but not weight; the contribution of probiotics remain inconclusive

- HFD accelerates early life disease activity of IBD related intestinal inflammation independent of the obese phenotype
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