Host-Microbe Interactions: Identifying Novel Molecular Targets for Health Promoting Foods

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OPINION

Gut microbiota: a potential new territory for drug targeting

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Table 1 | **Examples of gut microbiota-related diseases and therapeutic strategies**

Disease or disorder	Association of gut microbiota with disease	Evidence of gut microbiota-targeted therapy	Refs
Chronic peptic ulcer	*Helicobacter pylori* infection is the pathogenic key to the development of most chronic peptic ulcers	Regimen of *H. pylori* eradication with antibiotics and proton-pump inhibitory agents	26,57
Antibiotic-associated diarrhoea	The suppression of antibiotic-sensitive bacteria and over-growth of antibiotic-resistant species lead to intestinal dysfunction	Treatment with probiotics, such as the yeast *Saccharomyces boulardii*, together with antibiotics is effective in the prevention of antibiotic-associated diarrhoea	58,59
Ulcerative colitis	Abnormal immune response to commensal bacteria, and increased numbers of intestinal microorganisms, but reduced numbers of protective bacteria such as *Lactobacilli* and *Bifidobacteria*	Short-term benefits were observed with antibiotic or probiotic/synbiotic therapy	42,60
Crohn's disease	Inadequate clearance of ingested microorganisms by dysfunctional intestinal macrophages (hypothesized mechanism)	Reinstating the balance of intestinal microflora with probiotics, prebiotics and/or antibiotics, such as the non-absorbable antibiotic rifaximin	61,62
Obesity	The relative abundance of the two predominant bacterial divisions, the *Bacteroidetes* and the *Firmicutes*, affect the efficiency of energy harvest from diet	It is suggested that manipulation of the commensal microbial composition could be a novel therapeutic approach for obesity	5,6
Diabetes	No gut microbiota-related mechanism is established, but it appears that diabetes is associated with the gut microbiota	Oral administration of probiotics shows a significant antidiabetic effect in diabetic models	34–38
Colorectal cancer	Conversion of dietary procarcinogens into DNA-damaging agents or generation of carcinogens by particular commensal bacteria are thought to be certain causes of colorectal cancer	Reduced prevalence of colon cancer was observed in interleukin 10 knockout mice by probiotic *Lactobacilli* administration, and strong antitumour activity was achieved by *Bifidobacterium longum* therapy *in vivo*	63,64
Idiopathic parkinsonism	Partial involvement of microorganisms such as *H. pylori*	*H. pylori* is important in the aetiology/pathogenesis of idiopathic parkinsonism and useful for disease categorization and subsequent treatment	65–67

