Networking with your microbiota
Influence of gut microbiota in energy balance

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« Influence of gut microbiota in energy balance »

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The gut microbiota contains up to 1000 species \((10^{14} \text{ cells})\) dominated by 3 (of 70) divisions:

- **Firmicutes** \((E. \text{ rectale}-\text{Cl. Coccoides, Cl. leptum})\)
- **Bacteroidetes** \((\text{Bacteroides, Prevotella})\)
- **Actinobacteria** \((\text{Bifidobacterium})\)
Gut microbiota functions and interactions with host

- Improves digestion
- Supplies micronutrients
- Improves bioavailability
- Polysaccharides fermentations, SCFA...
- Modifies bioactivity
- Bile acids metabolism
- Detoxification and activation of bioactive compounds

- Epithelial cells proliferation, gut barrier integrity
- Direct immune defenses (against pathogens)
- Non-immune defenses (gut barrier integrity)
- Immunotolerance...
- Energy homeostasis
The presence of bacteria promotes fat mass development

Conventional mice
Gut microbiota donor

Conventionalized (CONV-D)

Mice allowed to acquire the gut microbiota

Germ-free

Conventionalized (CONV-R)

Backhed et al. 2004 PNAS
Gut microbiota participates to the high-fat diet-induced metabolic diseases

Germ free mice resist to the high-fat diet-induced glucose intolerance and insulin resistance

Backhed et al 2007 PNAS
Dietary fibres
non digestible carbohydrates

Lipogenic substrates
Short Chain Fatty Acids (SCFA) acetate

Promote absorption and extraction of energy from the diet

Butyrate
Acetate
Propionate
butyrate

Cani and Delzenne Curr Pharm Design 2009
Backhed et al. 2004 PNAS
GPR 43 inhibits lipolysis
Relevance of gut microbiota in the development of obesity

- Question 1. Are all bacteria similarly related to fat mass development?
- Question 2. Are there way to target bacteria through nutritional approach, in order to control fat mass development, obesity and related disorders?
Question 1
Shifts in bacterial phyla/strains/species upon obesity

1. Decrease in phylogenic bacterial diversity in obese versus lean subjects
   

2. Decrease in bacteroidetes/Firmicutes ratio in obese subjects
   

3. Reduction of Firmicutes in obese subjects upon dieting and weight loss
   

4. The number of Bifidobacteria inversely correlates, whereas Staphylococcus aureus or bacteroides positively correlate with the occurrence of overweight (children, pregnant women)
   
Nutritionnal model of obesity

Normal chow

High-fat

Obese, Type 2 Diabetes, Low grade Inflammation

Cani et al Diabetes 2007
Relevance of gut microbiota in the development of obesity

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Prebiotics like fructans are able to selectively modulate gut microbiota...

Saulnier et al. *Current Opinion in Biotechnology* 2009
Gibson and Roberfroid, *J. Nutr., 125*, 1401, 1995; Roberfroid M *J Nutr.*, 137 (3 supl 2) 2007
Experimental groups

- 12 weeks-old male C57bl6/J mice
- 4 groups
  - CT : A04 diet;
  - HF : high-fat diet
  - HF-OFS : HF diet containing 10% Raftilose®
  - HF-CELL : HF diet containing 10% Avicel ® (microcristalline cellulose)

Prebiotics treatment restores *Bifidobacterium* *spp.* content
Metabolic endotoxemia is associated with fat intake, obesity, diabetes

High-fat diet

Obese, IGT

Type 2 diabetes

↑ Plasma LPS

Creely et al. Am J Physiol Endocrinol Metab. 2007
Body weight/fat mass positively correlate with serum endotoxin, and negatively correlate with Bifidobacteria.
Prebiotics improve glucose tolerance and glucose-induced insulin-secretion
Glucose intolerance and fasting plasma insulin positively correlate with plasma endotoxin, and negatively correlate with *Bifidobacterium spp.*
Counteracting the drop in bifidobacteria allows to lessen obesity and associated disorders (fat mass development, glucose intolerance, and endotoxemia).

Questions:
Mechanism?
Relevance in humans?
Endocrine L-cells express proglucagon gene, leading to different peptides

Prebiotics feeding promotes the differentiation and thereby increases the number of endocrine L cells in the intestine of rats.


Similar effect for Neuro-D

Similar effect for GLP-2
Relevance of GLP-1 and GLP-2 in the effect of prebiotics on obesity

- **GLP-1**
  - Mice treated with high fat diet +/-OFs for 4 weeks
  - Use of GLP-1 receptor antagonist (chronic infusion) and use of GLP-1 receptor knock out mice (Cani et al Diabetes 2006)

- **GLP-2**
  - Ob/Ob mice: obese with endotoxemia due to loss of gut barrier integrity
  - Use of GLP-2 receptor agonist and inverse agonist (Cani et al Gut 2009)
Body weight gain and Energy Intake in mice lacking GLP-1 receptor functionality

Data with different superscript letters are significantly different, $P<0.05$

Proglucagon mRNA

Relevance of GLP-1 and GLP-2 in the effect of prebiotics on obesity

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- **GLP-2**
  - Ob/Ob mice : obese with endotoxemia due to loss of gut barrier integrity
  - Use of GLP-2 receptor agonist and antagonist (Cani et al Gut 2009)
Prebiotic counteracts endotoxemia and metabolic disorders in ob/ob mice, by improving gut permeability

Cani P.D. et al. Gut 2009
Prebiotic counteracts endotoxemia and metabolic disorders in ob/ob mice, by improving gut permeability

GLP-2 antagonists blunt the increase in occludin and ZO-1 overexpression linked to prebiotics ingestion
GLP-2 R antagonist abolishes the improvement of endotoxemia and inflammation by prebiotics

**A**

- **Plasma LPS (EU/ml)**
  - Ob-CT
  - Ob-Pre
  - Ob-Pre-Ant
  - Ob-Ant

**B**

- **CD68 mRNA levels (relative expression)**
  - Ob-CT
  - Ob-Pre
  - Ob-Pre-Ant
  - Ob-Ant

Cani P.D. et al. *Gut* 2009
PREBIOTICS

1. Modulation of gut microbiota
   - Bifidobacterium spp.

2. GLP-2

Blood

Gut epithelium

- Metabolic endotoxemia
- Systemic inflammation
- Steatosis
- Lipogenesis
- Inflammation
- Oxidative stress

Cani P.D. et al. Gut 2009
Proof of concept

Counteracting the drop in bifidobacteria by prebiotics allows to lessen obesity and associated disorders (fat mass development, glucose intolerance, and endotoxemia), namely by modulating the endocrine function of the gut.

Questions:
Mechanism?
Relevance in humans?
Prebiotics modulate satiety in human healthy volunteers

- 16 g/j of OFS, single-blind study, cross-over, n=10. 2 x 2 wks R/ and 2wk wash-out

**Breakfast**

**Diner**

OFS increases satiety at breakfast and diner
Reduces Total Energy intake by about 10%

Cani et al, Eur J Clin Nutr, 2005
With consequences on gut peptides release...

Cani et al. Am J Clin Nutr (accepted for publication in August 2009)
Relevance of *Bifidobacterium spp.* targeting


» Prebiotics (fructans) decrease BMI and increase gut peptides secreted by L cells in overweight and obese patients *(Abrams J. Pediatrics, 2007; Parnell and Reimer, *J. Nutr.*, 2009)*

Other target bacteria?


» Faecalibacterium Prausnitzii are increased upon prebiotics treatment (Ramirez-Farias et al. *Br. J. Nutr.* 2008)

Targeting gut microbiota with probiotics could also be an interesting tool…
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