

Nutrition, microbiota and metabolic diseases

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5th Better Foods for Better Health,
Veyrier-du-Lac - France, April 2016

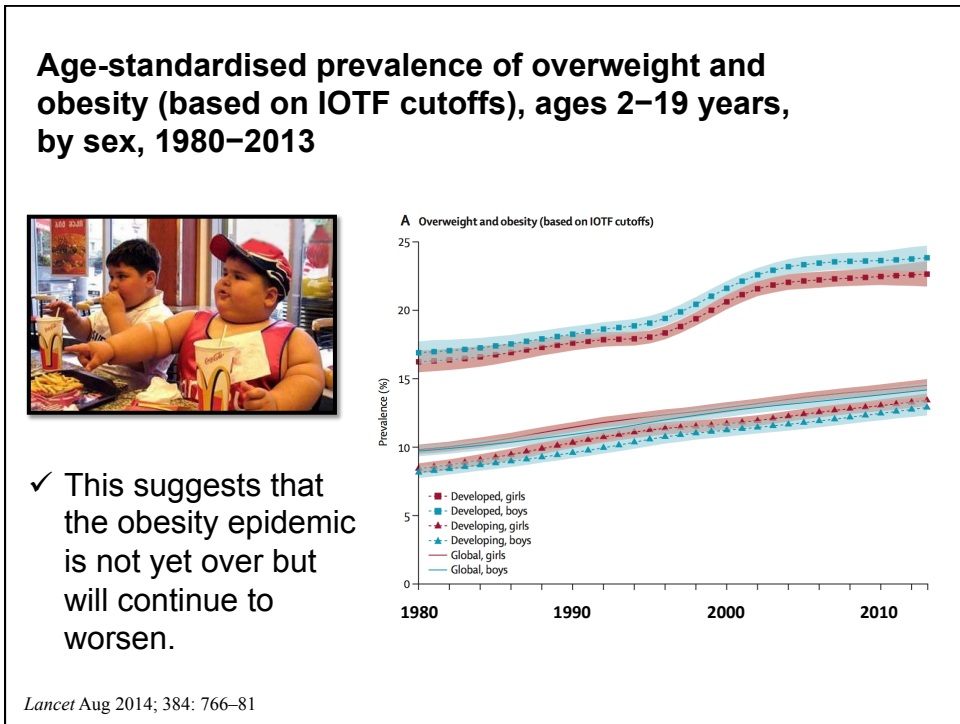
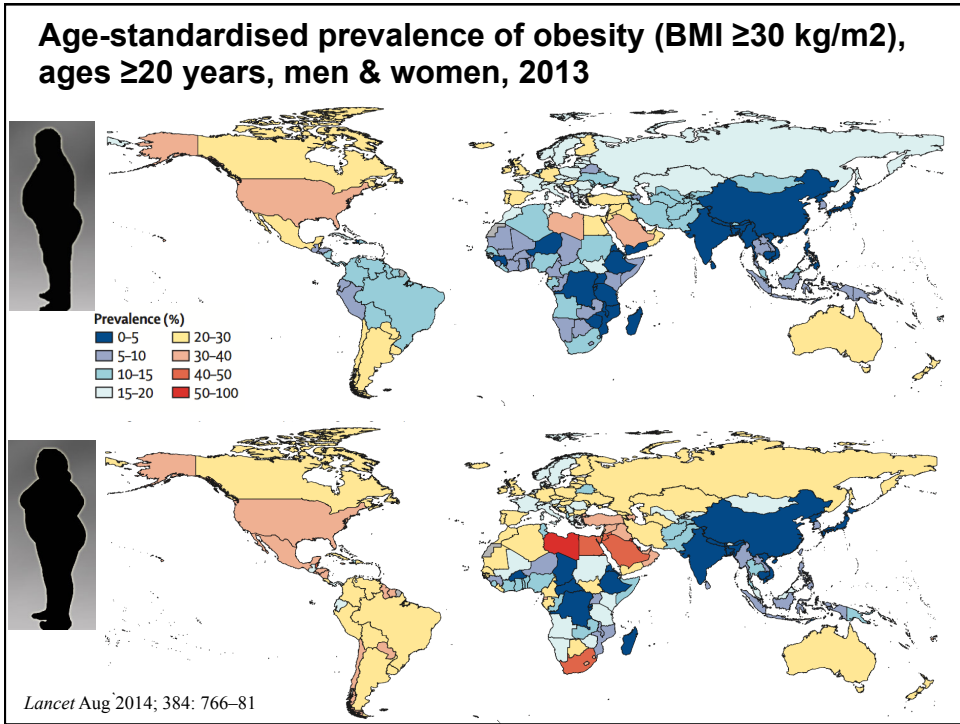


Obesity – an epidemic



- The incidence of obesity is increasing dramatically since the 1980's.
- Obesity is set to overtake infectious diseases as the most significant contributor to illness worldwide.
- Obesity has been classified as an *epidemic* by the World Health Organization.





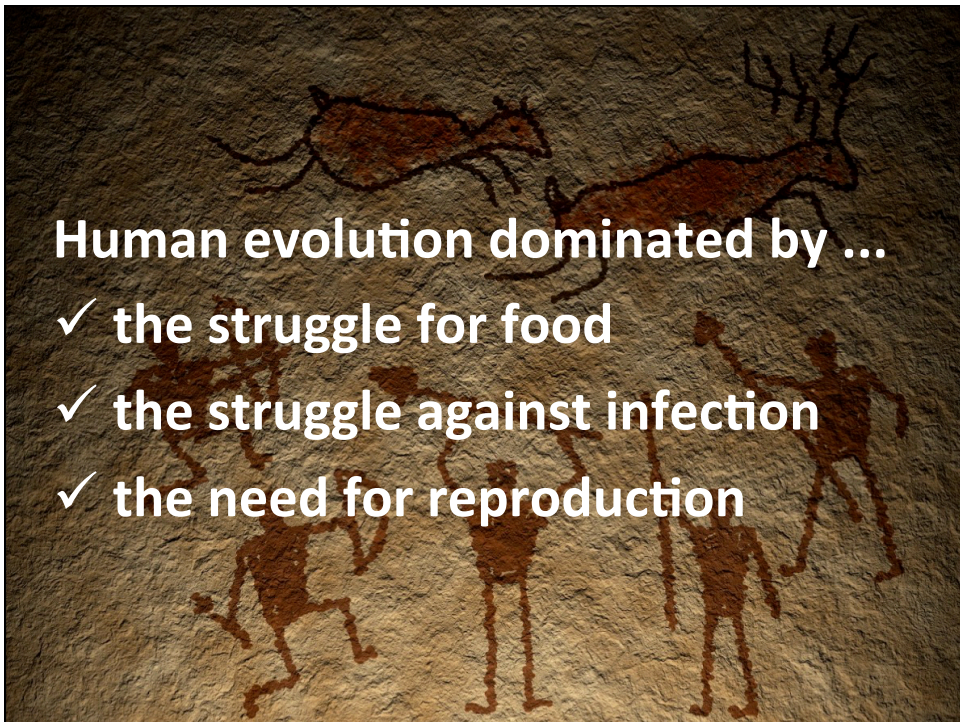
Obesity – to be in bad health



- Obesity is associated with numerous conditions including diabetes, hypertension, cardiovascular disease events, certain cancers etc.
- This translates into reduced life expectancy, poor quality of life and certainly drives healthcare costs.

Human evolution dominated by ...

- ✓ the struggle for food
- ✓ the struggle against infection
- ✓ the need for reproduction

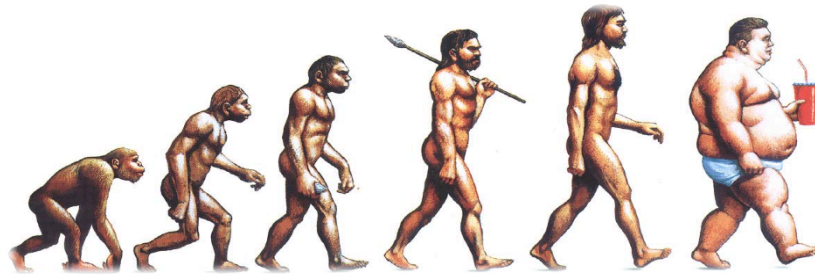


What are the reasons for that?

