The microbiota of the gastrointestinal canal, upper respiratory tract, and skin plays a role in health

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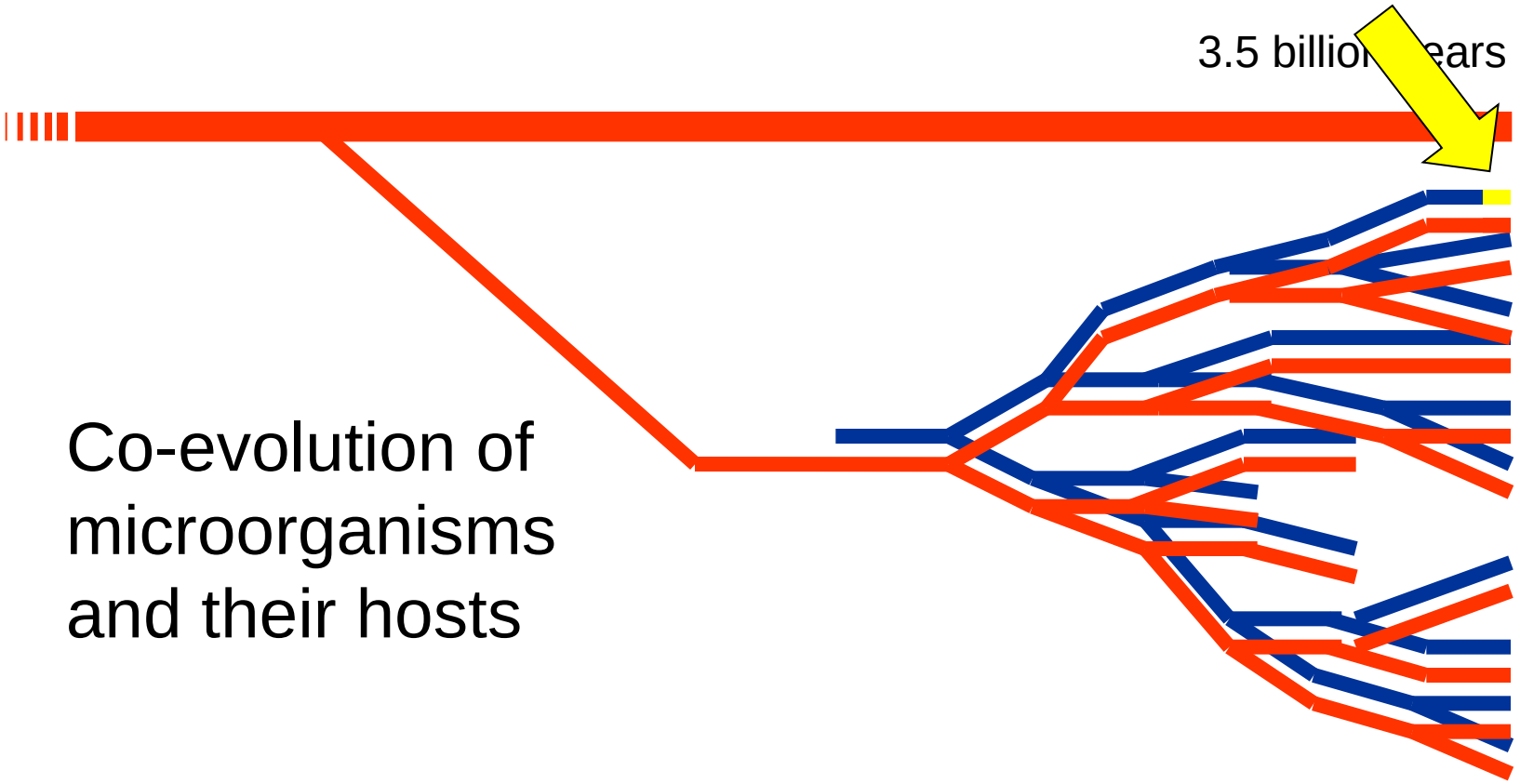
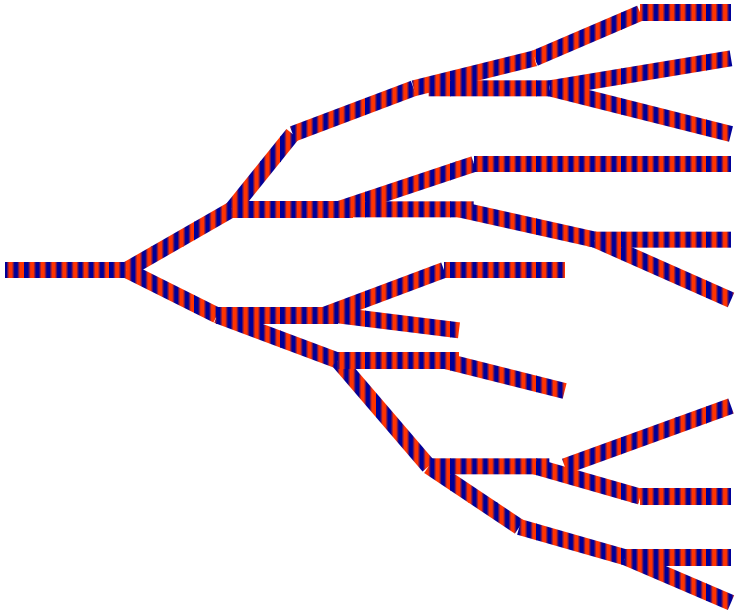
History of the relationship between bacteria and their hosts

