Role of intestinal microbiota in gastrointestinal performance

Innovative health-promoting food

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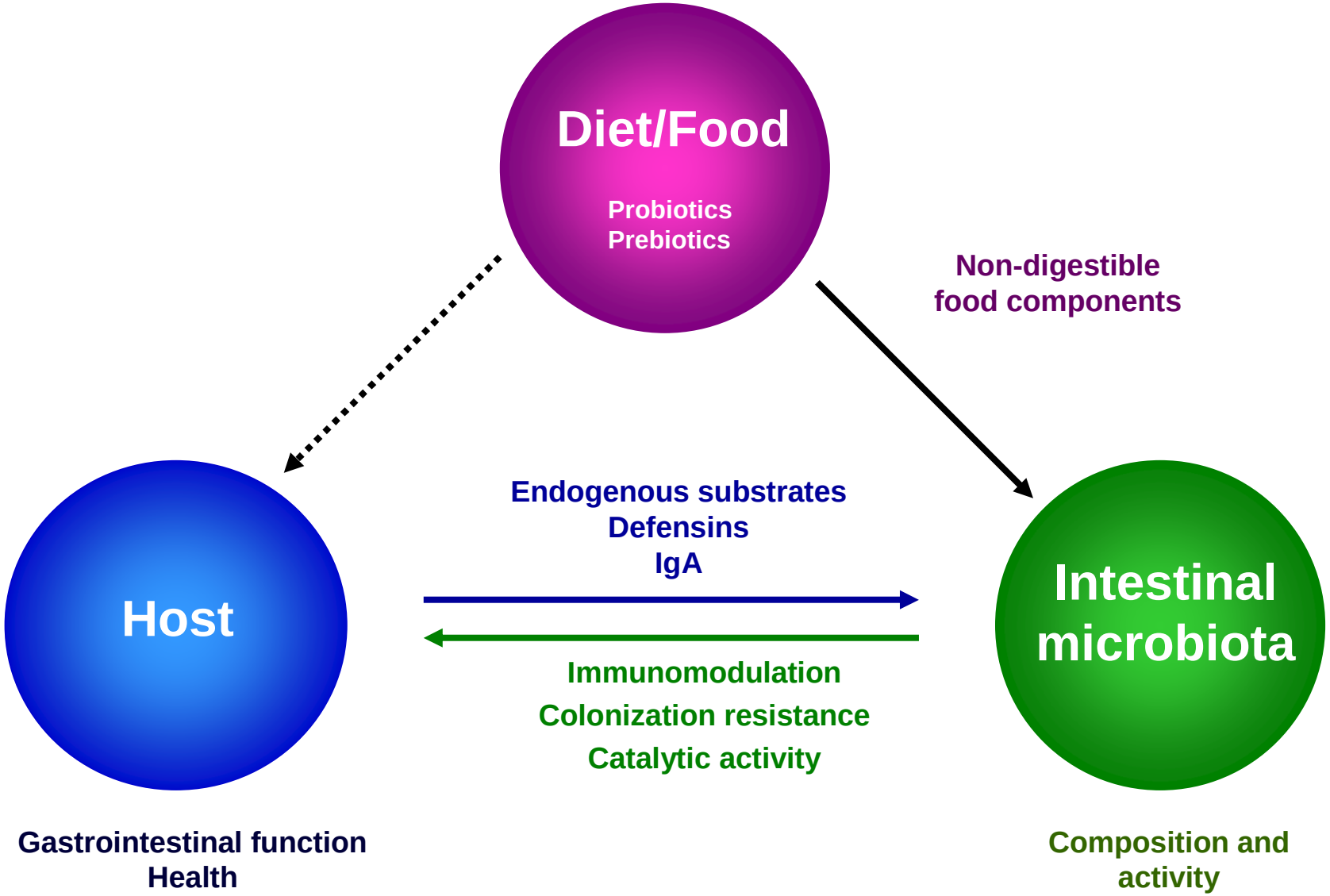
Leibniz Gemeinschaft

Dietary effects mediated by the gut microbiota



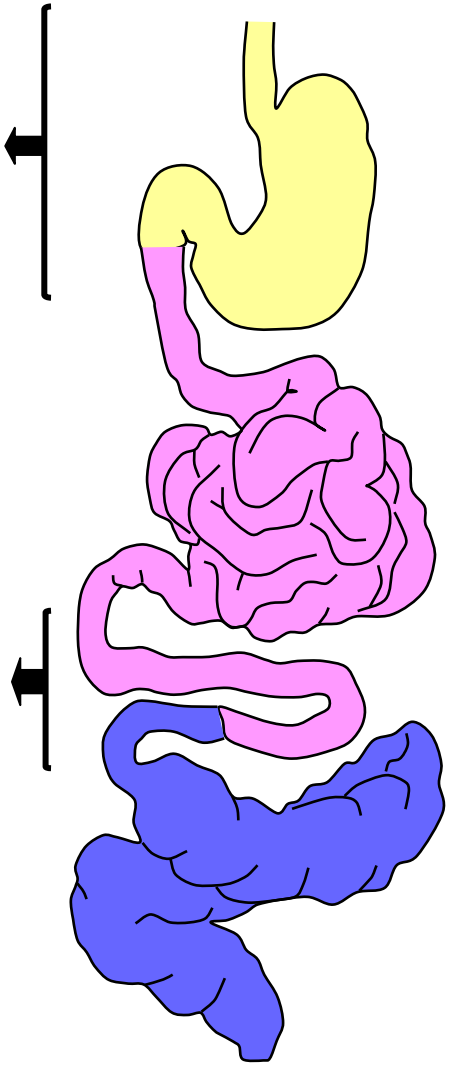
The gastro-intestinal microbiota

Stomach:
10^{0}-10^{3} cfu ml^{-1}

Lactobacillus
Streptococcus
Staphylococcus
Enterobacteriaceae

Ileum and Caecum:
10^{3}-10^{9} cfu ml^{-1}

Bifidobacterium
Bacteroides
Lactobacillus
Streptococcus
Enterobacteriaceae
Staphylococcus
Clostridium