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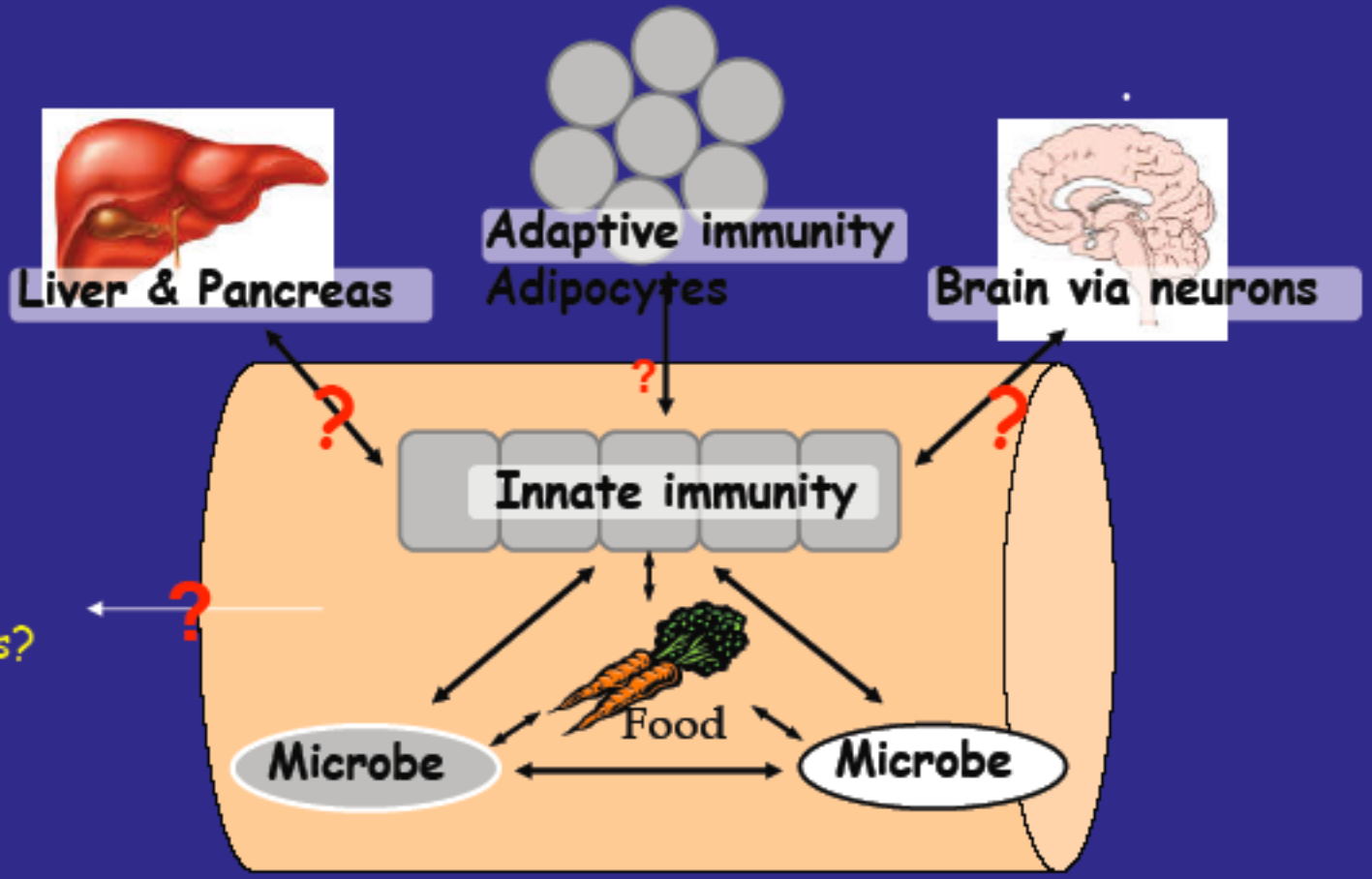
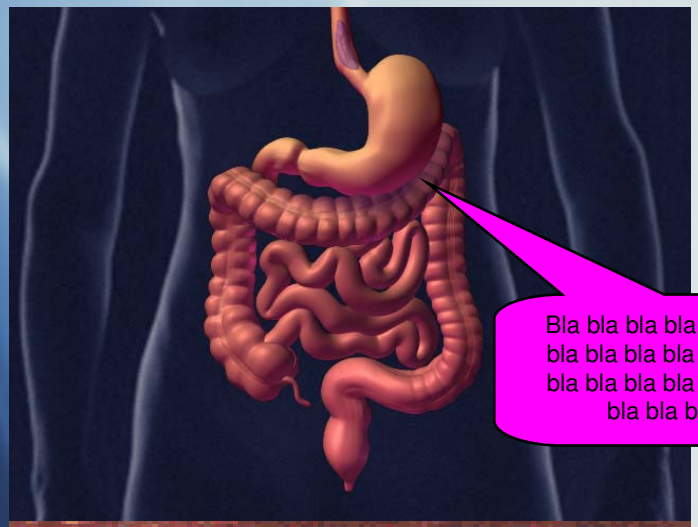
The microflora in numbers

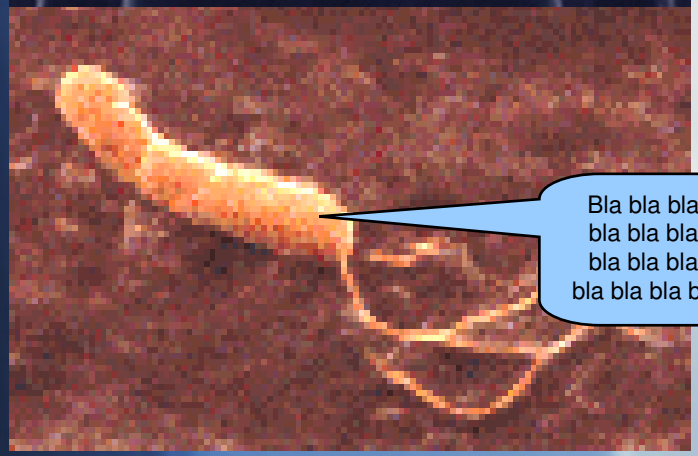
- Number of genes ~ 50-100 times our own genes
- Human gut contains ~ 10^{12} organisms per ml colonic content $\rightarrow$ ~1 kg
- ~ 10 times more prokaryotes than eukaryotes in & on our bodies
- In colon; anaerobes: aerobes 1000:1

Hypothesis: Gut flora are involved in host physiology.