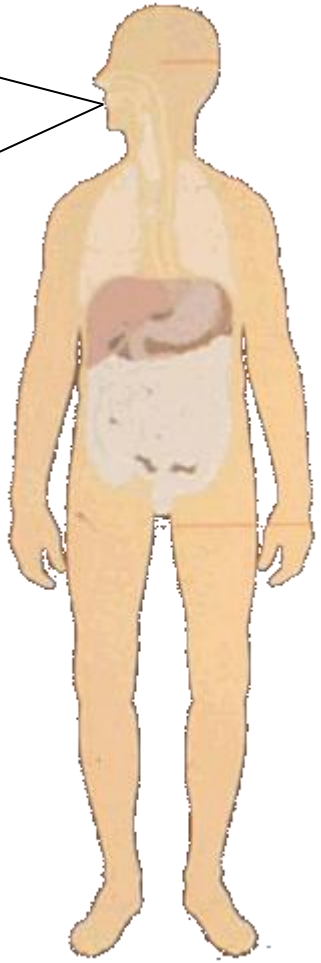


Co-evolution of microorganisms and their hosts

History of the relationship between bacteria and humans

Mutual adaptation and functional integration



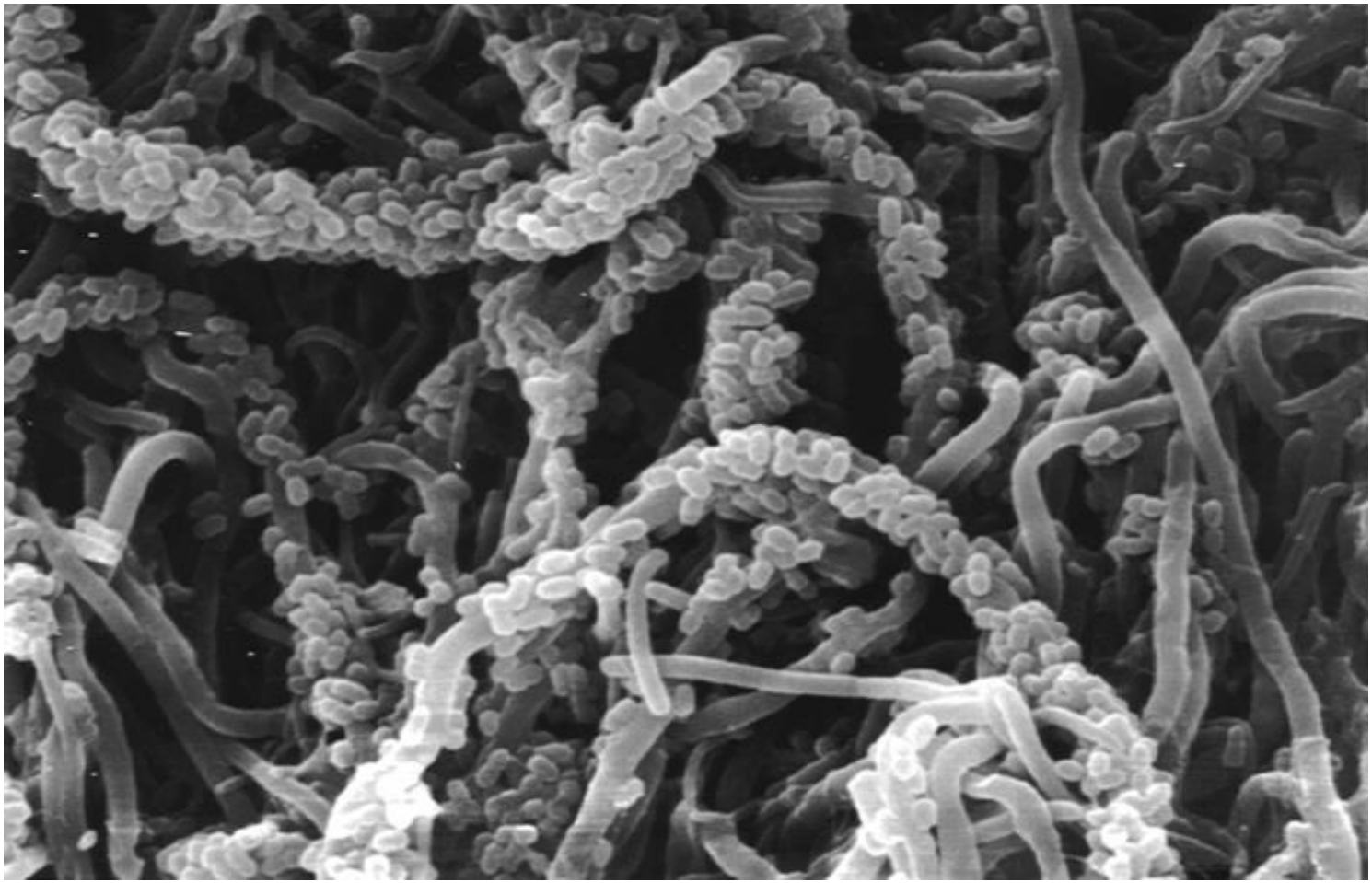


10^{13} own cells

10^{14} bacteria

”Superorganism”

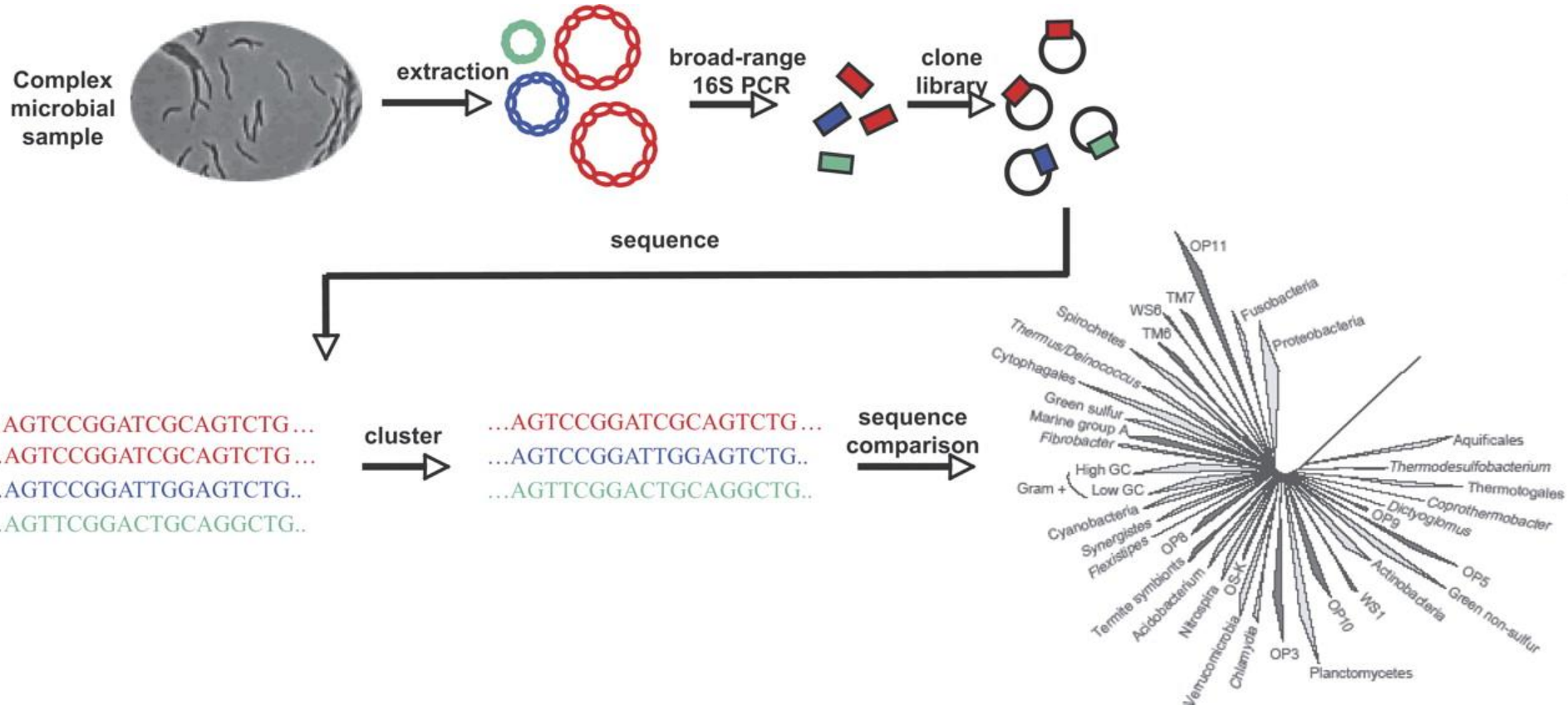
Coevolution of Bacteria Within Ecosystems



Antagonism Between Two Skin Bacteria

Detailed mapping of the human commensal microbiota

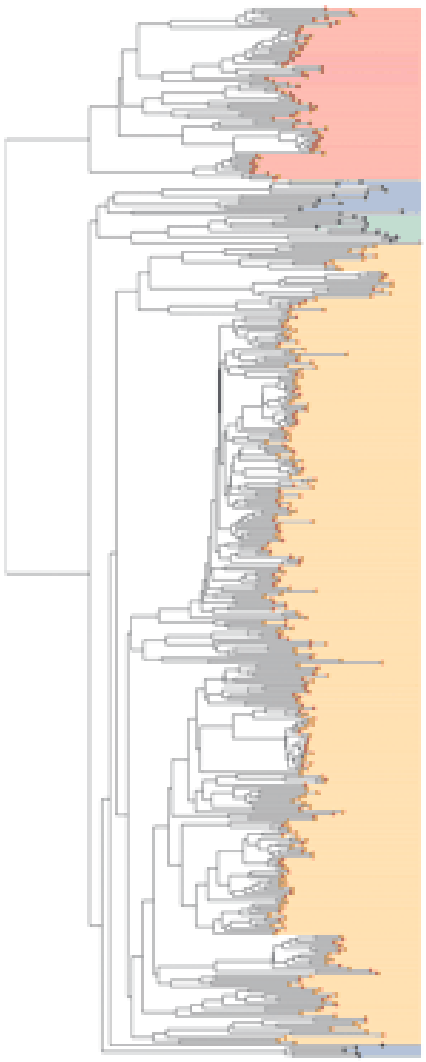
Mapping of Complex Microbiotas by 16S rRNA Gene Amplicon Analysis



Diversity of the Human Intestinal Microbial Flora

Based on mucosal samples obtained from sites within six subdivisions of the colon and stool samples from 3 healthy individuals