Duodenum and Jejunum:
10^{2}-10^{5} cfu ml^{-1}

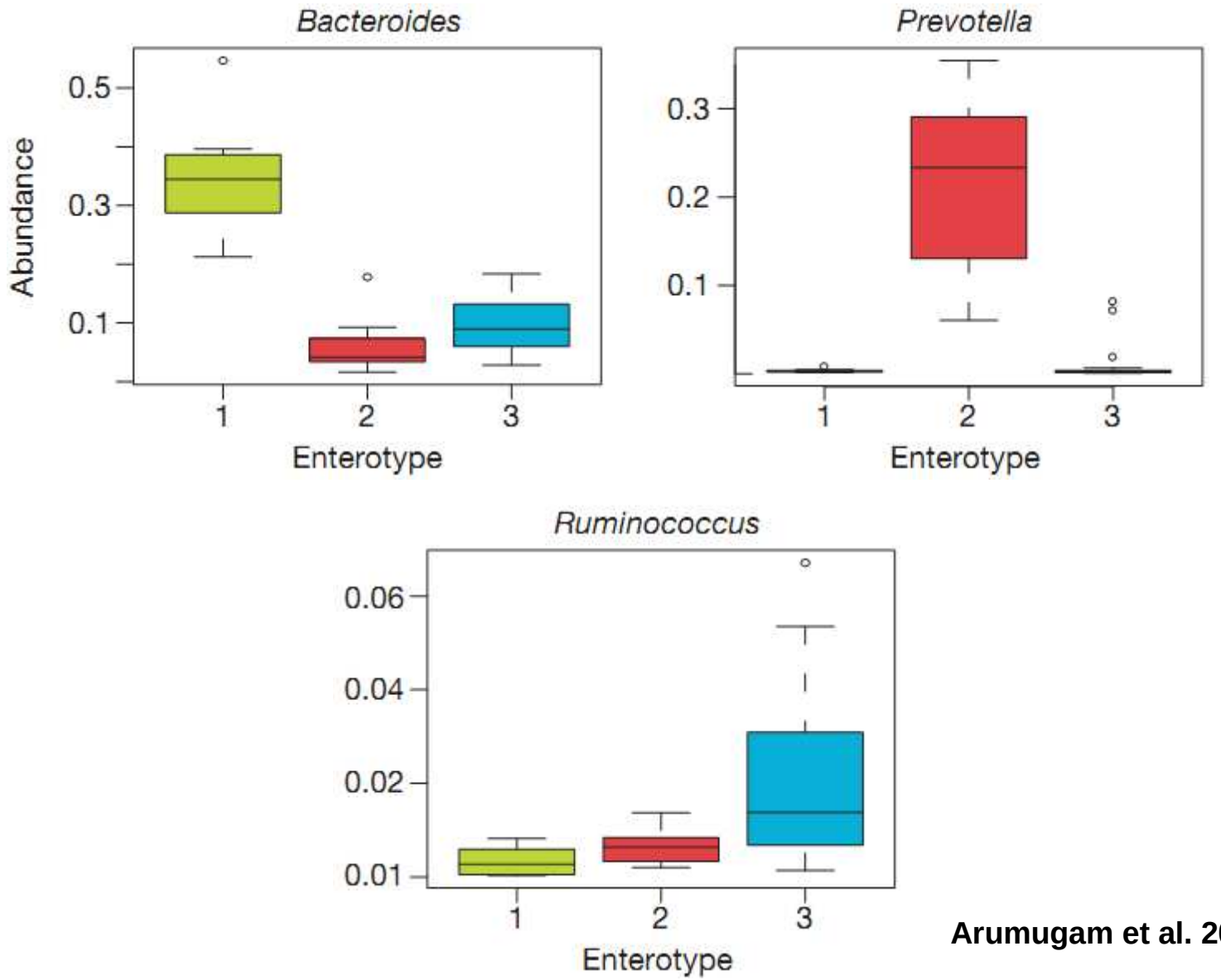
Lactobacillus
Streptococcus
Bifidobacterium
Enterobacteriaceae
Staphylococcus

Colon:
10^{10}-10^{12} cfu g^{-1}

Bacteroides
Eubacterium
Clostridium
Peptostreptococcus
Streptococcus
Bifidobacterium
Fusobacterium
Lactobacillus
Enterobacteriaceae
Staphylococcus

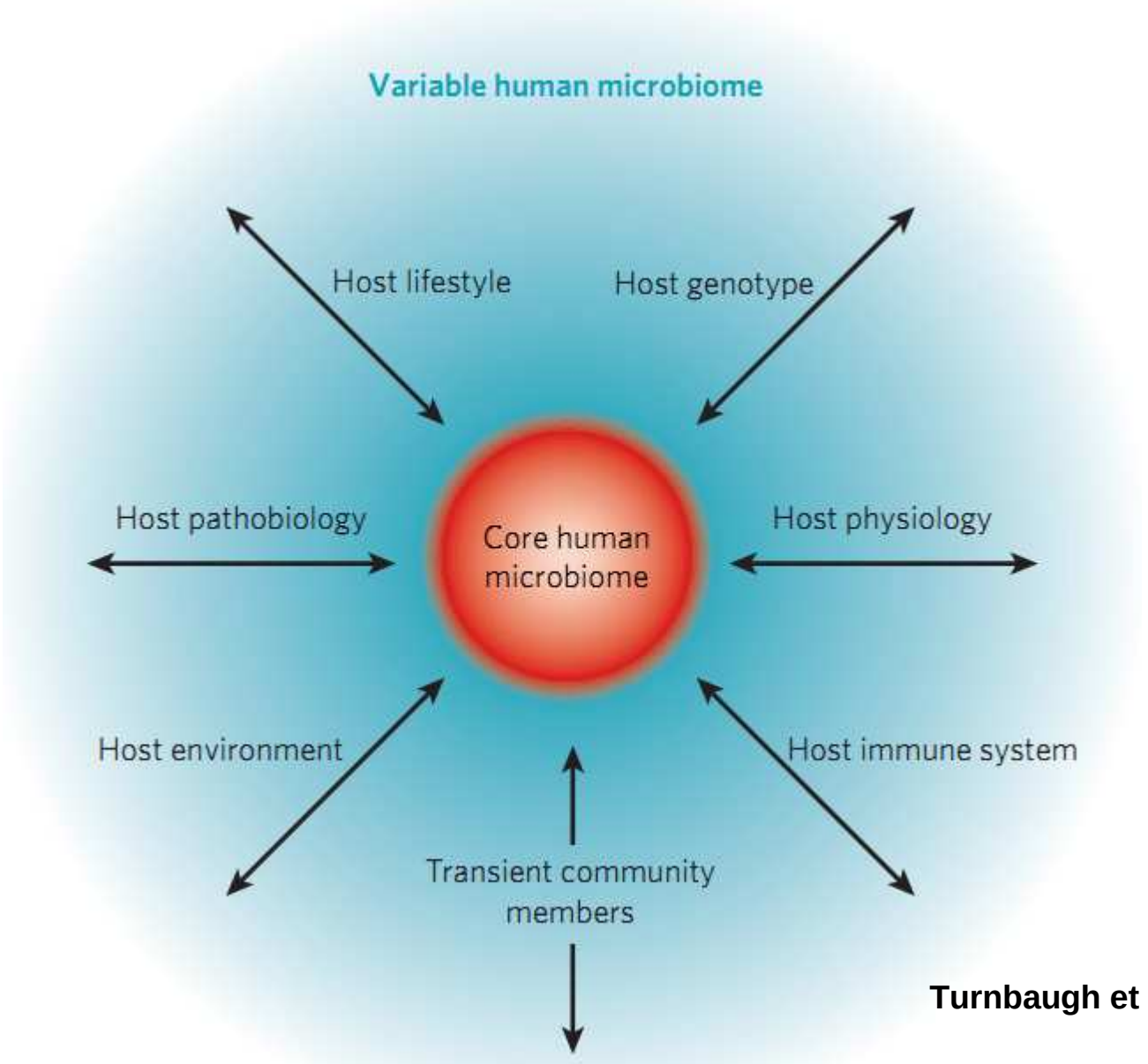
cfu = colony forming units

Three enterotypes have been found in humans



Arumugam et al. 2011. Nature

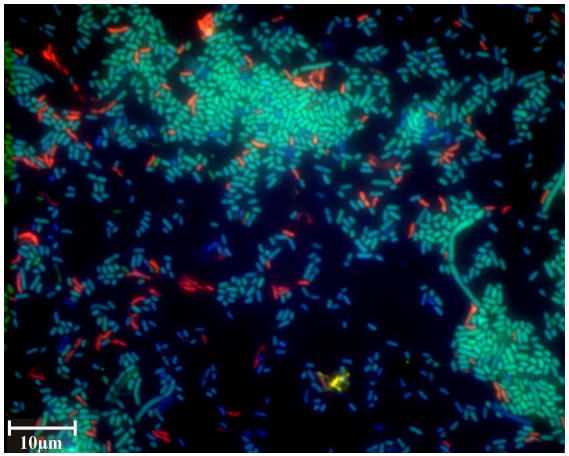
Microbiome concept

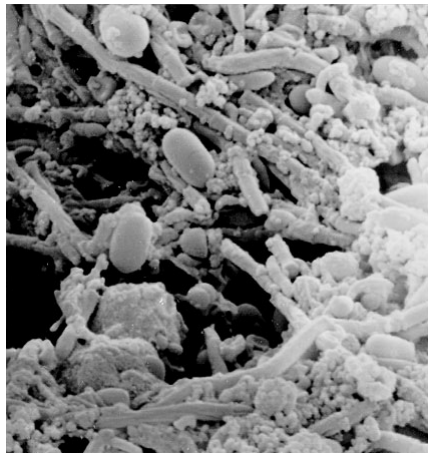


Turnbaugh et al. 2007. Nature

Characteristics of the human intestinal microbiota

- Up to 10^{14} cells (10^{13} body cells)
- High diversity (>400 species; many undescribed)
- 100-fold more bacterial than host genes
- High individual variability
- Great metabolic potential
- Predominantly anaerobic metabolism