- Body weight and energy balance are important aspects of physiology and thus extremely finely regulated.
- Dieting induces compensatory “starvation” signals aiming to promote hunger and to sustain energy.
- This was a rationale strategy during the evolution of these homeostatic mechanisms – food shortage has been the norm.
- But not today when palatable and high energy density food is easily availability without having to expend energy.



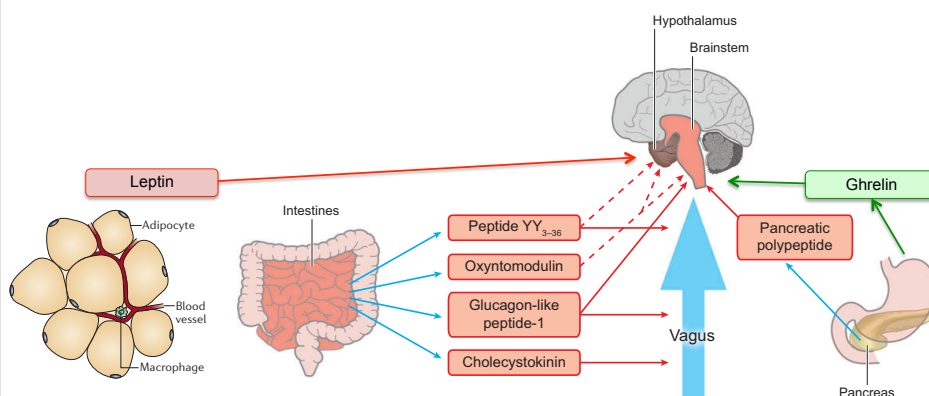
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So what are those signals involved in energy balance and where do they origin from?



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Modified from Chaudri OB et al. *Annu Rev Physiol* 2008; 70: 239–55

The Phylogenetic Tree of Life



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BACTERIA 

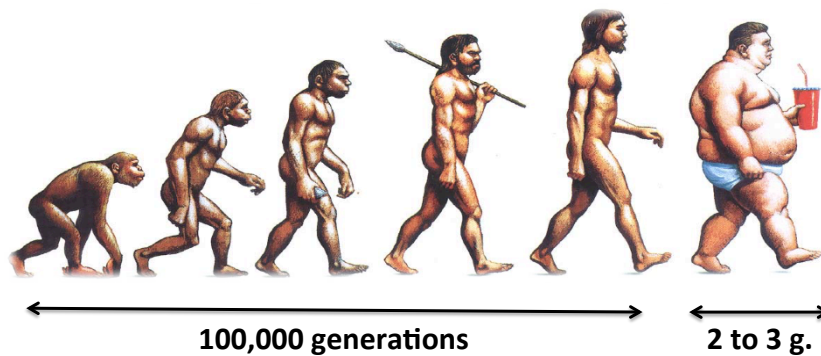
Man = a „supra-organism“
Microbiome = part of our genetic landscape
= the human metagenome

Heiobacterium
Amrobacter
pOPC19
...
ARCHAEA

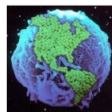
Important facts:
50% of stool solid mass = bacteria
bacterial outnumber human cells by factor 10 to 100
> 400 species, most non-cultureable
Yet: also archaea, fungi, protists, and virus

EUCARYA
Diphy
...
Eukaryota

***A co-evolution since the very beginning
accounts for a high grade of mutualism***

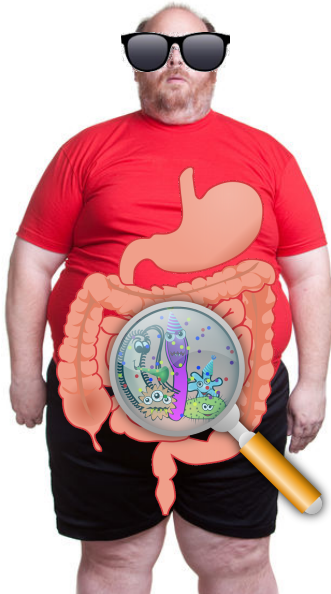


Bacterial
World ...



... a virtual organ
within an organ.

Obesity is associated with dysbiosis



- Disturbance of the mutualistic relationship with stereotypic alterations
- *Low Species Richness* und *Low Gene Count* (LGC)
- Reduction of certain “signature” strains e.g. *Faecalibacterium prausnitzii*
- Low grade inflammation on the host side

Hypothesis: the microbiota affects the host's energy storages through distinct signaling pathways



Germ-free
GF



Conventional
CONV-D



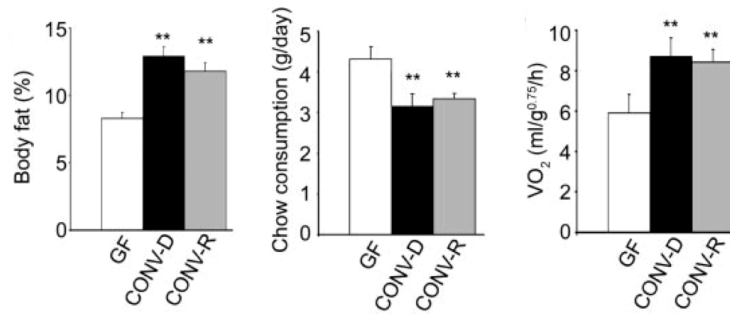
GF - conventionalized
CONV-R

Bäckhed et al. PNAS 2004; 101:15718–23.

The microbiota affects energy storage

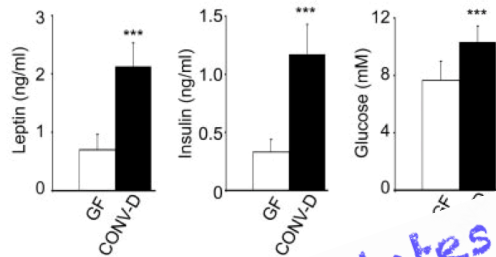


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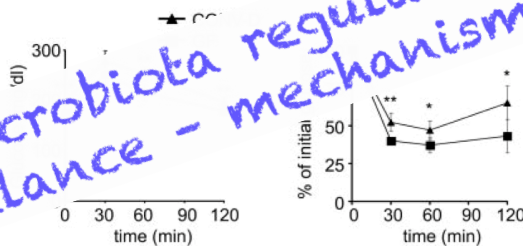
- Conventionalization of 7-10 week old GF mice resulted in a 60% increase
- within 14 days despite reduced chow consumption
- No differences between males and females
- Independently of T- and B-cell biology (Rag 1^{-/-})

Bäckhed et al. PNAS 2004; 101:15718–23.