Eckburg et al. Science 308:1635-8, 2005



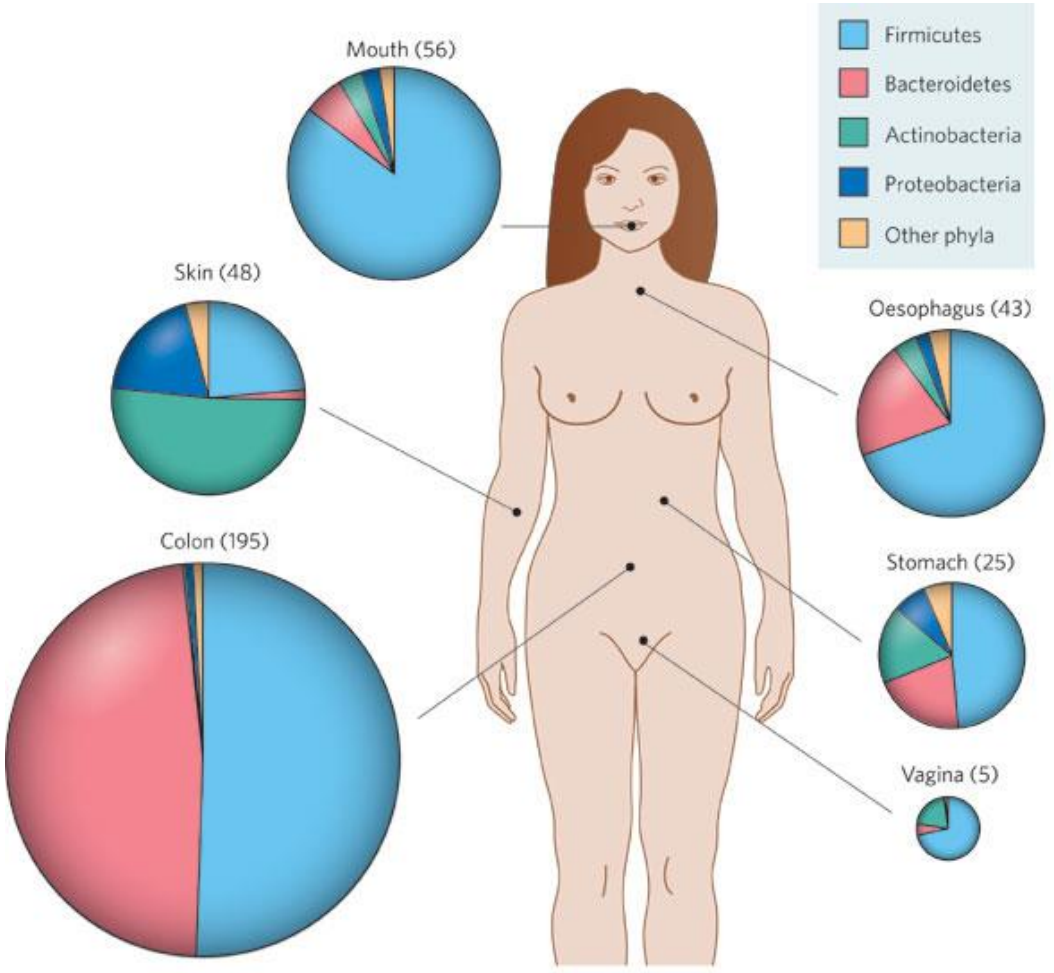
Bacteroides

Non-*alphaproteobacteria*
Unclassified near *Cyanobacteria*
Actinobacteria

Firmicutes

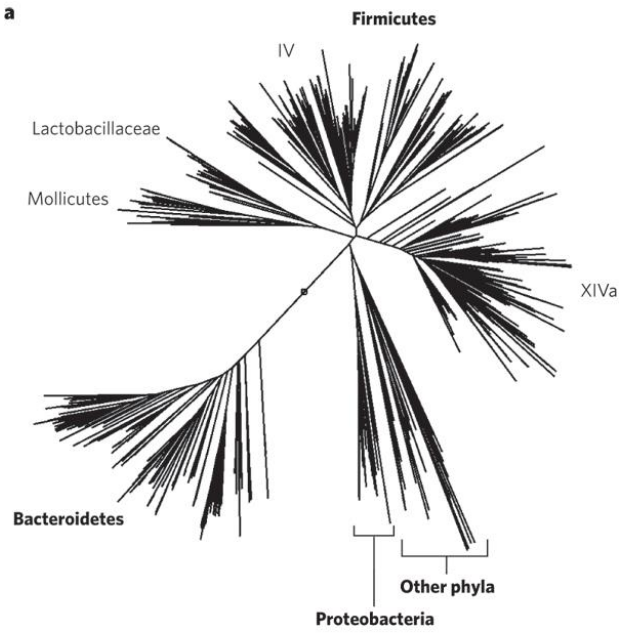
Fusobacteria
Alphaproteinobacteria

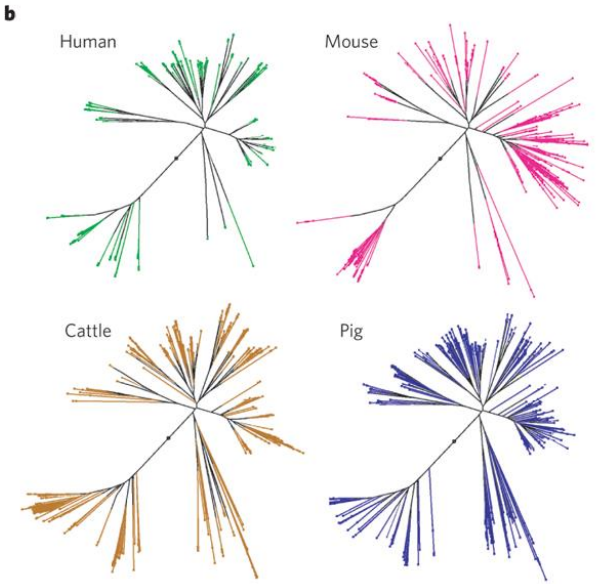
Site-Specific Distributions of Bacterial Phyla in Healthy Humans



Dethlefsen, McFall-Ngai & Relman. *Nature* 449, 811-818, 2007.

Comparison of Intestinal Microbiotas of Humans and Different Animals Based on 16S rRNA Sequences.

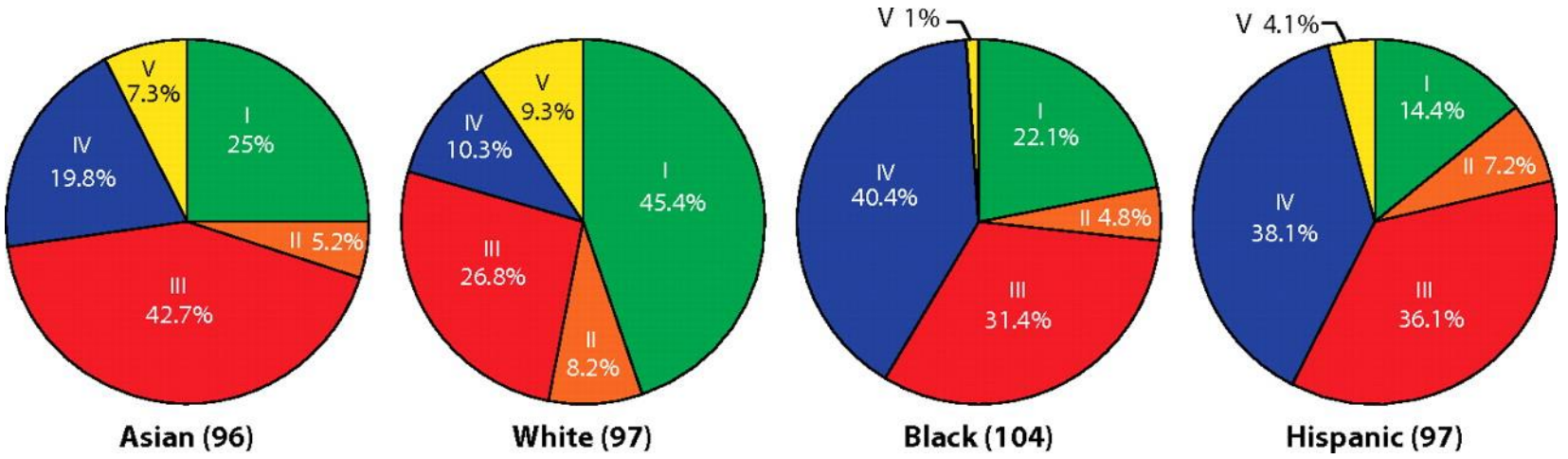




Species shared by at least two hosts are indicated by black lines, whereas coloured lines indicate host-specific lineages.

