Oslo, January 18, 2018

The Microbiome, Cancer and Cachexia

Prof. Laure Bindels, PhD
Outline

- Introduction to the gut microbiota
- Gut microbiota-host crosstalk in chemotherapy
- Diet-microbes-host interaction in cancer cachexia
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)
The gut microbiota: a hot topic
The gut microbiota: a hot topic

Courtesy of Prof Nathalie Delzenne
Microbiota evolution over time

- **Newborn**
  - Initial gut bacteria (founder species) depends upon delivery mode
  - C-section:
    - *Staphylococcus*, *Corynebacterium*, *Propionibacterium* spp.
    - Higher susceptibility to certain pathogens
    - Higher risk of atopic diseases

- **Early childhood**
  - New strains (less certain in origin) outcompete old ones
  - Rapid increase in diversity
  - Early microbiota development = high instability
  - Shifts in response to diet, illness

- **Adult**
  - Highly distinct, differentiated microbiota
  - Microbial community may continue to change, but at a slower rate than in childhood

- **Elderly**
  - Substantially different gut communities than in younger adults

**Notes:**

- Vaginal delivery:
  - *Lactobacillus*, *Prevotella* spp.
- Vertical inheritance from mother

**References:**

Dominguez-Bello et al., Gastroenterology 2011
The gut-microbiota 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

Delzenne et al., Nat Rev Endocrinol 2011
Experimental tools to study our microbial partners

Prebiotics i.e. inulin-type fructans

Probiotics i.e. lactobacilli

Bacteriocins Antibiotics

FMT

Gut microbiota

Adapted from Bindels & Delzenne, Int J Biochem Cell Biol 2013
The gut microbiota-host crosstalk

Neish, Gastroenterology 2009
Microbial metabolites

Holmes et al, Cell Metab 2012
Microbial metabolites

Microbial metabolites

- Glycerol
- Oleic acid
- N-oleoyl serinol
- Dipeptide aldehyde
- Amino acids
- E. coli
- GLP1 secretion
- Glucose homeostasis
- e.g. Gemella spp., engineered E. coli
- e.g. Species from the Clostridia class

Upregulated by NRPS and GPR119

Increased cytotoxic activity

Cathepsin L

5FU

FUMP

UPRT
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Microbiota in chemotherapy

Alexander et al, Nat Rev Gastroenterol 2017
Roy & Trinchieri,
Nat Rev Gastroenterol 2017
Microbes and Cancer*

Amiran Dzutsev, Jonathan H. Badger, Ernesto Perez-Chanona, Soumen Roy, Rosalba Salcedo, Carolyne K. Smith, and Giorgio Trinchieri

Cancer and Inflammation Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, email: trinchig@mail.nih.gov

Microbiota: a key orchestrator of cancer therapy

Soumen Rou and Gioraio Trinchieri

Gut microbiota modulation of chemotherapy efficacy and toxicity

James L. Alexander¹, 5, Ian D. Wilson², Julian Teare¹, Julian R. Marchesi¹−³, Jeremu K. Nicholson² and James M. Kinross¹, 5
Outline

- Introduction to the gut microbiota
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Cancer cachexia

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

Diagnostic of cachexia

- Muscle strength
- Body composition
- Anorexia
- Glasgow prognostic score (CRP & albuminemia)

Fearon et al., Lancet Oncol 2011
Multimodal approach

Physical activity
Nutritional support
Pharmacological approach

Evans et al., Clinical Nutrition 2008
Fearon et al., Nat Rev Oncol 2013
Argiles et al, Nat Rev Cancer 2014
Bindels & Thissen, Clin Nutr Exp 2016
Multimodal approach

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

Bindels et al, The ISME J 2016
Selected synbiotic approach

Bindels et al, The ISME J 2016
Benefits of the synbiotic approach

**Bcr-Abl**

![Bar chart showing mRNA levels](chart1.png)

**Organ weight**

![Bar chart showing organ weight](chart2.png)

**Morbidity score**

![Bar chart showing morbidity score](chart3.png)

**Survival**

![Survival curve](chart4.png)

*BaF* and *BaF-LrI* treatments significantly reduce Bcr-Abl mRNA levels, organ weight, and morbidity score compared to controls. The median survival is increased by 2 days for *BaF-LrI* treated mice compared to *BaF* treated mice. The *p* value for this difference is 0.007.

Bindels et al, The ISME J 2016
Acetate  Propionate  Butyrate

Propionate  Butyrate

Acetate  Propionate  Butyrate

Bindels et al, Br J Cancer 2012; Bindels*, Neyrinck* et al, Plos ONE 2015.
A role for the gut barrier?
A role for the gut barrier?

- Decreased in leukemic mice
- Increased by synbiotics

**Gut permeability**

<table>
<thead>
<tr>
<th>mRNA levels (relative expression)</th>
<th>CT</th>
<th>BaF</th>
<th>BaF-Lrl</th>
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<tr>
<td>occludin</td>
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<td>ZO-1</td>
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<tr>
<td>Muc2</td>
<td>*</td>
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<tr>
<td>proglucagon</td>
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**Paneth cell differentiation and antimicrobials**

<table>
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<th>mRNA levels (relative expression)</th>
<th>TCF4</th>
<th>Lysozyme</th>
<th>α-defensins</th>
<th>Reg3γ</th>
<th>Pla2g2</th>
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**Immune system**

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<tr>
<th>mRNA levels (relative expression)</th>
<th>CD3γ</th>
<th>Tbet</th>
<th>IL-17A</th>
<th>Foxp3</th>
<th>IL-10</th>
<th>Ebi3</th>
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Bindels et al, The ISME J 2016
A role for the gut barrier
A role for the gut barrier
A role for the gut barrier
LBP at the crossroad of cancer cachexia and gut dysbiosis
Conclusion & perspectives

RS
ITF
AXOS
POS
Dr M. Sboarina

Gut barrier
propionate

S. Pötgens

Bindels, Neyrinck et al, Plos ONE 2015
Primary Objective

• Composition and activity of the gut microbiota in acute myeloid leukemic patients

Urine, feces and blood samples

Nutritional assessments

Cachexia symptoms

Belgian Registration Number: B403201317128