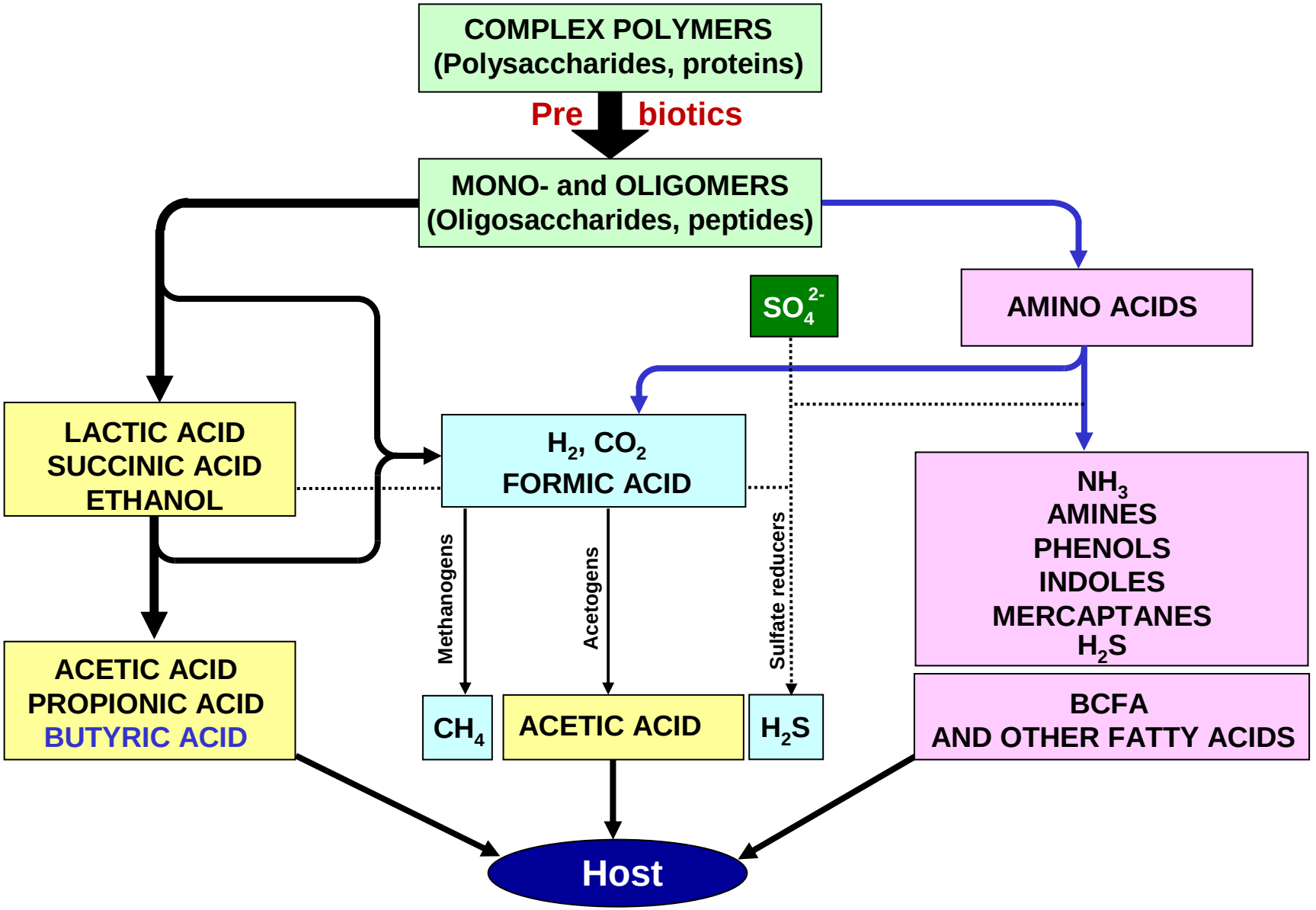




Functions of the gut microbiota

- Conversion of dietary fibre to short chain fatty acids
- Conversion of host compounds (mucins, bile acids)
- Conversion of xenobiotics
- Colonization resistance
- Modulation of host functions

Breakdown of complex polymers by intestinal bacteria



Definition of prebiotics

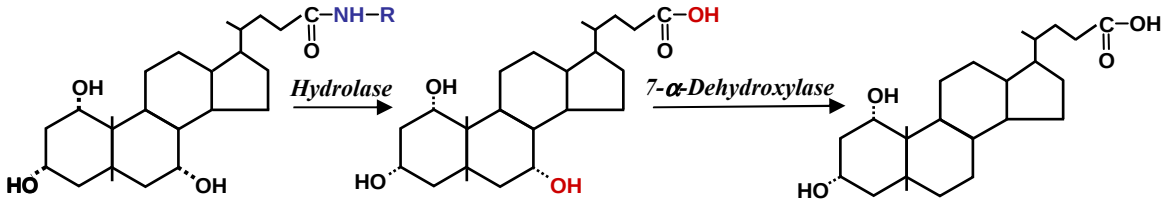
"A prebiotic is a non-viable food component that confers a health benefit on the host associated with modulation of the microbiota"

Food and Agriculture Organization of the United Nations (2007)

Substrates of the gut microbiota

Endogenous substrates (host-derived)

- Mucins and other glycoproteins
- Digestive enzymes
- Bile acids



Conjugated cholic acid | Cholic acid | Deoxycholic acid

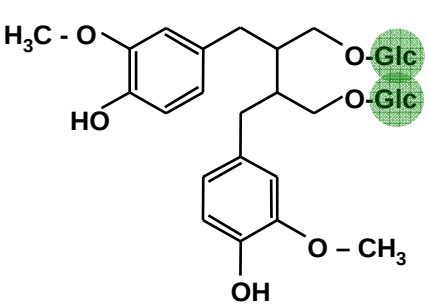
Dietary substrates

- Polysaccharides (dietary fibre, resistant starch)
- Non absorbable sugars and sugar alcolhols
- Dietary proteins
- Non-nutritive secondary plant metabolites

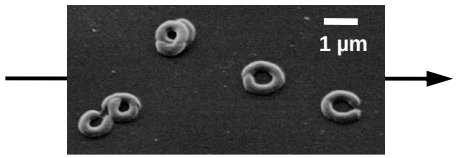
All substances that escape digestion in the small intestine are potential substrates of the colonic microbiota

Gut bacteria activate bioactive food components

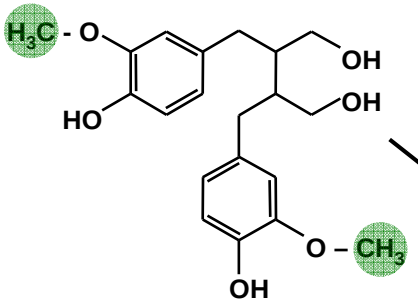
Activation of lignans



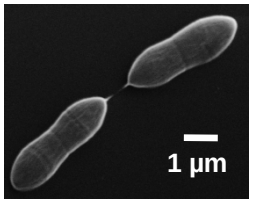
Secoisolariciresinol diglucosid (SDG)