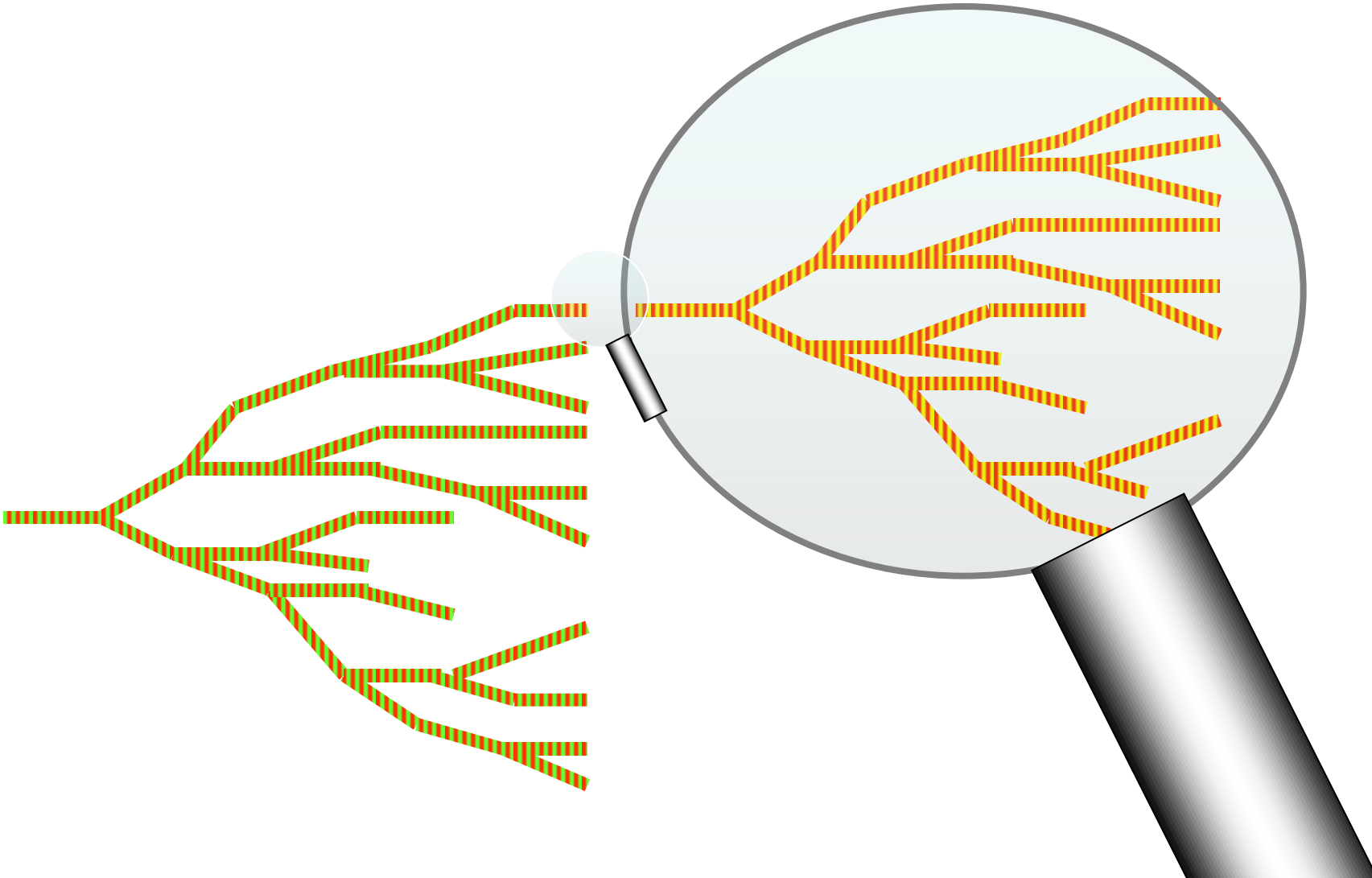
Dethlefsen *et al.* 2007. Nature 449:811-8.

Composition of the vaginal microbiota in women of different ethnic groups



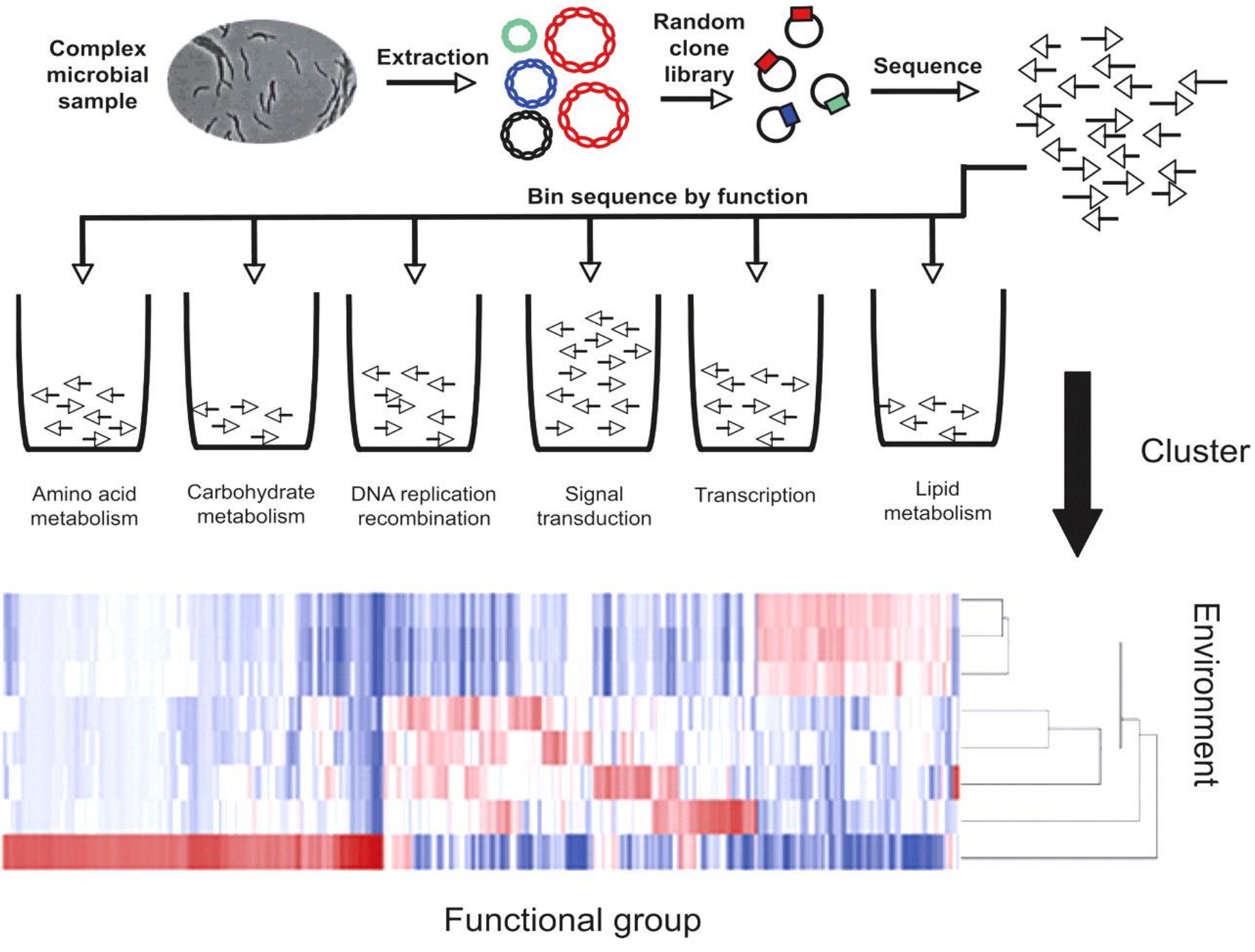
Ravel J et al. PNAS 2011;108:4680-4687

Coevolution between microorganisms and their human hosts within the last 100,000 years