How can we hear the dialogue: bacteria vs host - considering the enormous noise?





Core Facility for Germfree Research (CFGR)

Example of Microbe Regulated Targets I - Nuclear Receptors

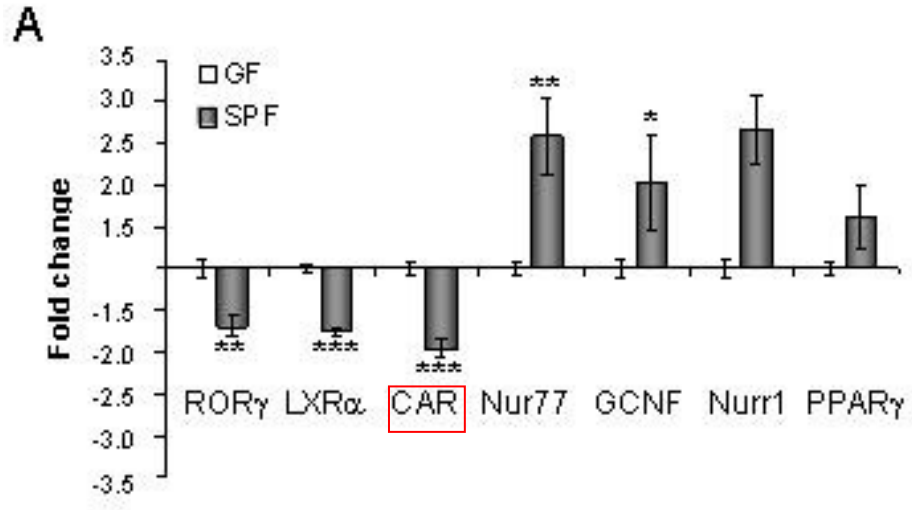
Physiological roles of Nuclear Receptors

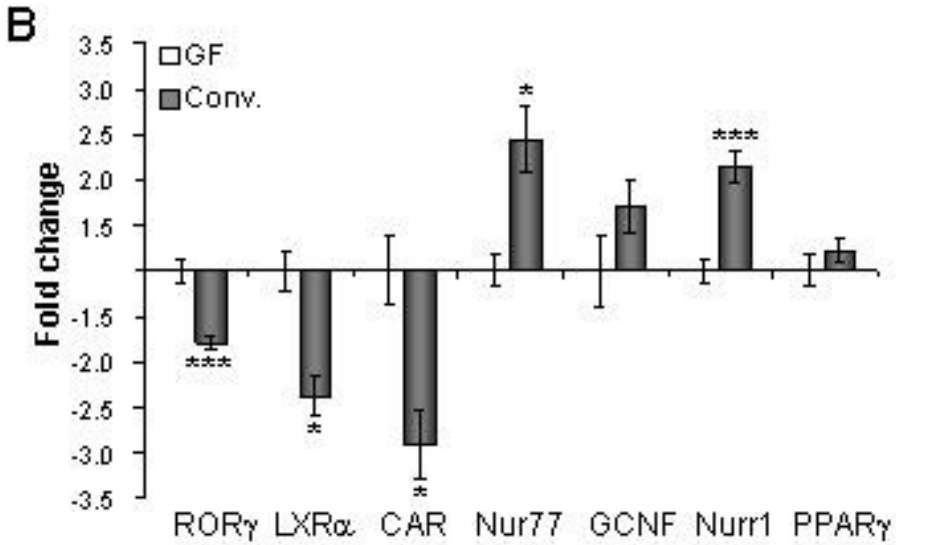
NR's are virtually involved in all aspects of physiology

- Development
- Differentiation
- Apoptosis
- Energy metabolism
- Metabolism (steroidogenesis, cholesterol, bile acids, xenobiotics)
- Growth/proliferation
- Reproduction
- Inflammation/immune system
- Stress response
- Neuro-functions
- Circadian rhythm

•Loss of NR function usually results in a severe phenotype

Hypothesis:
NRs are second messengers that rewire information from gut flora to modulate host physiology
37/49 expressed in gut, 7/37