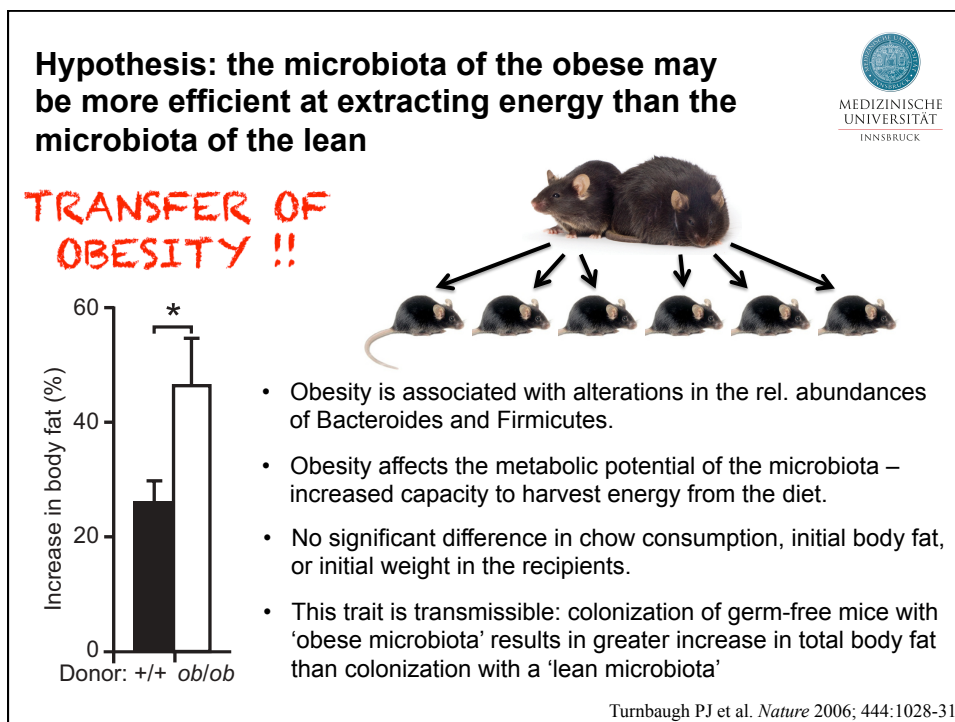
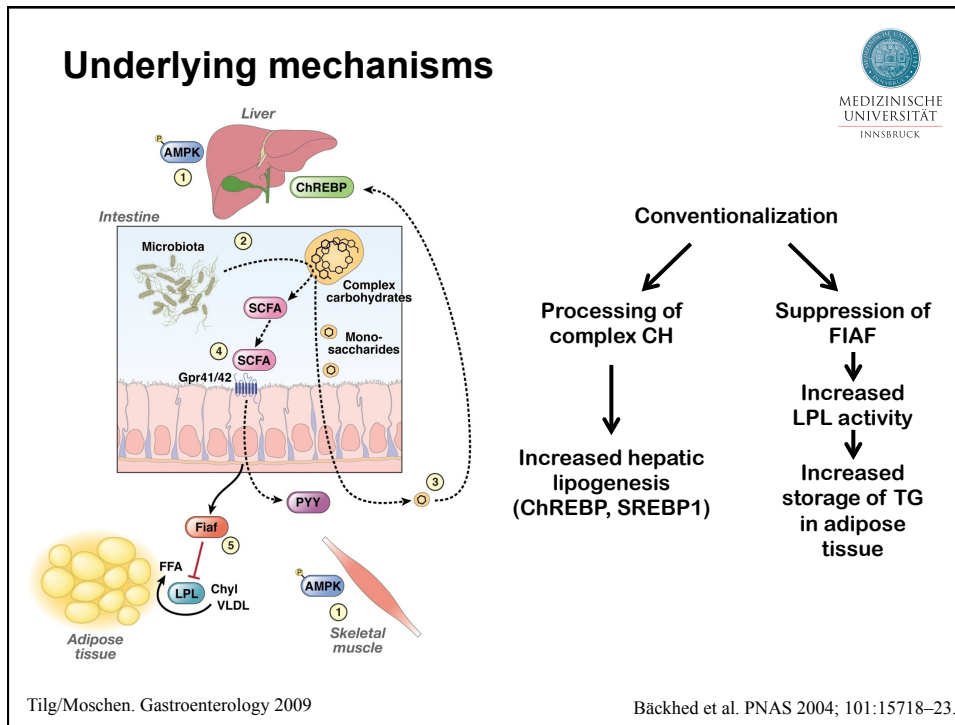
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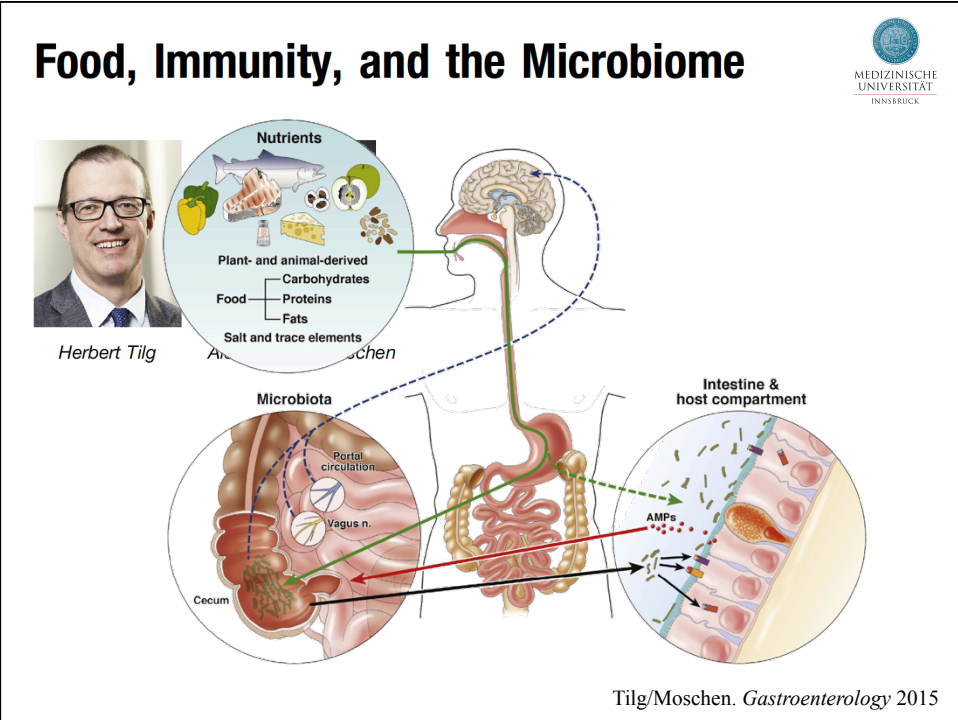
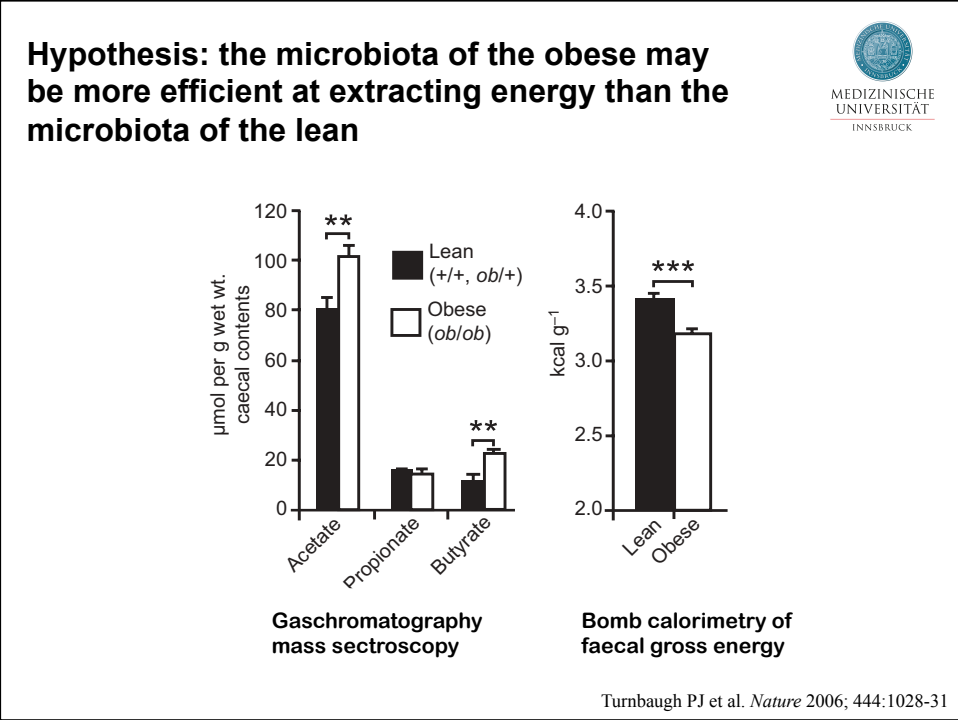
The microbiota regulates energy balance - mechanisms ?