Examples of Genetically Determined Differences in the Susceptibility to Infections

- HIV (mutation in co-receptor gene)
- Diphtheria (”diphtheria susceptibility gene”)
- Meningococcal meningitis
- Streptococcal toxic shock syndrome (MHC-II)
- *Helicobacter pylori* (Gastric ulcers and cancer)(Blood group)
- Aggressive periodontitis


Complex microbial sample
Extraction
Random clone library
Sequence
Bin sequence by function
Amino acid metabolism
Carbohydrate metabolism
DNA replication recombination
Signal transduction
Transcription
Lipid metabolism
Cluster
Environment
Functional group

Vol 464/March 2010/doi:10.138/nature08821 nature

ARTICLES

A human gut microbial gene catalogue established by metagenomic sequencing

Junjie Qin, Ruiqiang Li, Raes J, Arumugam M, Burgdorf KS, Manichanh C, Nielsen T, Pons N, Levenez F, Yamada T, Mende DR, Li J, Xu J, Li S, Li D, Cao J, Wang B, Liang H, Zheng H, Xie Y, Tap J, Lepage P, Bertalan M, Batto JM, Hansen T, Le Paslier D, Linneberg A, Nielsen HB, ..

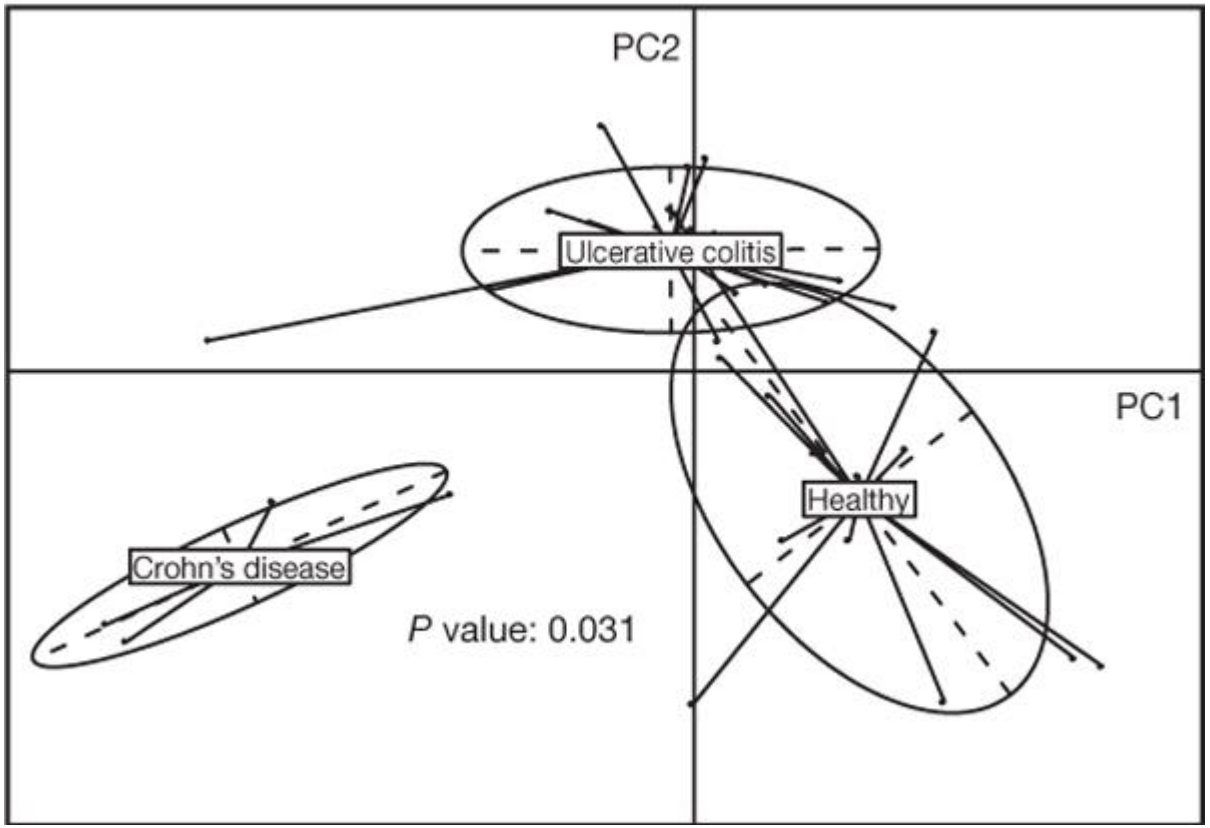
576.7 gigabases were sequenced from DNA isolated from faecal samples of 124 European individuals.

The entire cohort carried between 1,000 and 1,150 prevalent bacterial species (at least 160 per individual, which are largely shared.

3.3 million non-redundant bacterial genes (150 x larger than the human gene complement).

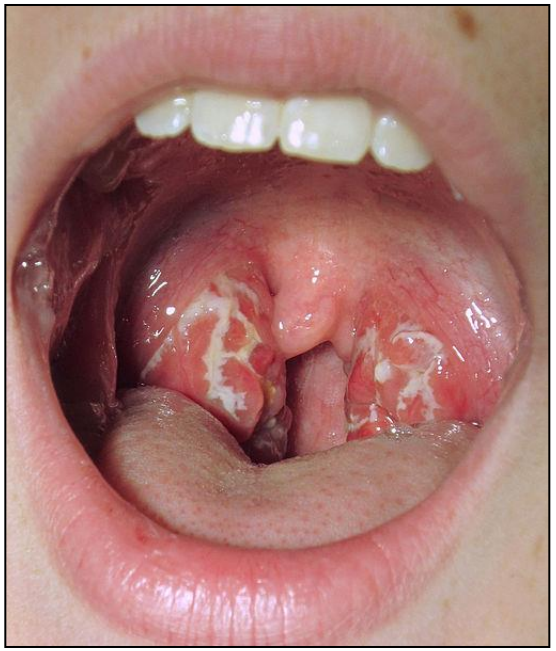
http://gutmeta.genomics.org.cn and http/www.bork.embl.de/~arumugam/Qin_et_al_2010/

Bacterial Species Abundance Differentiates Healthy Individuals and Patients with Inflammatory Bowel Disease.

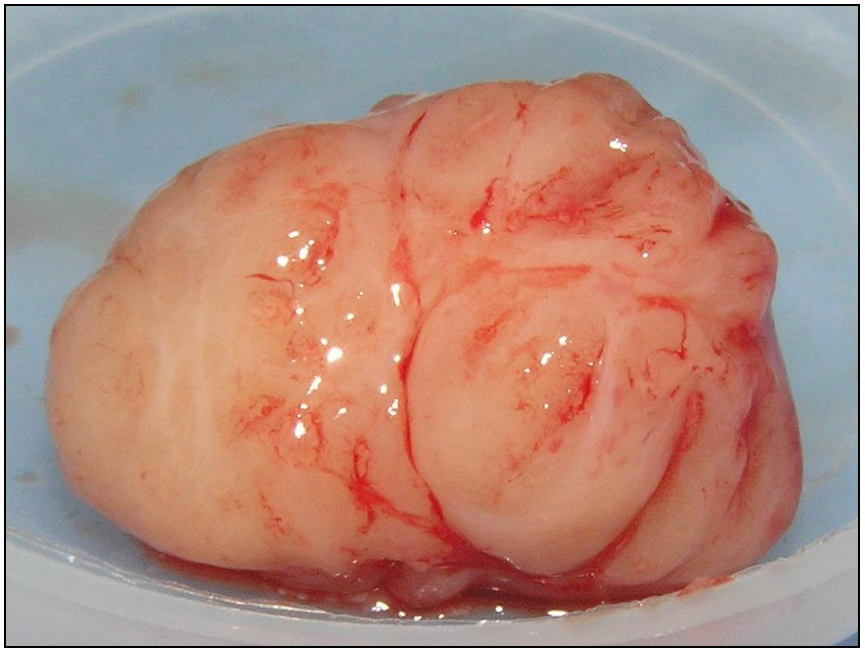


Qin *et al*. 2010. Nature 464:59-65.