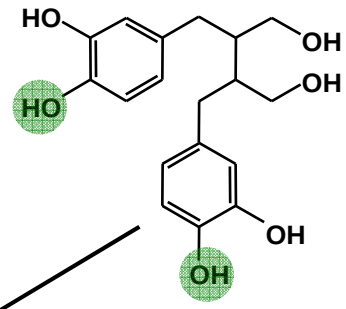
Clostridium saccharogumia



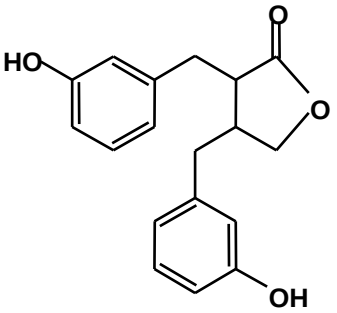
Secoisolariciresinol



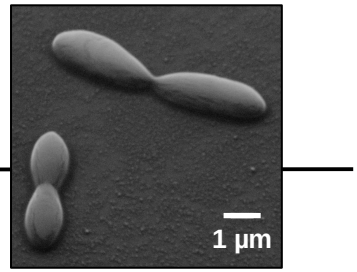
Blautia producta



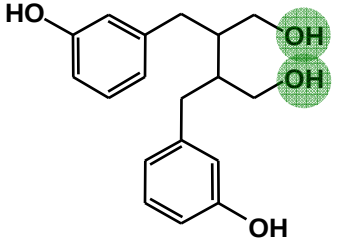
Clavel et al. (2005) Appl Environ Microbiol
Clavel et al. (2006) Anaerobe
Clavel et al. (2006) FEMS Microbiol Ecol
Clavel et al. (2007) Syst Appl Microbiol



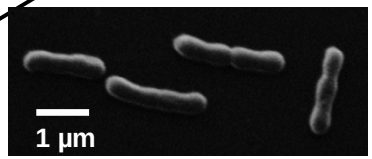
Enterolacton



Lactonifactor longoviformis

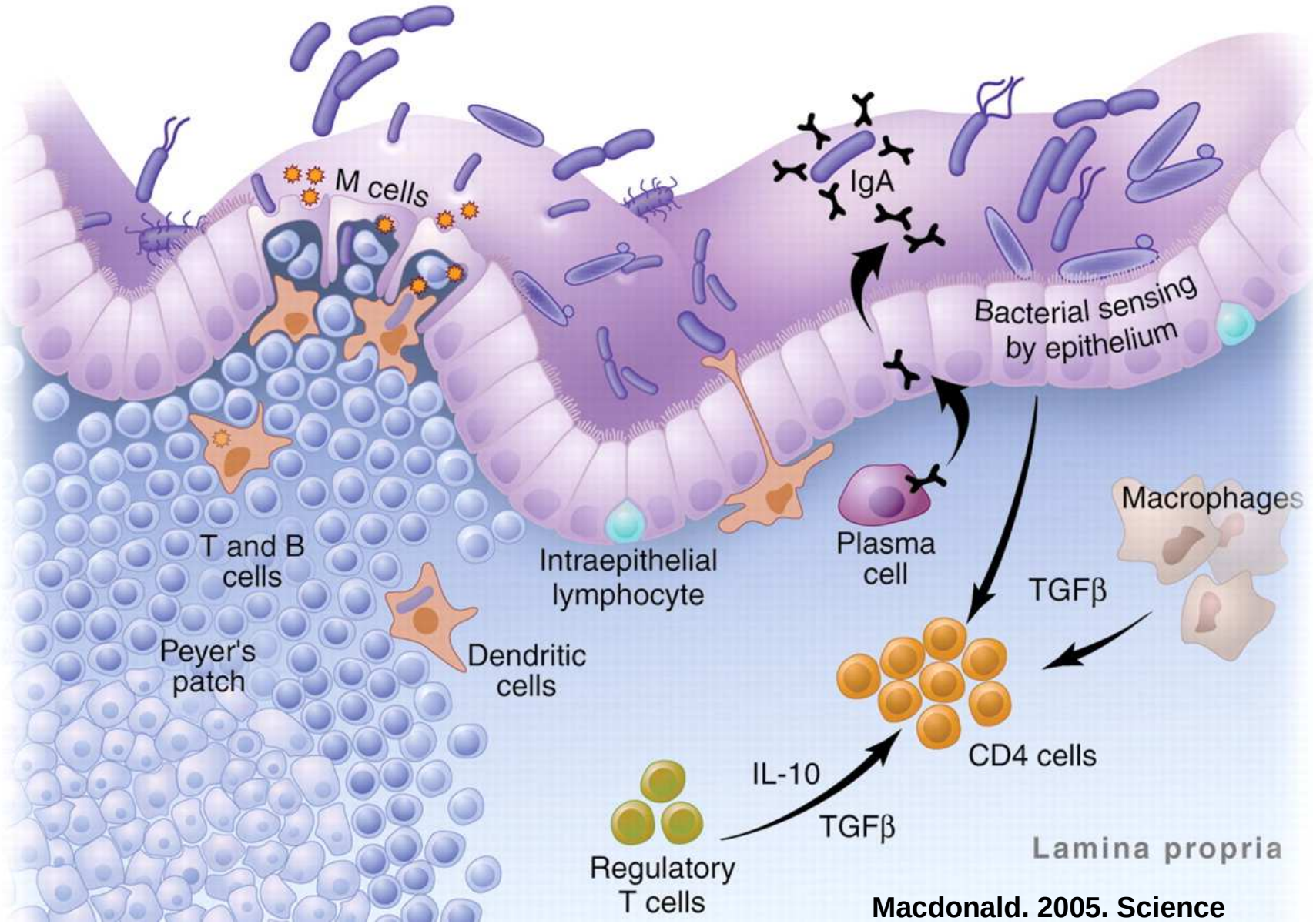


Enterodiol



Eggerthella lenta

Gut bacteria and mucosal immune system

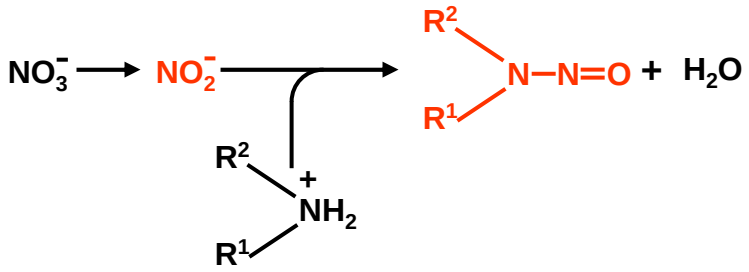


Macdonald. 2005. Science

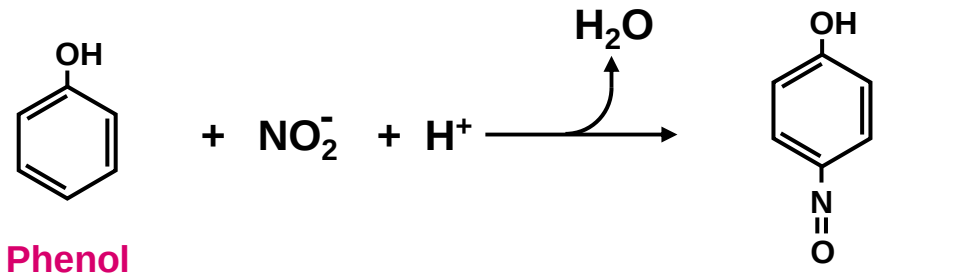
Formation of genotoxic substances

Examples:

Intestinal bacteria are capable of converting secondary amines to carcinogenic *N*-nitroso compounds:



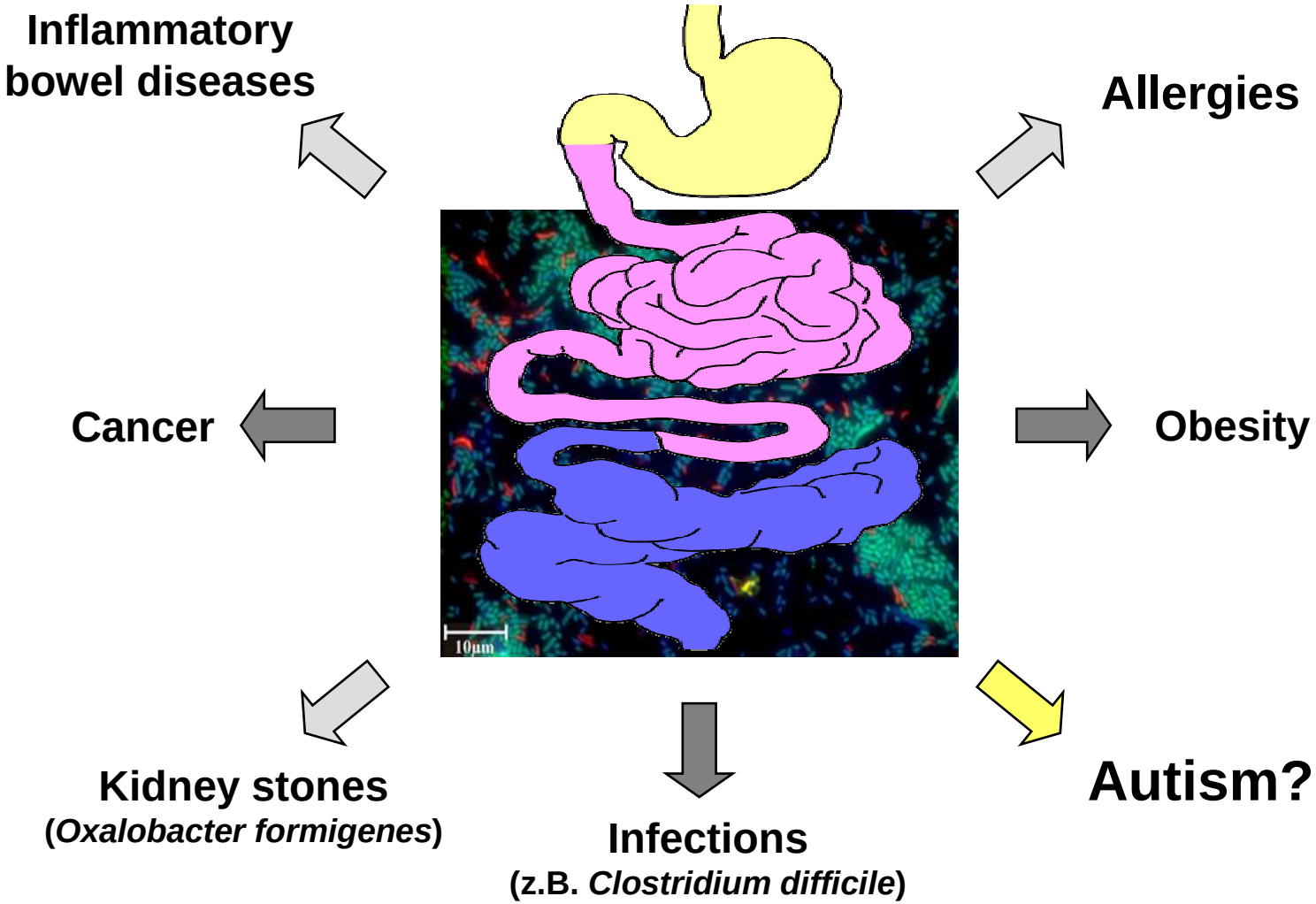
Reaction of phenol with nitrite produces *p*-nitrosophenol and *p*-diazoquinone, both of which are cancerogenic [Kikugawa, 1988, Food Chem Toxicol]:



Phenol

***p*-Nitrosophenol**

Gut microbiota and disease



Dietary manipulation of the gut microbiota

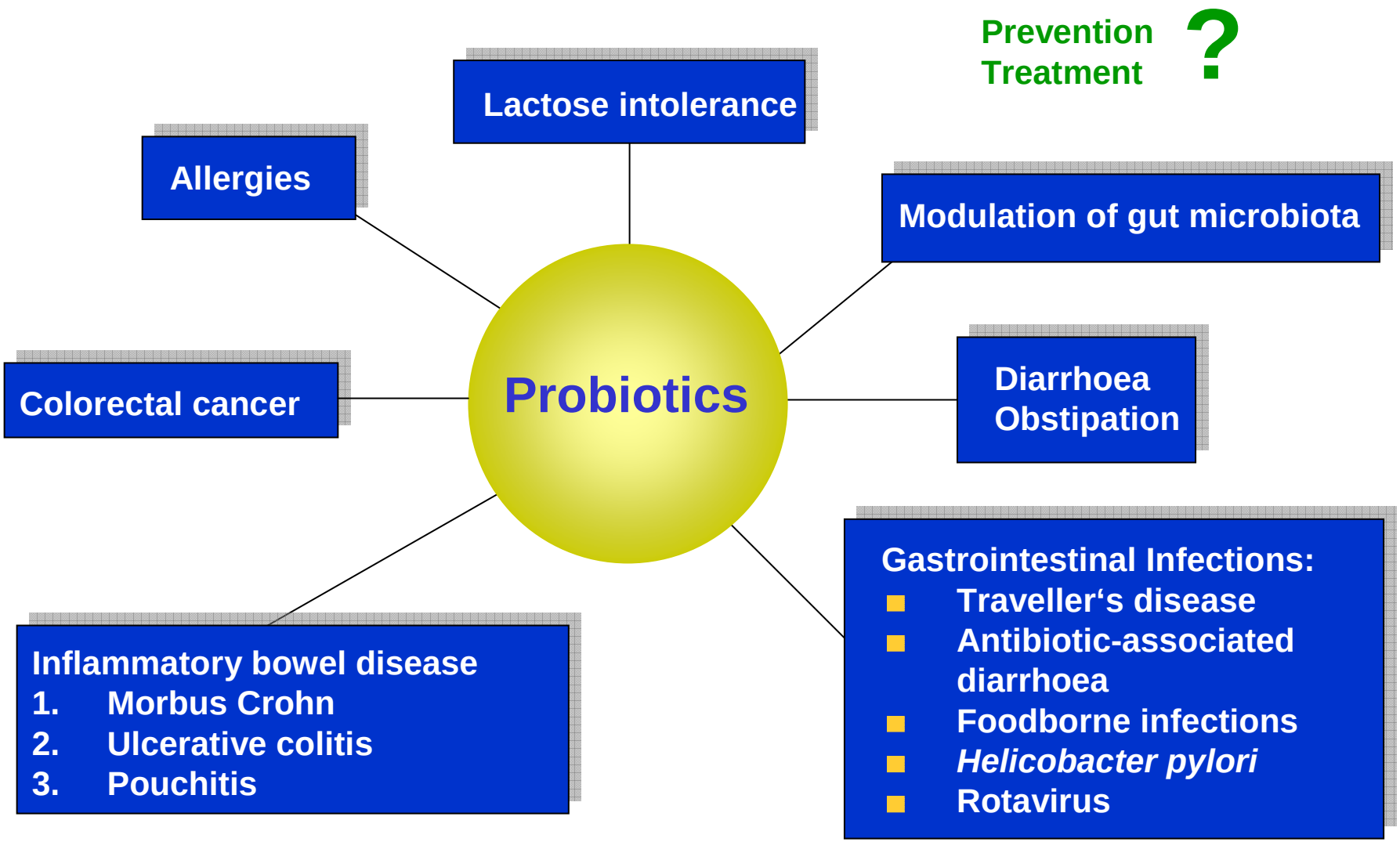
Is it possible to influence the gut microbota by dietary intervention in such a way that health-promoting effects are enhanced and adverse effects are minimised?