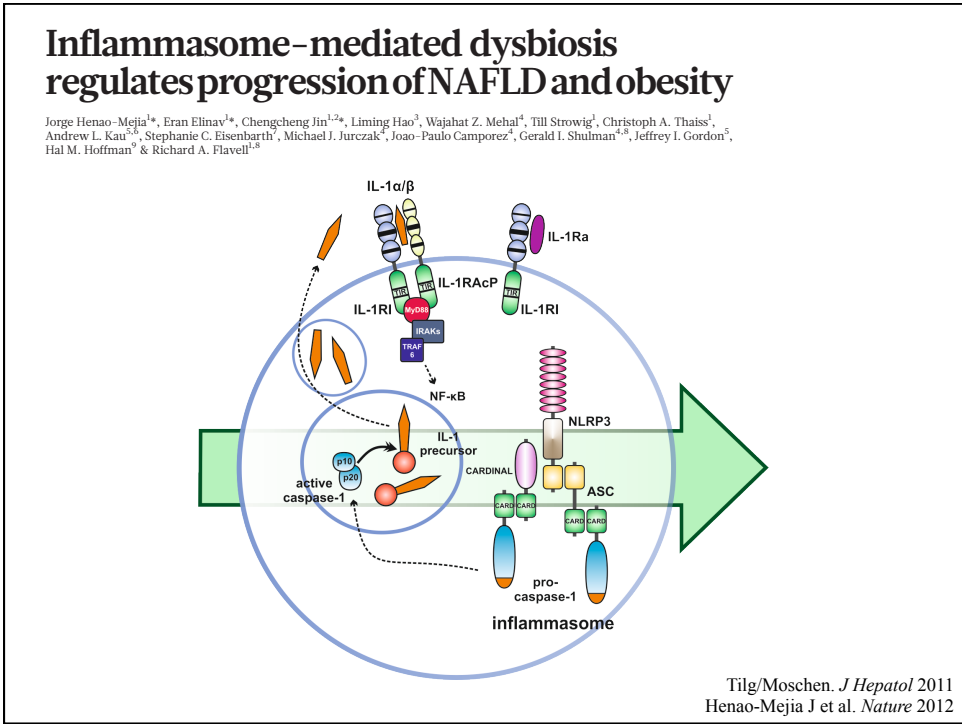
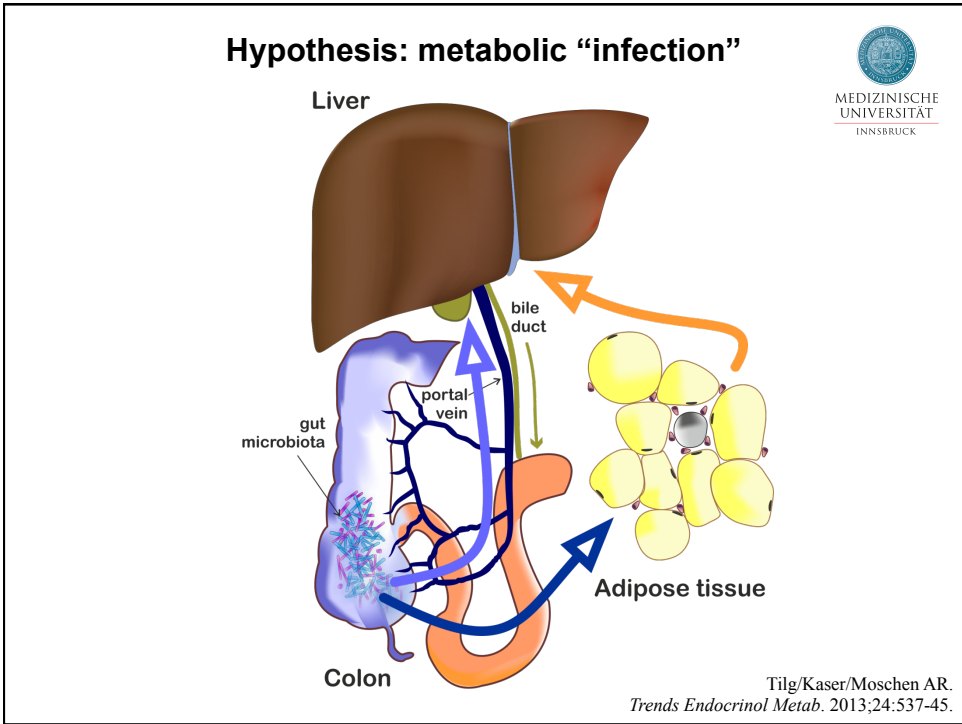


- increases circulating leptin, insulin, and glucose levels
- reduced glucose tolerance
- increased insulin resistance

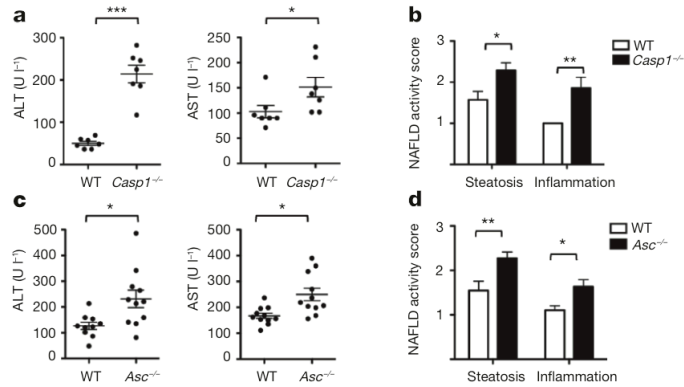
Bäckhed et al. PNAS 2004; 101:15718–23.







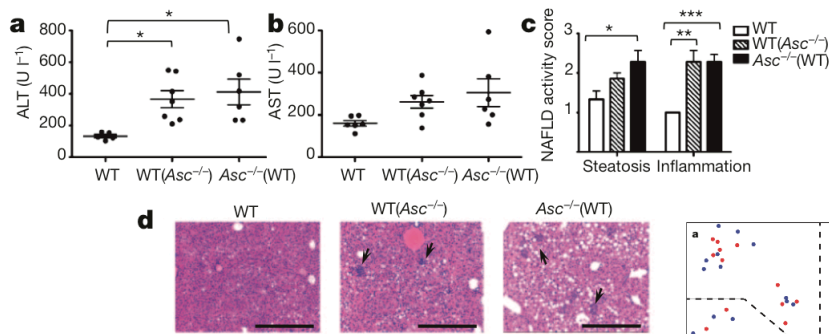
Increased severity of NASH in inflammasome-deficient mice.



First set of experiments: Casp1, Asc, Nlrp3, IL-18 knockout.