Bacteriology of the human tonsils



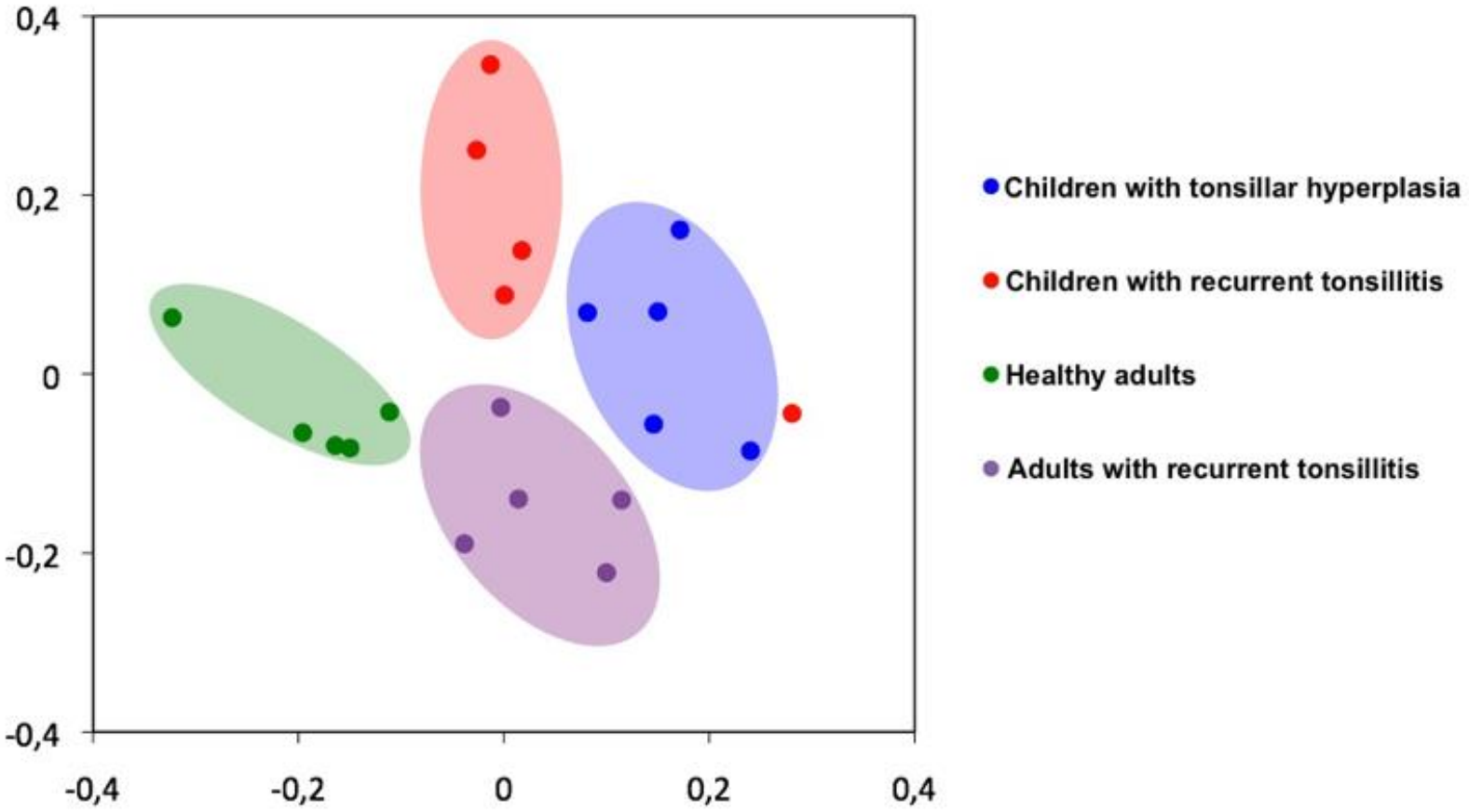
Acute tonsillitis



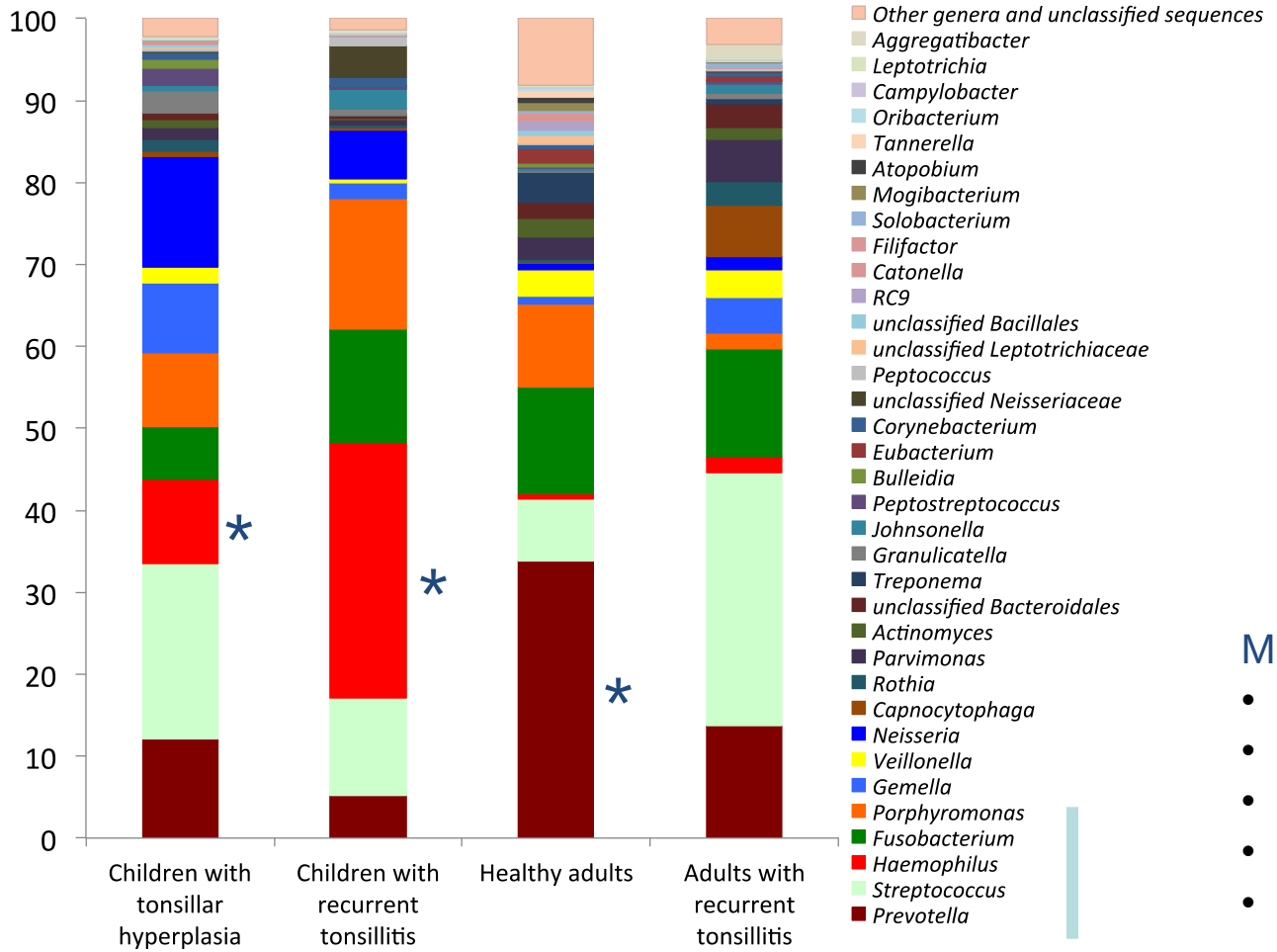
Hypertrophic tonsil

Jensen A, Fagö-Olsen H, Sørensen CH, Kilian M. PLoS One. 2013;8(2):e56418.

