The role of the microbiome in IBD

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(Wo)Man = a “supraorgansim”
Microbiome = part of our genetic landscape = the human metagenome
Just bacteria.... rather not ;-)
Generation of reference gene catalogues: Human microbiomes differ in species & genes

- n=124 individuals (Europeans)
- 3.3 Mio bacterial genes (>99%)
- approx. 1150 bacteria
- 160 bacterial species/individual
- 57 species common to >90%
- 530,000 genes/individual

ICG
- 10,000,000 bacterial genes in n=1267 individuals
- 500,000 genes per individuum
- approx. 50% of genes shared by 50% of individuals (metagenomic core)
- Comparable catalogues for Europeans, Americans, Japanese, Chinese

Li et al. Nat Biotechnol 2014; 32: 834-41
A co-evolution from the very beginning accounts for a high grade of mutualism
Low Species Richness and Low Gene Count (LGC) characterize Dysbiosis associated with diseases.

**Intestinal disorders**
- Crohn’s disease
- Ulcerative colitis
- Chronic irritable bowel syndrome (Irritable Bowel Syndrome, IBS)
- Atrial fibrillation

Dysbiosis reflects an alteration of the mutualistic host-microbe relationship with recurring features:

- Low species richness and low Faecalibacterium prausnitzii
- Low grade inflammation


Lepage Gastroenterol 2011

Methods: Looked for recurrence of mucosal inflammation in CD after IC-resection by reinfusion of ileal content via a protective proximal loop ileostomy.

Results: Recurrence of inflammation within only 8 days!

Conclusion: The “enemy” lies within ‘fecal stream’

H&E staining of ileal biopsy specimens (A) before and (B) after reinfusion.

D’Haens et al. Gastroenterology 1998
"Dysbiosis" in IBD (or in general)

- Structural microbial alterations
- Reduced diversity and less stable composition
- Increased adherence to epithelial surface (UC)
- No clear signature for specific microbes (pathobionts)

Lupp C et al. Cell Host & Microbe 2007

Frank A et al. PNAS 2007
Becker et al. ILAR J 2015
Norman et al. Cell 2015

Host-Mediated Inflammation Disrupts the Intestinal Microbiota and Promotes the Overgrowth of Enterobacteriaceae

Cause – or effect?

What are the host factors driving dysbiosis?
The Treatment-Naive Microbiome in New-Onset Crohn’s Disease

- 447 kids and adolescents <17a, treatment-naive
- 221 Controls
- Sampling: stool, rectum and TI biopsies

Gevers D et al. Cell Host & Microbe 2014
The Treatment-Naive Microbiome in New-Onset Crohn’s Disease

- Disease activity correlates with microbial alterations
- Antibiotics worsen „dysbiosis“
- Composition of the gut microbiota predicts disease course
- In early-stage disease mucosal microbiome superior to stool analysis

Gevers D et al. Cell Host & Microbe 2014
Dysbiotic gut microbiota causes transmissible Crohn’s disease-like ileitis independent of failure in antimicrobial defence.

* TNFΔARE mice overproduce TNFα and develop spontaneous ileitis.

Schaubeck M et al. Gut 2015
Dysbiotic gut microbiota causes transmissible Crohn’s disease-like ileitis independent of failure in antimicrobial defence

Schaubeck M et al. Gut 2015
Early life microbiome and risk of disease

Immune exclusion (barrier) Hyporesponsiveness

Brandtzaeg P. Nat Rev Gastroenterol Hepatol 2010
Immunometabolic homeostasis – a window of opportunity
Microbial Early Life Exposure Long-lasting Effects on Natural Killer T Cell Function

Olszak T et al. Science 2012
• Host factors shaping microbial communities are important for building and maintaining a homeostatic relationship and to defend host integrity from aggressive bacteria.
Lcn2 is strongly induced in patients with IBD.
Study objective: To investigate the role of Lcn2 in IBD.

Moschen et al. Cell Host & Microbe 2016
In the steady-state Lcn2−/− mice are healthy, while IL10−/−/Lcn2−/− show massive inflammation...
In the steady-state $\text{Lcn2}^{-/-}$ mice are healthy, while $\text{IL10}^{-/-}/\text{Lcn2}^{-/-}$ show massive inflammation ...
IL10−/−/Lcn2−/− animals exhibit an altered microbial ecology ...
... and transmissible to cross-fostered animals

Moschen et al. Cell Host & Microbe 2016
... and transmissible to cross-fostered animals
Food, Immunity, and the Microbiome

Herbert Tilg

Nutrients
- Plant- and animal-derived
  - Carbohydrates
  - Proteins
  - Fats
  - Salt and trace elements

Microbiota
- Cecum
- Portal circulation
- Vagus n.

Intestine & host compartment
- AMPs

Tilg/Moschen. Gastroenterology 2015
Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome

- Dietary emulsifiers (PS80, CMC), detergent-like molecules are ubiquitous components of processed foods (and drugs)
- They can disrupt the protective mucus layer covering the intestinal surface
- Facilitating deeper encroachment of microbiota into the mucosa

Chassaing B et al. Nature 2015
Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome

Chassaing B et al. Nature 2015
Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome

Broad use of emulsifiers:
- perturbed host-microbiota relation
- altered microbial composition
- resulting in low-grade inflammation
- promotes IBD in susceptible host
- promotes obesity/MetS

Chassaing B et al. Nature 2015
Precision editing of the microbiome

- Intestinal inflammation on metagenomics level = Molybdenum-cofactor dependent metabolic pathways
- Molybdenum-cofactor dependent metabolic pathways confer fitness advantage for Proteobacteria
- Molybdenum-cofactor consists of Molybdopterin and Molybdenum-oxide
- Tungsten drives Molybdenum out of its bond with molybdopterin

Zhu W/Winter MG et al. Nature 2018;553:208-211
Precision editing of the microbiome

Zhu W/Winter MG et al. Nature 2018;553:208-211
Precision editing of the microbiome

Zhu W/Winter MG et al. Nature 2018;553:208-211
THANKS FOR LISTENING :-)