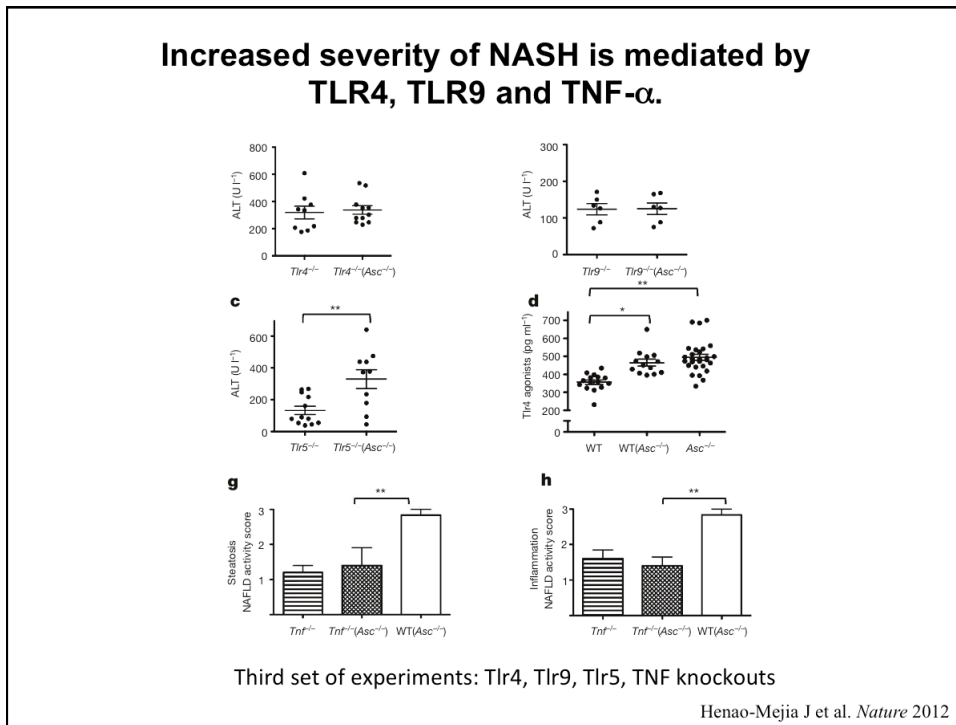
Henao-Mejia J et al. *Nature* 2012


Increased severity of NASH is transmissible to co-housed WT animals.



Second set of experiments (co-housing): Asc and IL-18 ko


Henao-Mejia J et al. *Nature* 2012

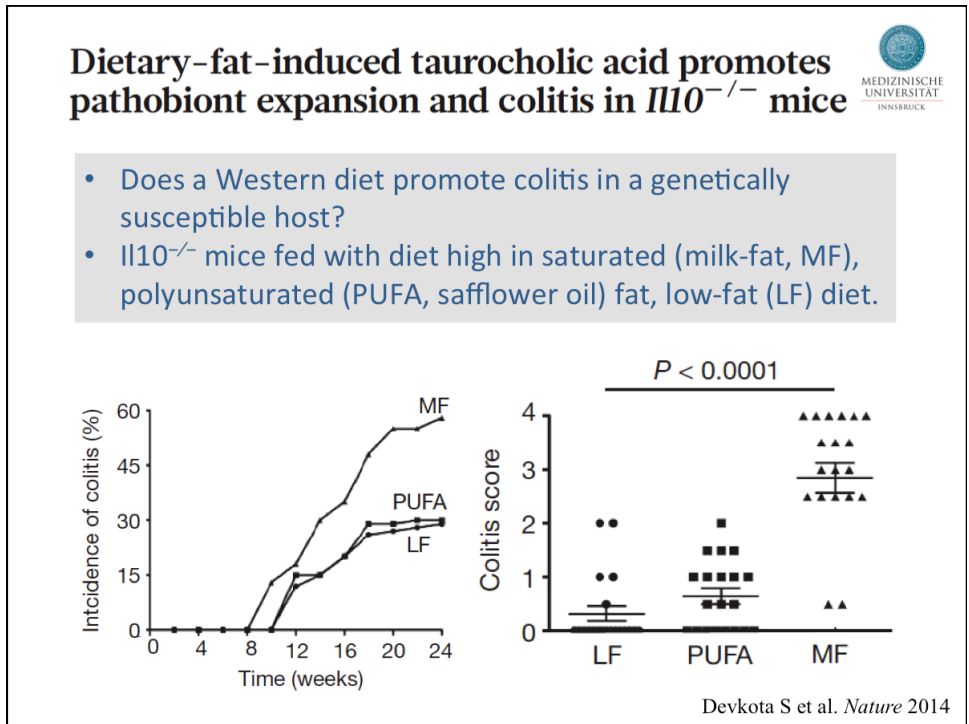
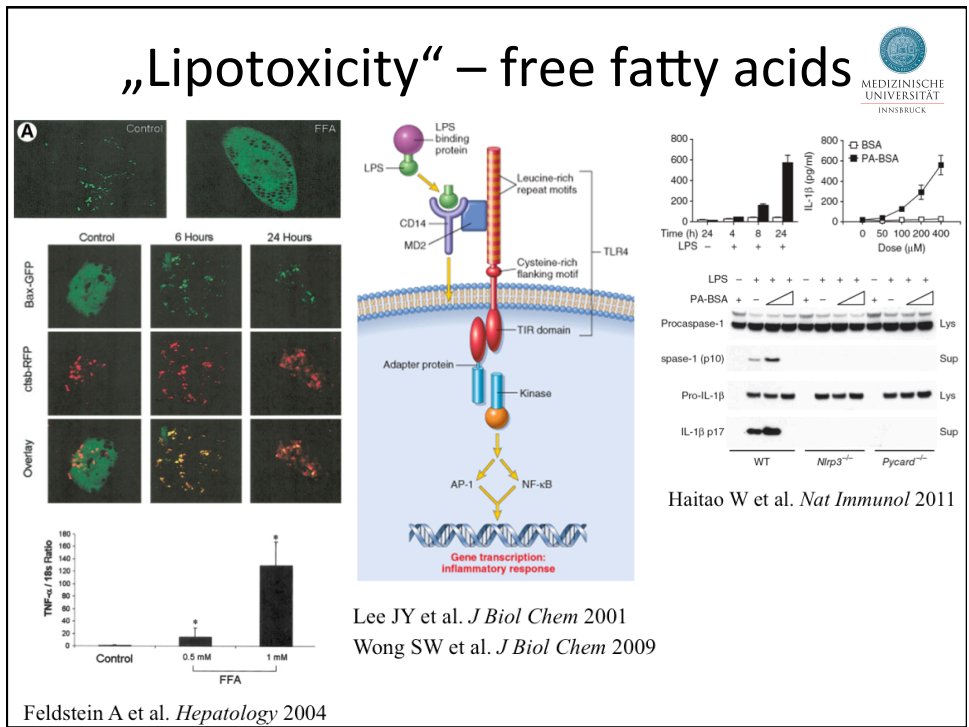