Community Structure Differences Identified by Weighted UniFrac Distance Analysis.



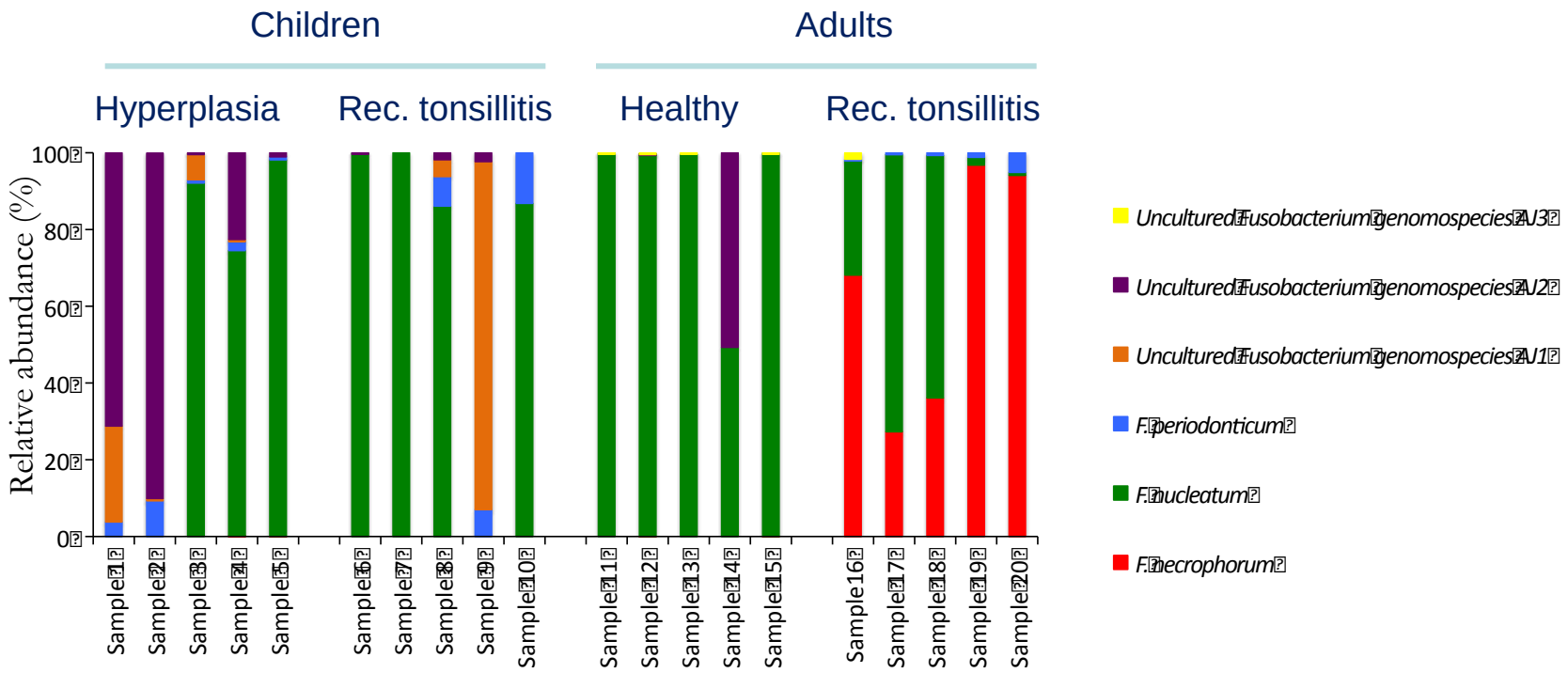
Distribution of the 30 Most Abundant Genera out of a total of 93 Genera Detected



Most prevalent genera:

- *Prevotella*,
- *Streptococcus*,
- *Haemophilus,*
- *Fusobacterium*,
- *Porphyromonas*

Distribution of Fusobacterium species



The *”Superorganism”*

Why did ”we” select this evolutionary pathway?

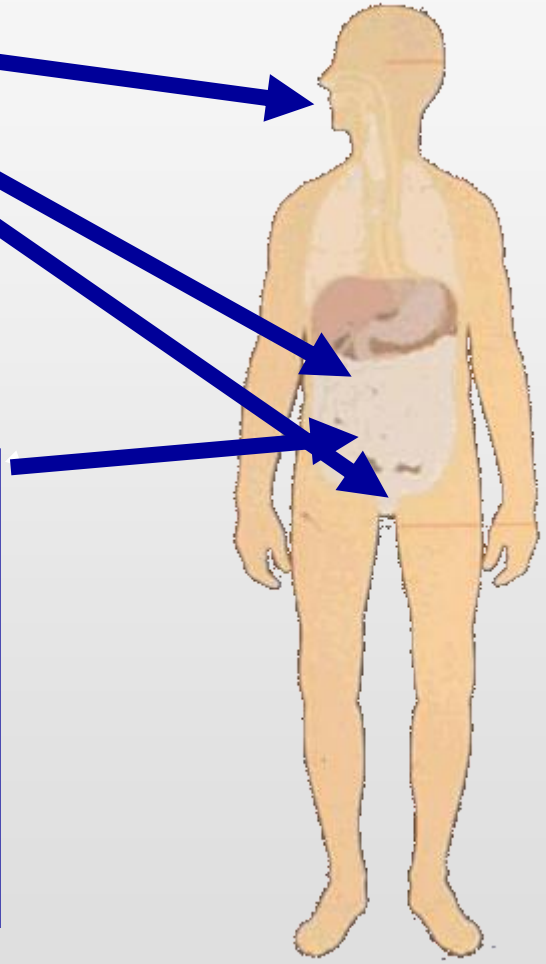
Functions of the commensal microbiota(1)

Resistance to infections:

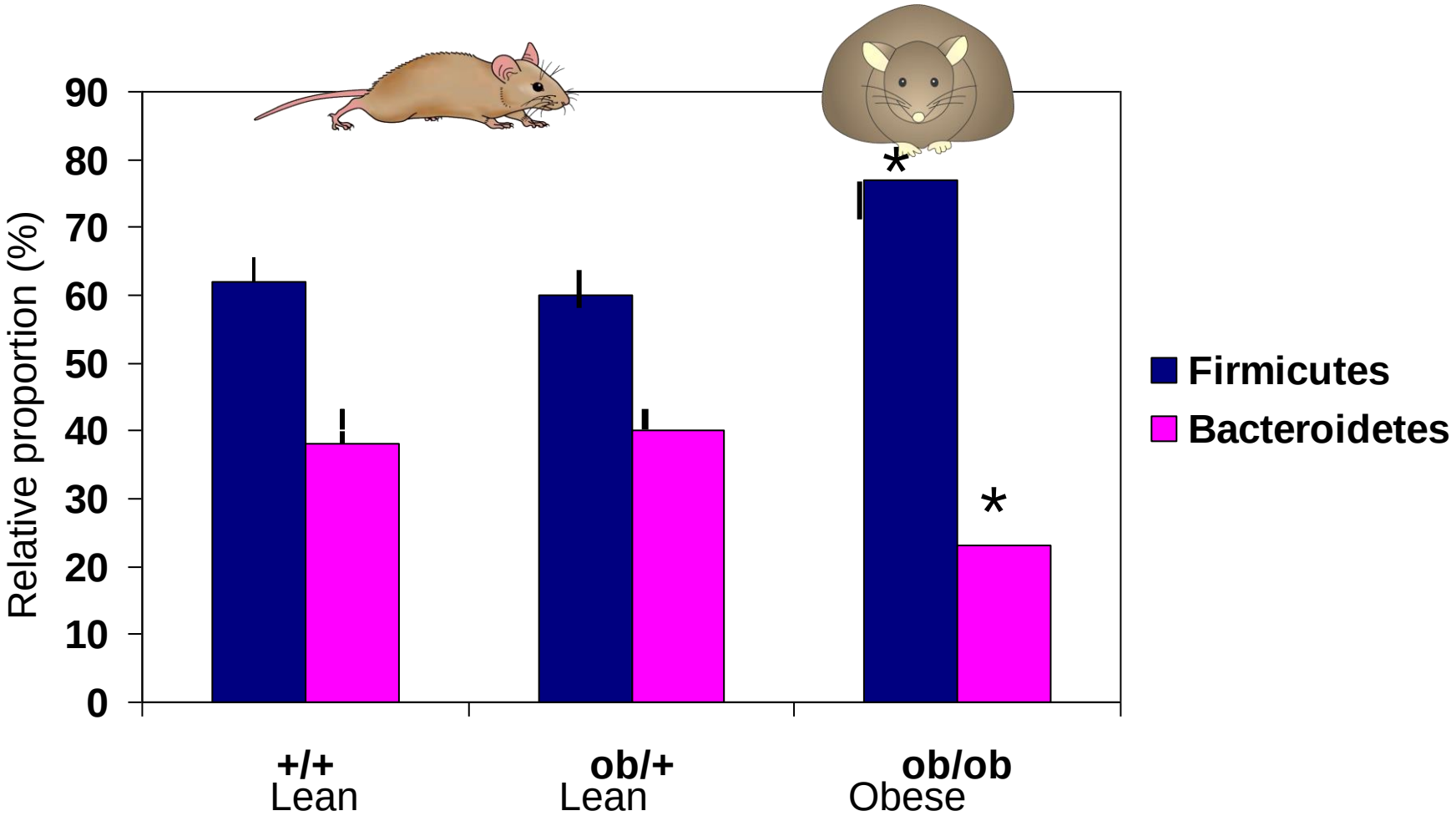
Inhibits colonization by pathogenic microorganisms