Lundin et al Cellular Microbiology 2008

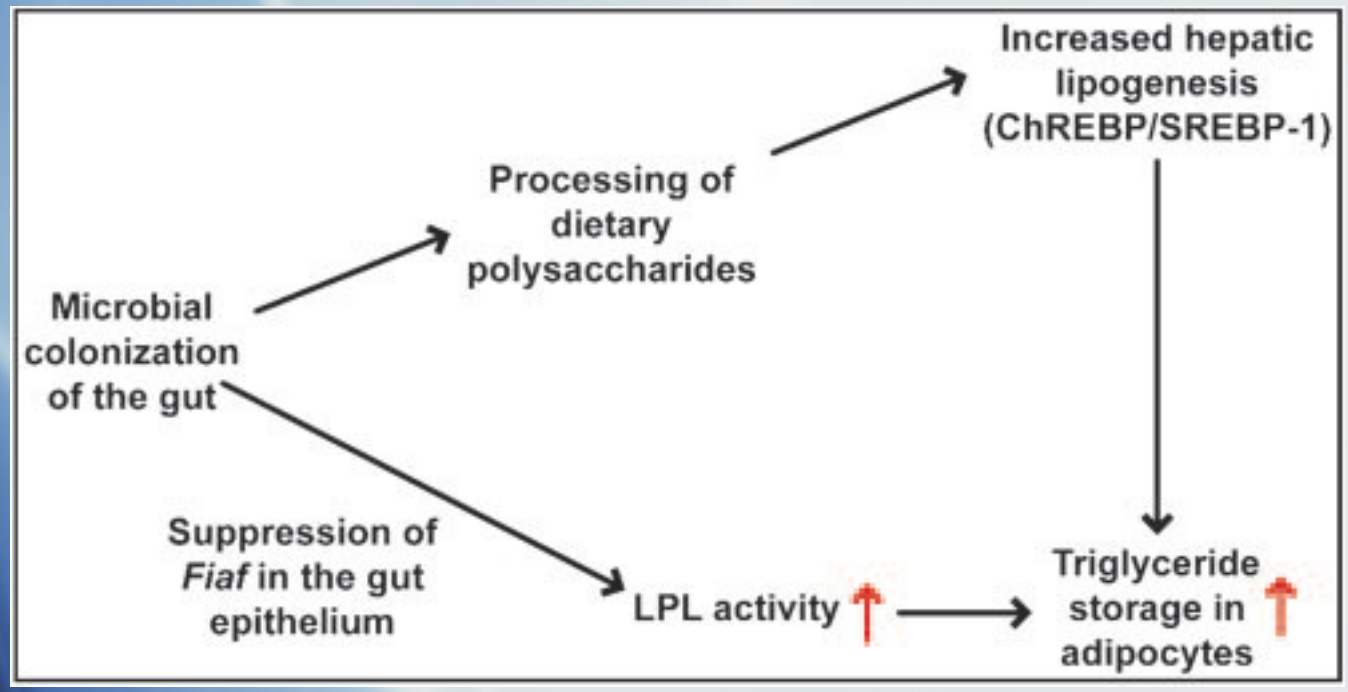
PPARγ

Peroxisome Proliferator Activated Receptor-γ
Ubiquitously expressed transcription factor
Essentail for
Adipose differentiation
Lipid storage
Glucose homeostasis
Synthetic ligands - type II Diabetes
Natural ligands?

Example of Microbe Regulated Targets II - FIAF

Fiaf (fasting-induced adipocyte factor)

- Member of angiopoietin-like family of proteins (angiopoietin-like protein 4)
- Produced by brown & white fat, liver & intestine
- Secreted protein
- Potent inhibitor of lipoprotein lipase (LPL)



Microbial suppression of intestinal Fiaf promotes adiposity (Bäckhed et al, PNAS, 2004)