Definition of probiotics

“Live microorganisms which when administered in adequate amounts confer a health benefit on the host."

Food and Agriculture Organization of the United Nations (2001)

Possible effects of probiotics



Probiotic effects

- Restoration of barrier function
- Inhibition of bacterial translocation
- Formation of bacteriocins
- Inhibition of pathogens
- Modulation of immune response
- Induction of defensins

Probiotics and inflammatory bowel diseases

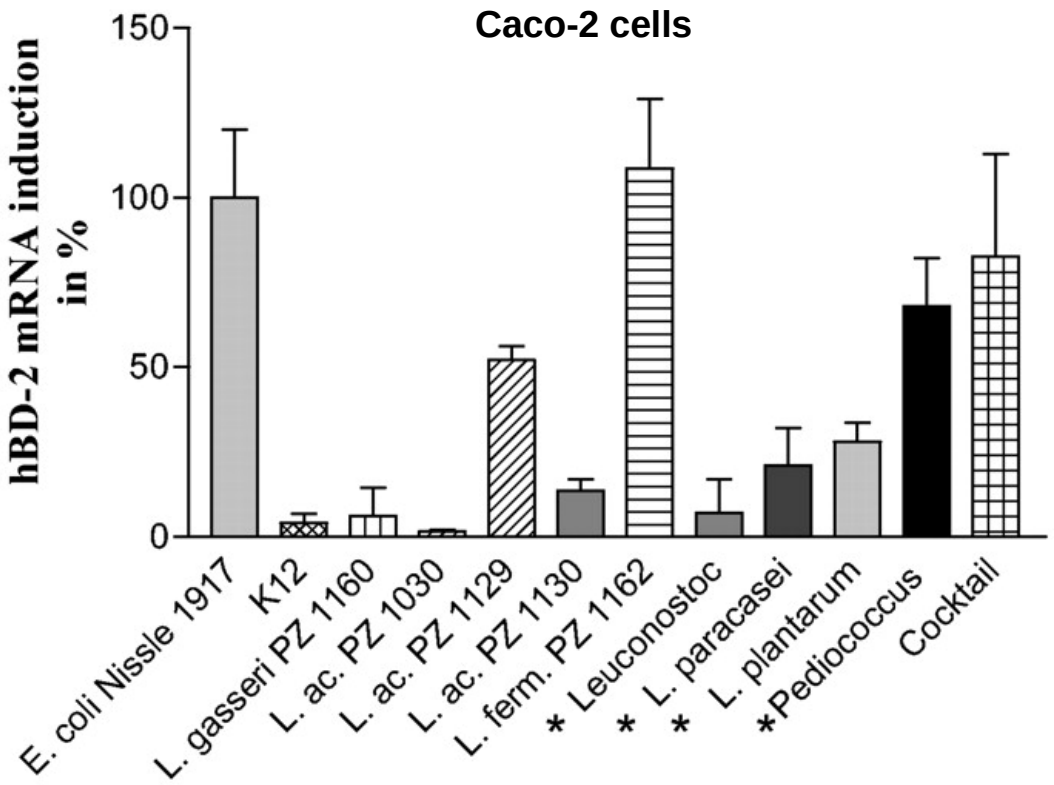
- **Lactobacilli prevent colitis in IL-10-deficient mice** (Madsen et al. 1999. Gastroenterology 116:1107-1114; Veltkamp et al. 1999. Gastroenterology 116: A83)**.**

- **In ulcerative colitis patients *E. coli* Nissle maintains remission as effectively as standard medication** (Kruis et al. 1997. Aliment Pharmacol Ther 11: 853; Rembacken et al. 1999. Lancet 354: 635; Kruis et al. 2001. Gastroenterology 120: A127)**.**

- **A mixture of lactic acid bacteria (VSL#3) reduces the incidence of chronic pouchitis** (Gionchetti et al. 2000. Gastroenterology 119:305).

- **VSL#3 induces remission in 77% of 34 patients with mild to moderate ulcerative colitis** (Bibiloni et al. 2005. Am J Gastroenterol 100:159)

Induction of human β-defensin-2

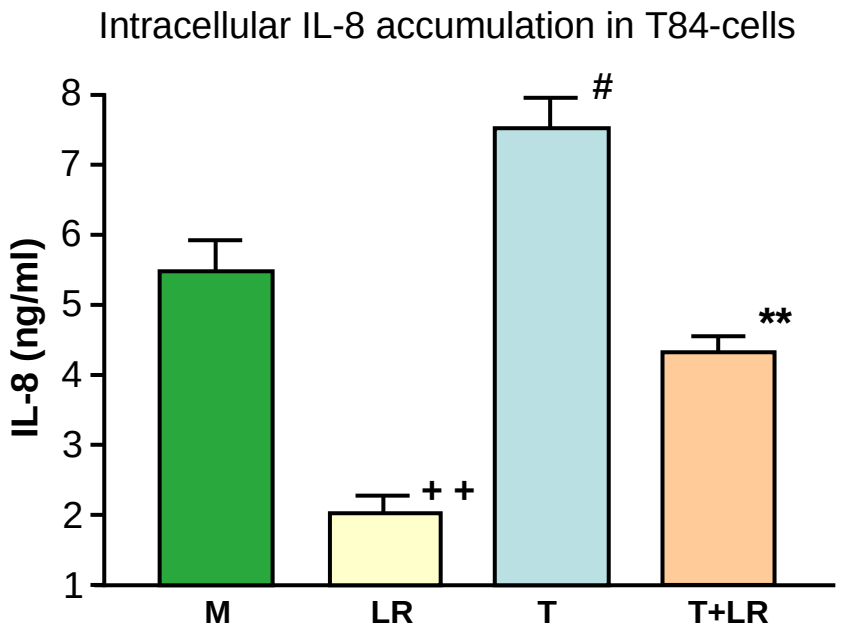


Wehkamp J et al. (2004) Infect Immun 72: 5750

Attenuation of inflammatory response (1)

Lactobacillus reuteri (live) inhibits TNFα-induced secretion of pro-inflammatory interleukin 8 (IL-8)

Ma et al. 2004. Infect Immun 72: 5308



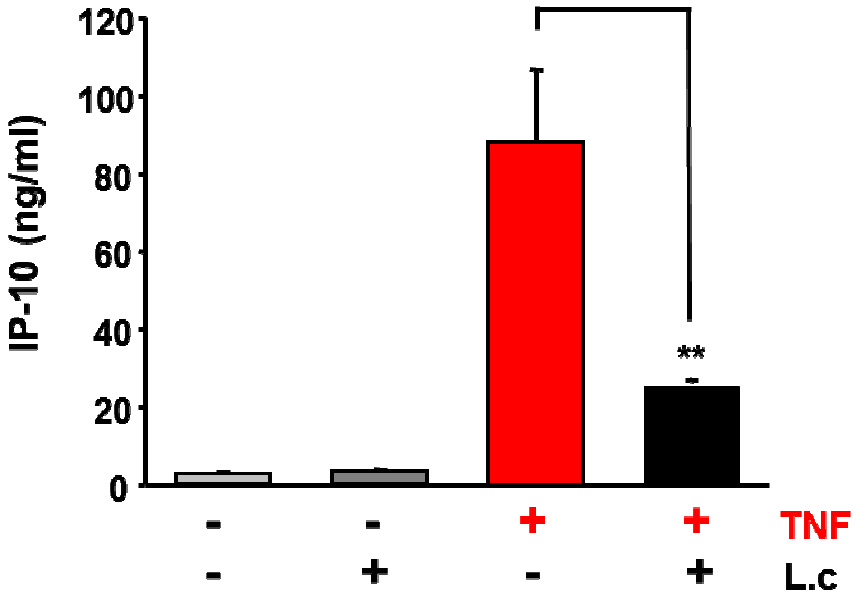
M = Medium
LR = *Lactobacillus reuteri*

ST = *Salmonella enterica* serovar Typhimurium
LR+T = *Lactobacillus reuteri* + TNFα