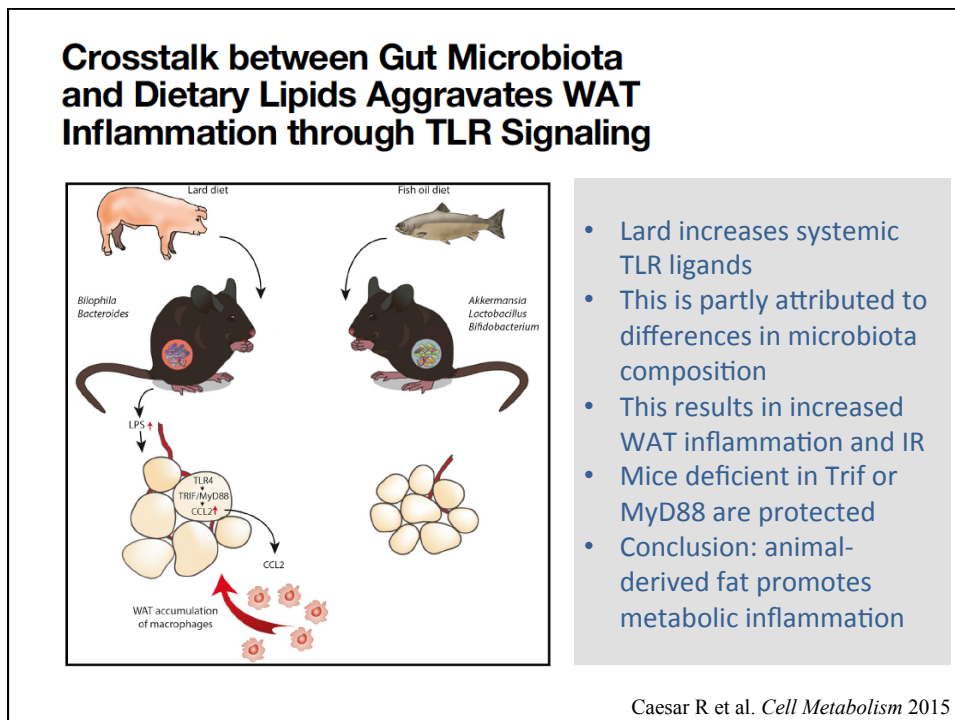
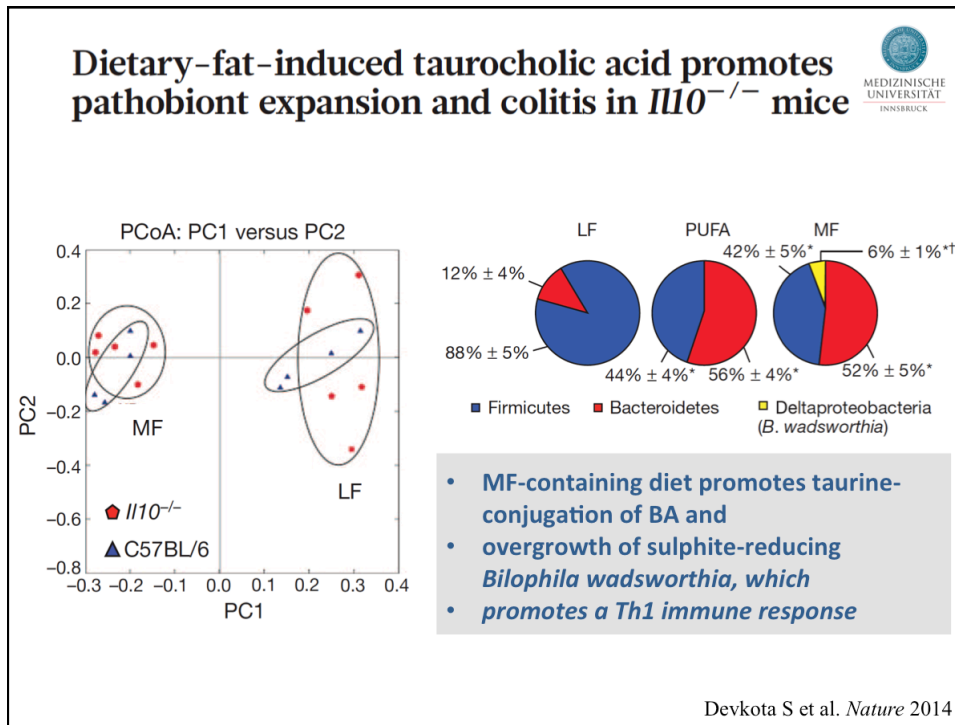


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Does food trigger inflammation? (Pro-inflammatory mechanisms)







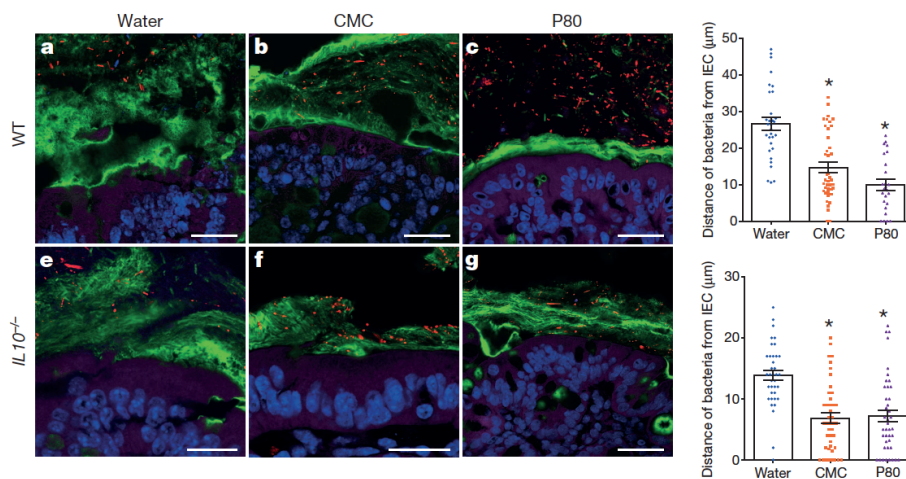
Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome



- 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

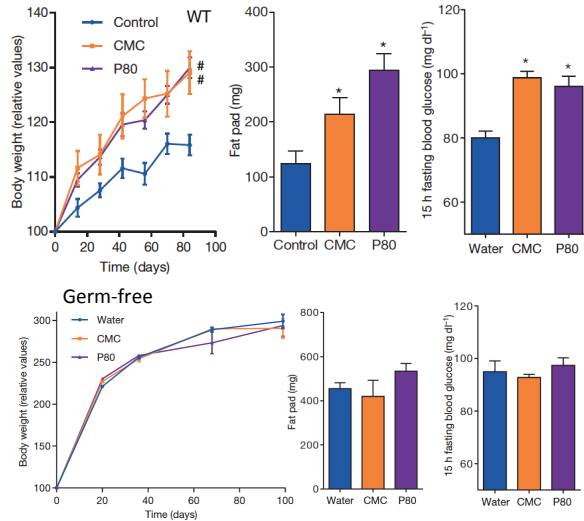
Chassaing B et al. *Nature* 2015

Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome



Chassaing B et al. *Nature* 2015

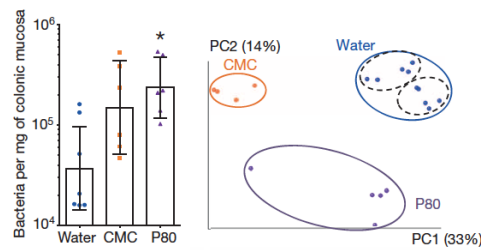
Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome



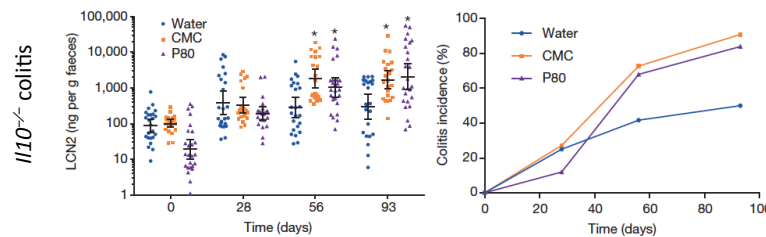
- SW mice were exposed to PS80 or CMC via the drinking water
- Dietary emulsifiers promote weight gain
- fat acquisition
- and insulin resistance
- This effect is dependent on the microbiota

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



A

Cruciferous vegetables (broccoli, cabbage, and brussels sprouts)