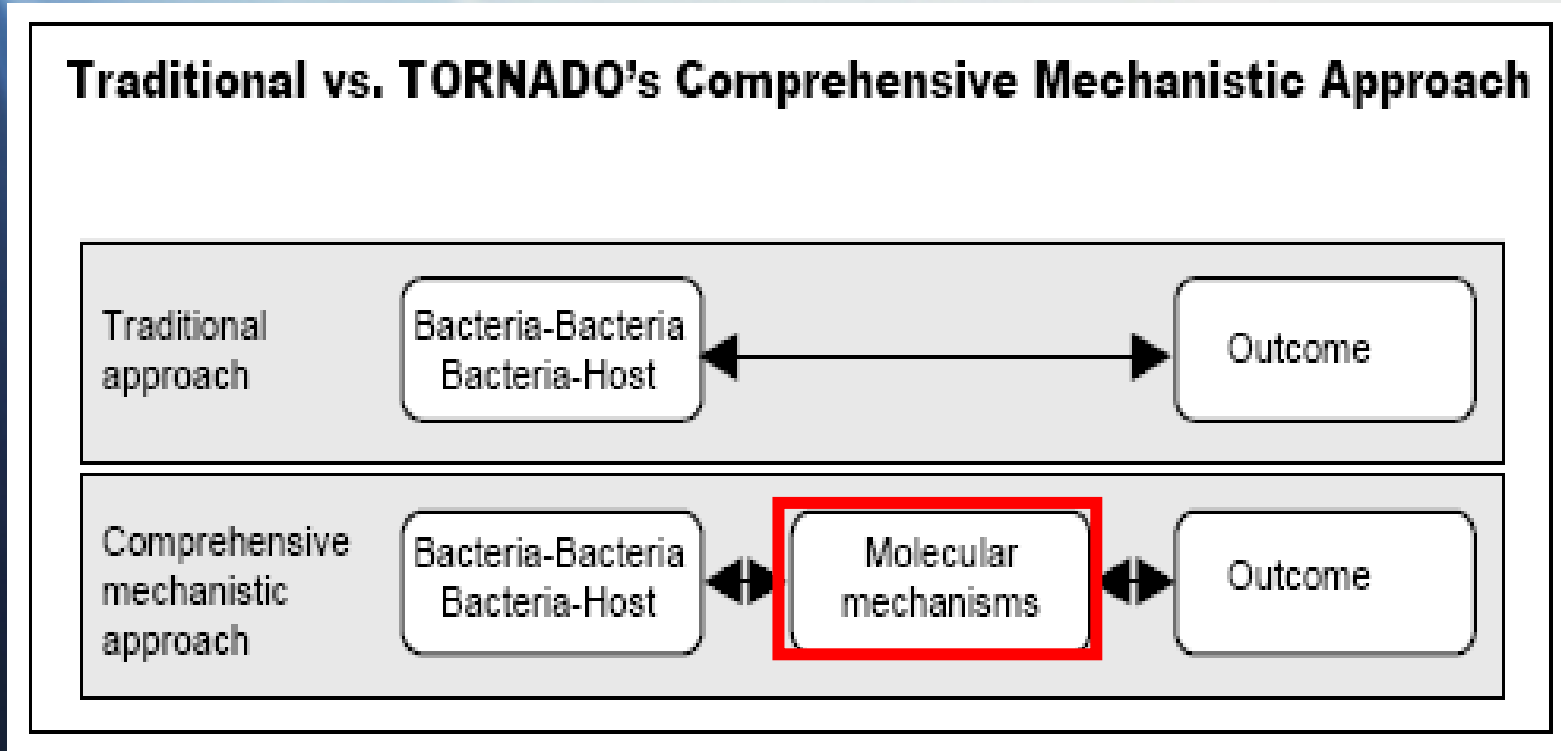
5: Lee HY, Park JH, Seok SH, Baek MW, Kim DJ, Lee KE, Paek KS, Lee Y, Park JH.
Human originated bacteria, Lactobacillus rhamnosus PL60, produce conjugated linoleic acid and show anti-obesity effects in diet-induced obese mice.
Biochim Biophys Acta. 2006 Jul;1761(7):736-44. Epub 2006 May 20.
PMID: 16807088 [PubMed - indexed for MEDLINE]

12: Ali AA, Velasquez MT, Hansen CT, Mohamed AI, Bhathena SJ.
Modulation of carbohydrate metabolism and peptide hormones by soybean isoflavones and probiotics in obesity and diabetes.
J Nutr Biochem. 2005 Nov;16(11):693-9. Epub 2005 Aug 2.
PMID: 16081264 [PubMed - indexed for MEDLINE]

14: Ali AA, Velasquez MT, Hansen CT, Mohamed AI, Bhathena SJ.
Effects of soybean isoflavones, probiotics, and their interactions on lipid metabolism and endocrine system in an animal model of obesity and diabetes.
J Nutr Biochem. 2004 Oct;15(10):583-90.
PMID: 15542349 [PubMed - indexed for MEDLINE]

TORNADO

- Molecular Targets Open for Regulation by the gut flora – New Avenues for improved Diet to Optimize European health



Objectives

- Identify molecular targets for bacteria (locally & systemically)
- Identify biomarkers to monitor effects on HEALTH/disease
- Identify novel mol targets for health promoting foods
- Address development effects/effect of ageing on gut flora
- Supply EU with 'template protocol' to substantiate health claims
- PROBIOTICS HEAVILY ADDRESSED IN TORNADO

Collaborators

- Sven Pettersson
- Velmurugesan Arulampalam
- Linda Aronsson