Attenuation of pro-inflammatory response (3)

Lactococcus lactis (VSL#3) inhibits TNFα-induced secretion of IP-10 (T-cell chemokine interferon-inducible protein) and IP-10-mediated transmigration of T-cells

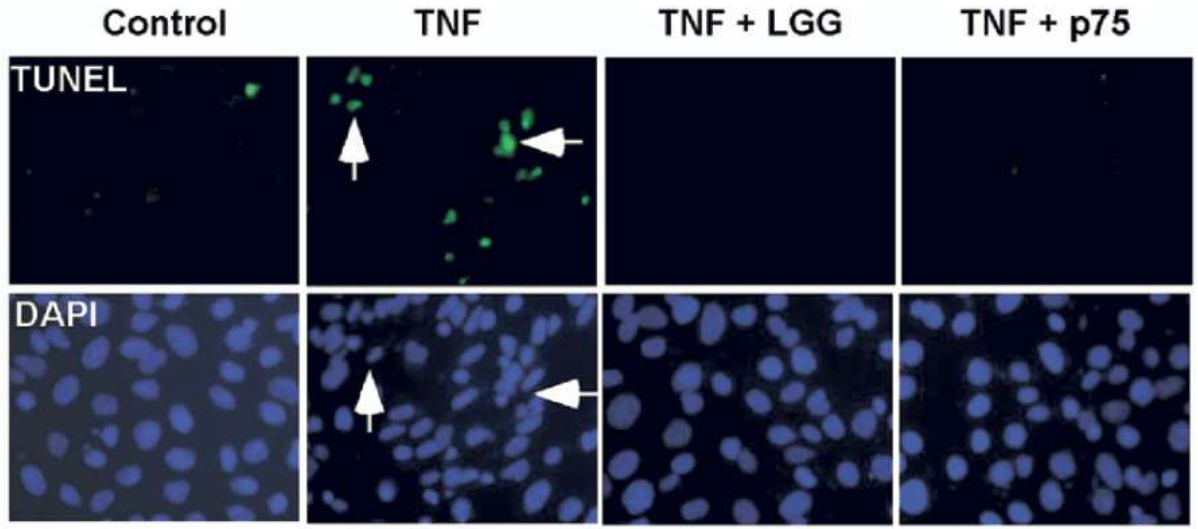
Hörmannsperger et al. 2009. PLOS One 4: e4365

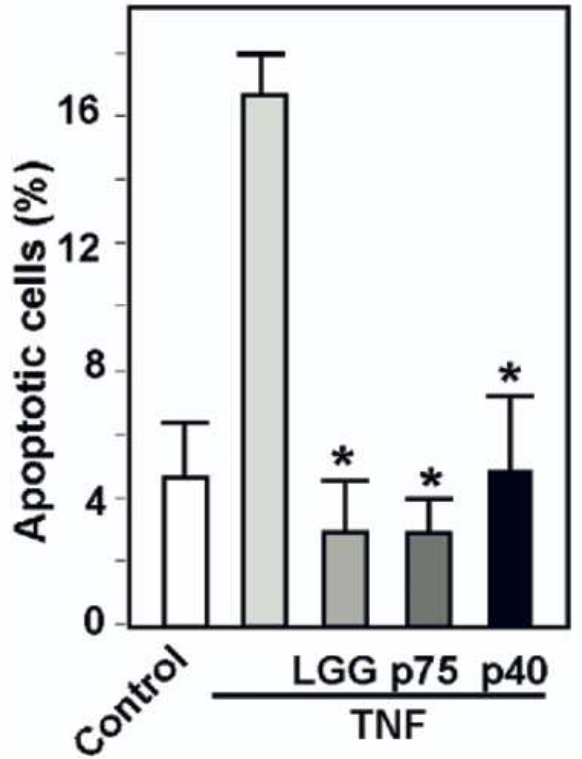


Inhibition of apoptosis

Lactobacillus rhamnosus GG forms proteins that inhibit cytokine-induced aptoptosis in human und murine epithelial cells

Yan F and Polk DB (2002) J Biol Chem 277: 50959
Yan F et al. 2007. Gastroenterol 132: 562-575