Indole[3,2-b]carbazole

6-Formylindole[3,2-b]carbazole

Gastric acid

B

Cell membrane

ABR

Chaperone

Cytoplasm

Arnt

Nucleus

AKR

AKR-regulated genes

DNA

C

Parietal cells

Stem cell

Basement membrane

Specialized intraepithelial lymphocytes

Goblet cell

Mucus

Antimicrobial peptides

Defenses

Mucus

Goblet cell

Paneth cells

Stem cell

Tissue regeneration and repair

CD4⁺CD45^{RO}⁺ Intestinal lymphoid cells

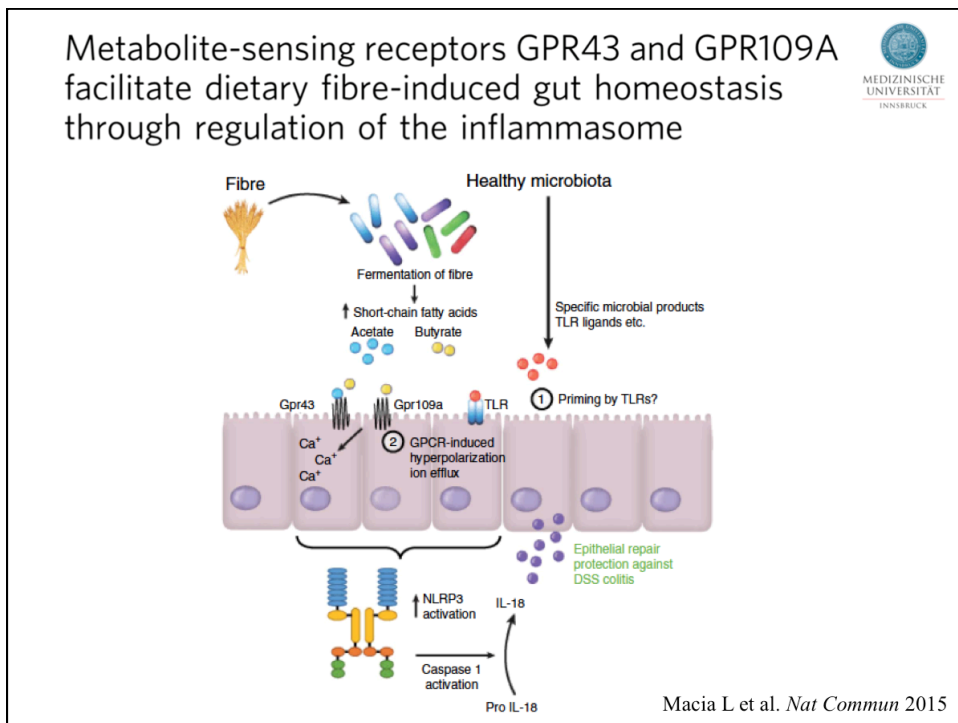
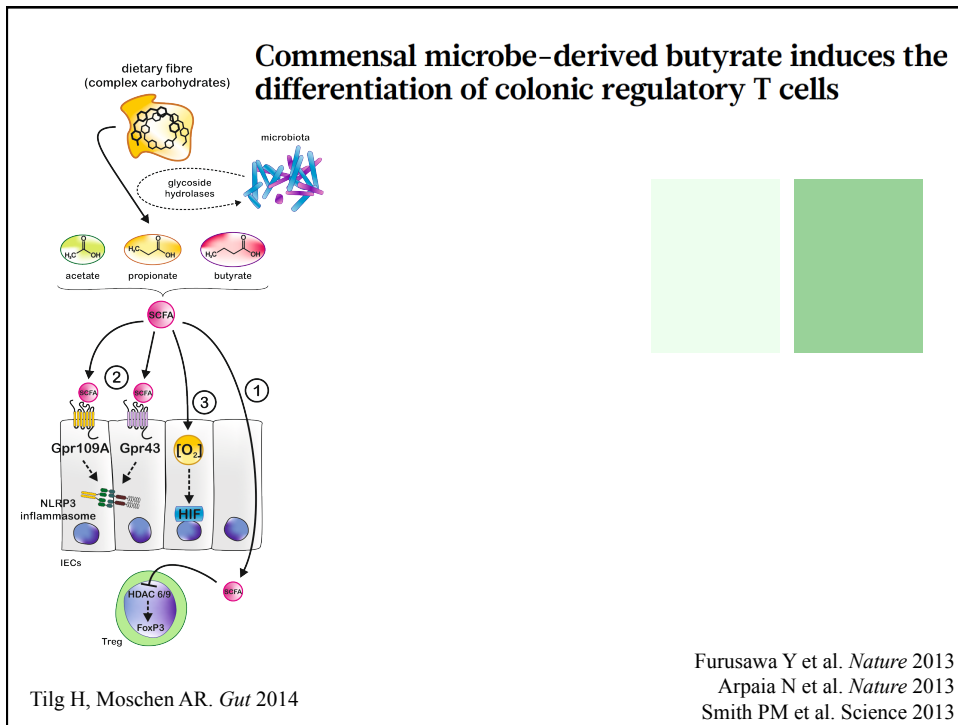
Interleukin-22

• Let's eat Broccoli ;-)

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Tilg H. *N Engl J Medicine* 2012
Li Y et al. *Cell* 2011
Kiss E et al. *Science* 2011

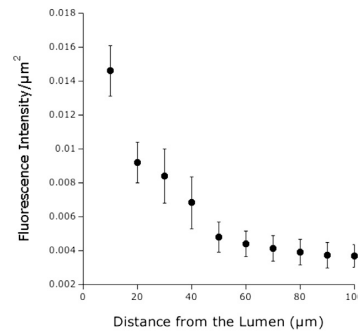
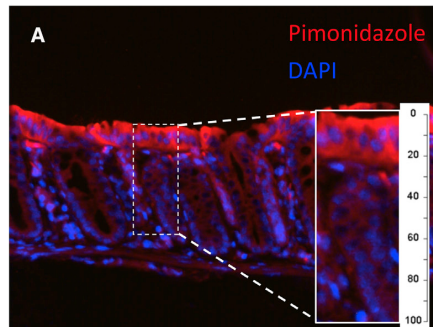




Crosstalk between Microbiota-Derived Short-Chain Fatty Acids and Intestinal Epithelial HIF Augments Tissue Barrier Function

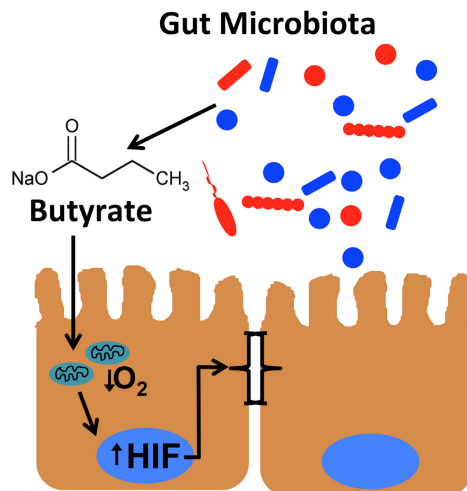


- SCFA particularly butyrate serves as the preferred metabolic substrate for IEC
- Is there an impact on epithelial oxygen consumption?

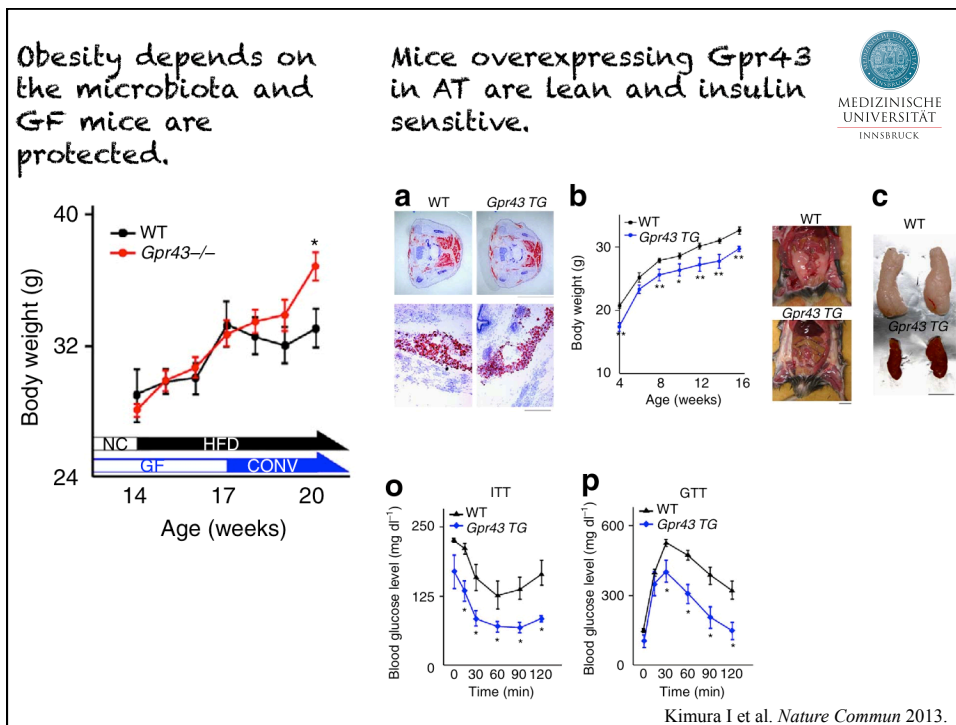
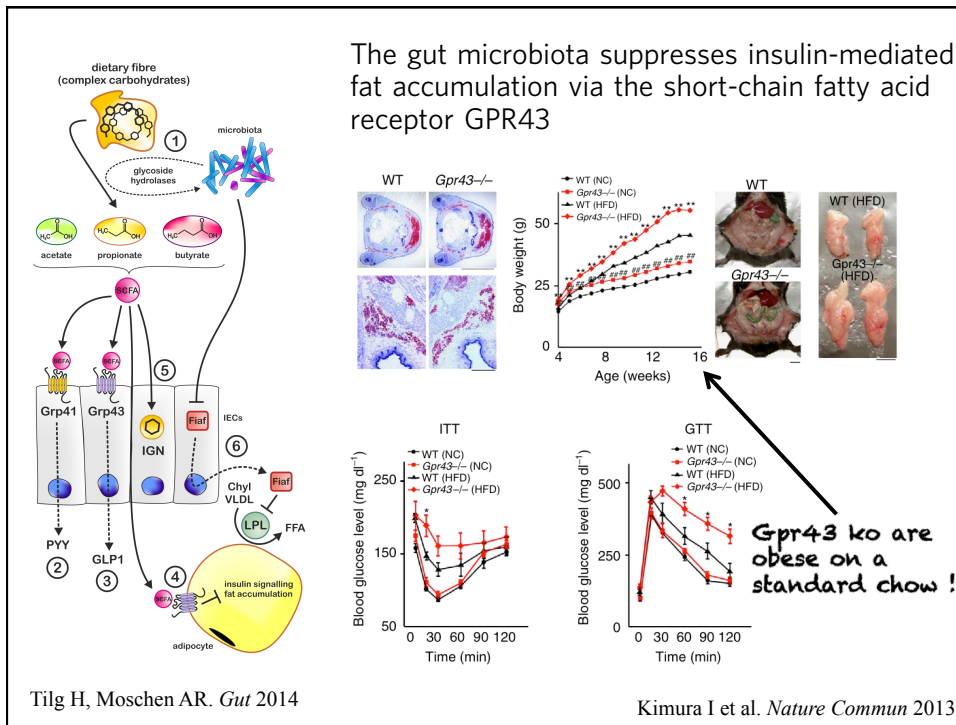


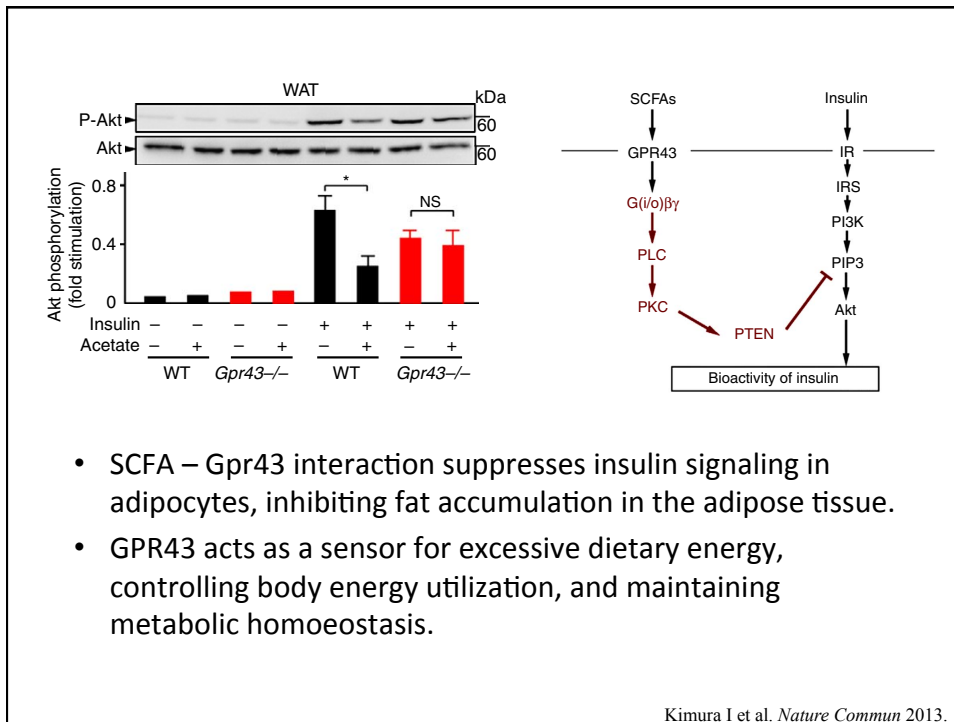
Kelly CJ et al. *Cell Host & Microbe* 2015

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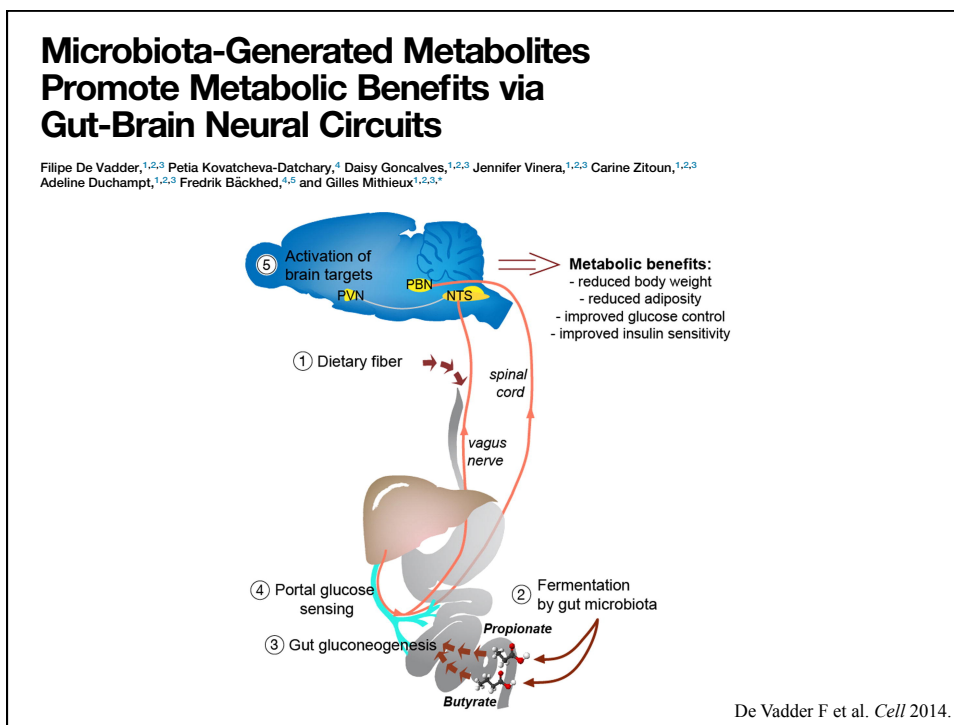



Kelly CJ et al. *Cell Host & Microbe* 2015





- SCFA – Gpr43 interaction suppresses insulin signaling in adipocytes, inhibiting fat accumulation in the adipose tissue.
- GPR43 acts as a sensor for excessive dietary energy, controlling body energy utilization, and maintaining metabolic homoeostasis.





**You „AhR“ what you eat?
You are what you host?**

- The gut microbiota represents a key factor in regulating hepatic steatosis, metabolic syndrome, insulin resistance and diabetes.
- Diet is the key „environmental factor“ modulating body weight and gut microbiota
- So far multiple mechanisms implicated: TLRs, inflammasomes, Fiaf, SCFA, AMPK, ChREBP, cytokines, ER stress, BA – FXR, ...



Open questions

- Significant lack of clinical data
- What is the optimal / most feasible way of targeting the microbiota in IBD?
- Is it FMT or next generation probiotics?
- Is it targeting specific „pathobionts“?
- Could dietary interventions modify the microbiota compositions and immunity beneficially?