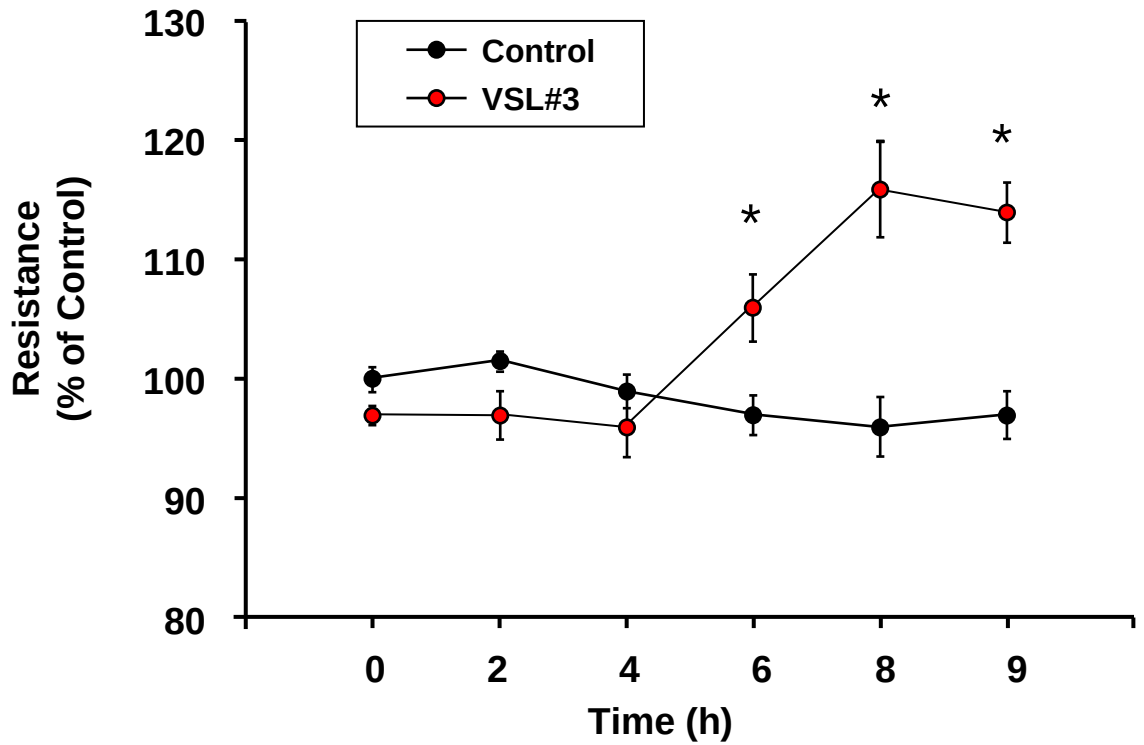




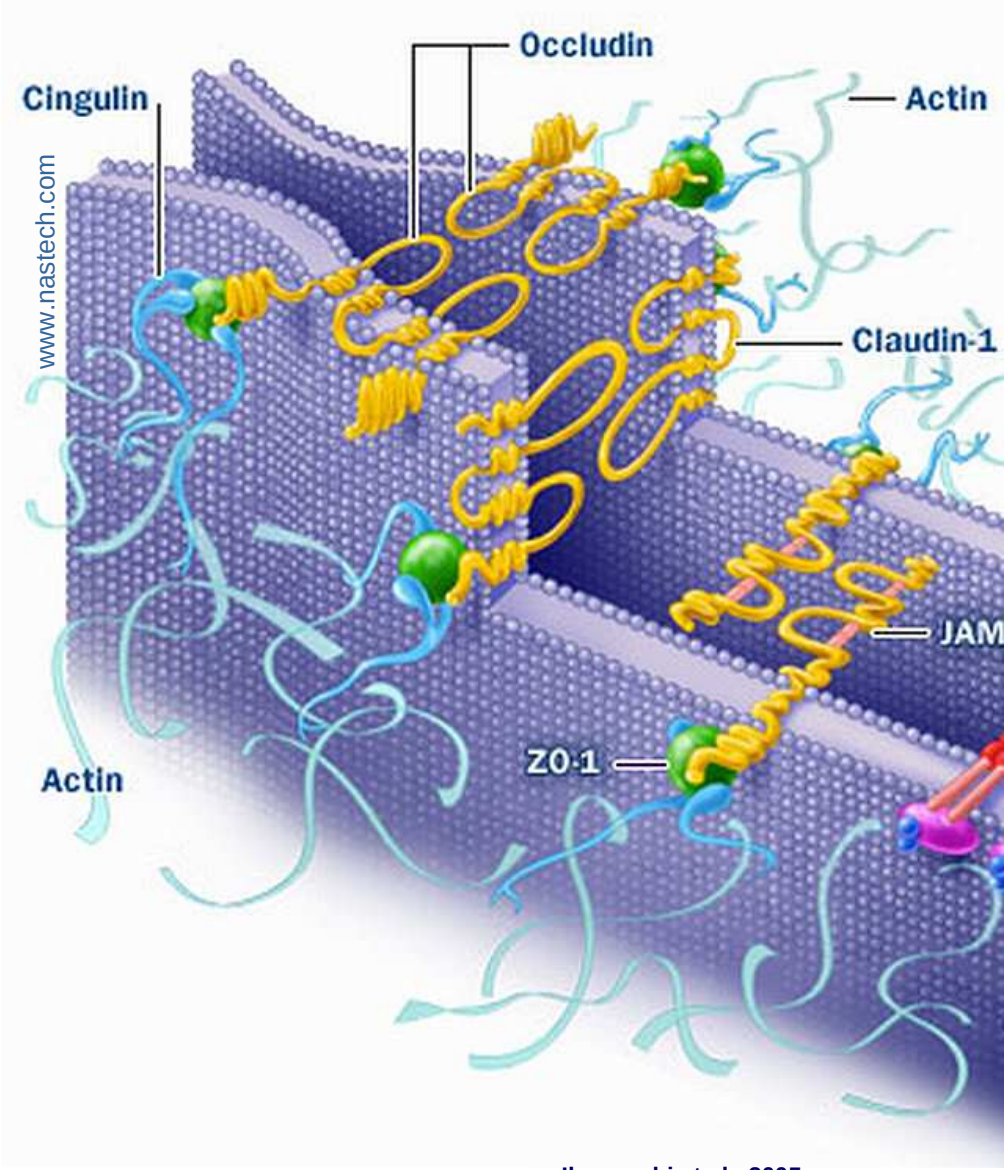
Attenuation of intestinal permeability (1)

Probiotic bacteria (VSL#3) decrease intestinal permeability in mice and humans

Madsen et al. 2001. Gastroenterology 121: 580



Enhanced expression of tight junction proteins



Ikenouchi et al., 2005

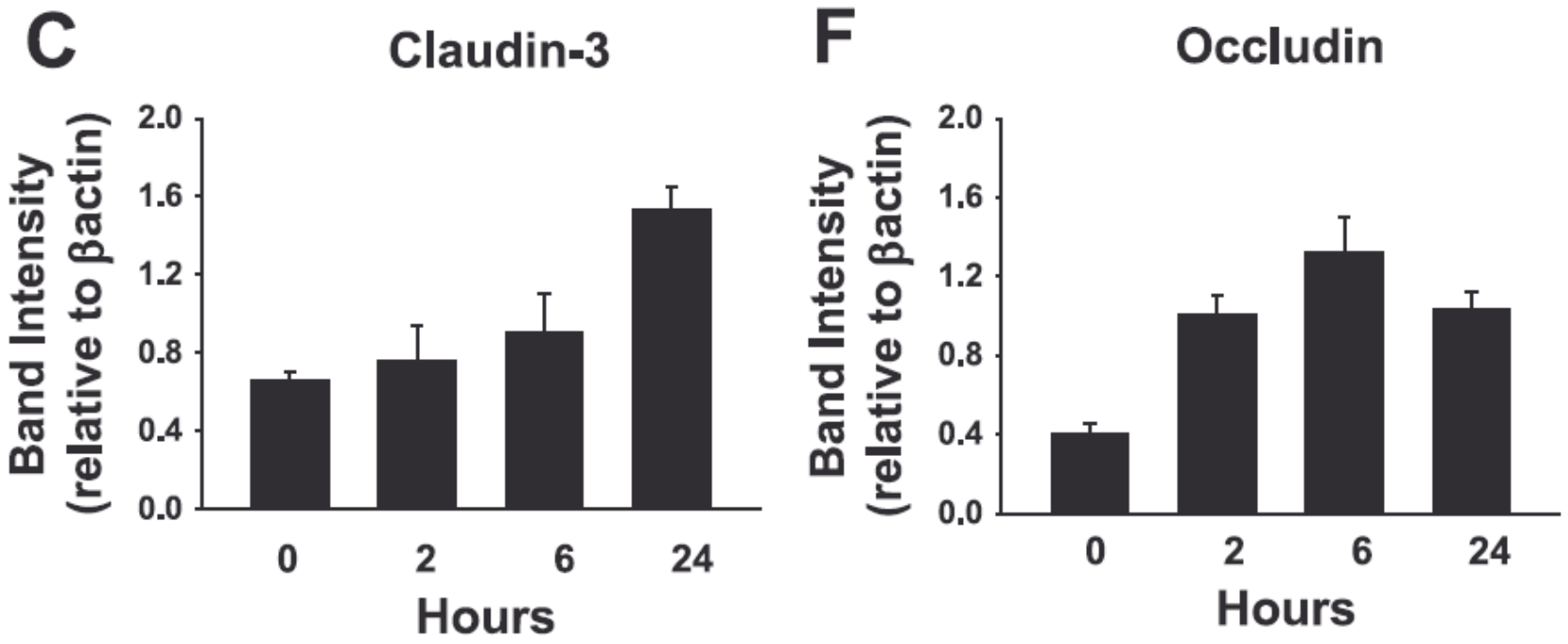
In the duodenum of healthy subjects, *L. plantarum* WCFS1 induces increased formation of tight junction proteins ZO-1 and occludin

Karczewski J et al. (2010) Am J Physiol Gastrointest Liver Physiol 298: G851-859

Attenuation of intestinal permeability (2)

Bioactive factors of *Bifidobacterium infantis* enhance epithelial barrier function (T84-cells)

Ewaschuk JB et al. 2008. Am J Physiol Gastrointest Liver Physiol 295: G1025



Duration of treatment

Summary and conclusions

- The intestinal microbiota is characterized by high diversity and high inter-individual variability
- The gut microbiota has a major impact on host physiology
- Nutrition profoundly affects the gut microbiota
- Probiotics and prebiotics may help in the prevention of various diseases
- Mechanisms underlying probiotic effects include changes in intestinal metabolism and environment as well as effect on gut barrier function and the immune system
- Exploration of the gut microbiome may help to develop individualized nutrition concepts that aim at an optimal function of the gut microbiota