(Bacteriocins; hydrogen peroxide; organic acids; effects on host innate and adaptive immunity)

Facilitates extraction of energy and nutrients from food.
Provides nutrients and accessory growth factors (e.g. vitamin K).
Regulates host fat storage
The number of genes available is potentiated by a factor 100.



Obesity and the Intestinal Microbiota



Ley *et al.* 2005. *PNAS* 102, 11070-5.

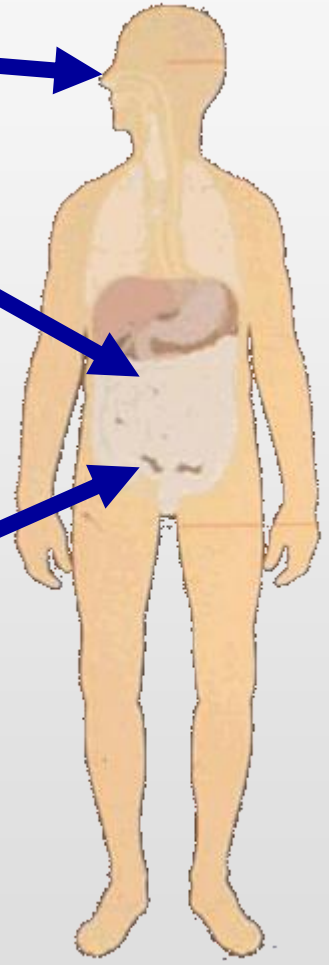
Functions of the commensal microbiota (2)

Maturation of host immune system (innate and adaptive) and fine-tuning of its reaction patterns.

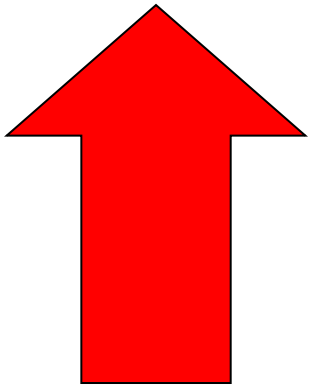
Attenuation of local inflammation

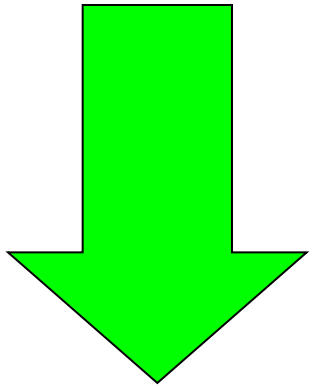
Post-natal differentiation of mucosal structure and function (incl. intestinal angiogenesis.

Continuous communication with host cells (e.g. affecting the expression of cell surface carbohydrates).



Inflammation on mucosal membranes and systemically





Patogens

Commensals

Bacteroides thethaiotaomicron and Bacteroides fragilis

Lactobacillus and *Bifidobacterium* spp.

Streptococcus salivarius

Streptococcus mitis

Some *E. coli* strains

Vol 455|23 October 2008|doi:10.1038/nature07336

nature

LETTERS

Innate immunity and intestinal microbiota in the development of Type 1 diabetes

Li Wen[1]*, Ruth E. Ley[2]*†, Pavel Yu. Volchkov[3]*, Peter B. Stranges[3,4], Lia Avanesyan[3,4], Austin C. Stonebraker[4], Changyun Hu[1], F. Susan Wong[5], Gregory L. Szot[6], Jeffrey A. Bluestone[6], Jeffrey I. Gordon[2] & Alexander V. Chervonsky[3,4]

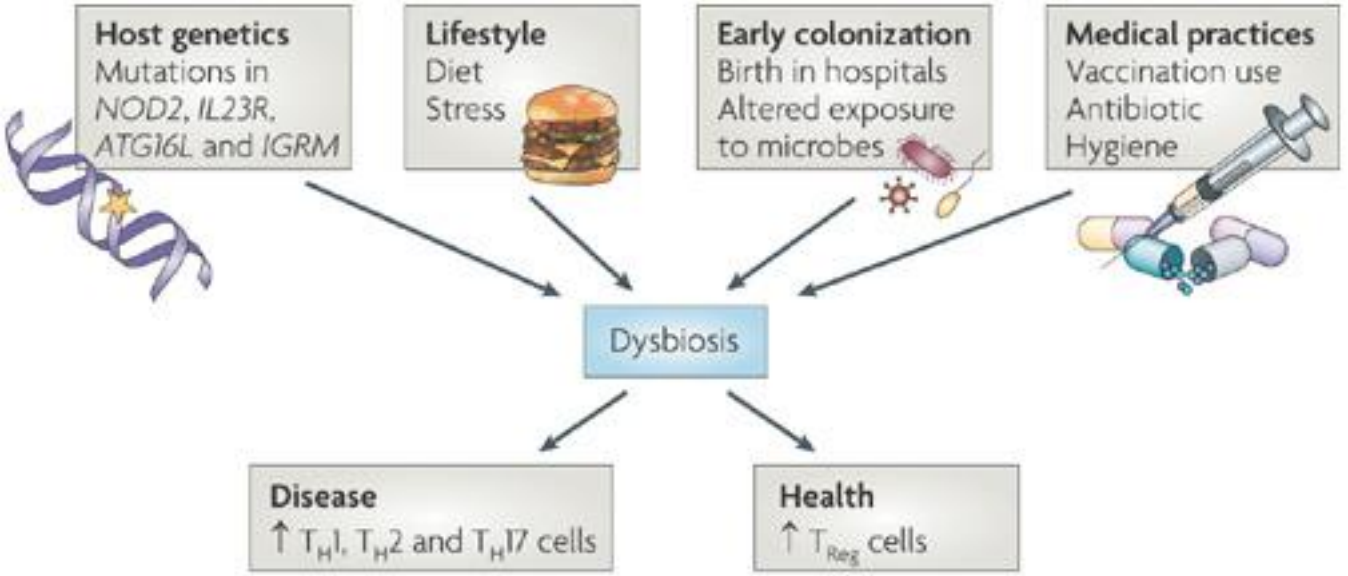
Type 1 diabetes (T1D) is a debilitating autoimmune disease that results from T-cell-mediated destruction of insulin-producing β-cells. Its incidence has increased during the past several decades in developed countries[1,2], suggesting that changes in the environment (including the human microbial environment) may influence disease pathogenesis. The incidence of spontaneous T1D in non-obese diabetic (NOD) mice can be affected by the microbial environment in the animal housing facility[3] or by exposure to microbial stimuli, such as injection with mycobacteria or various microbial products[4,5]. Here we show that specific pathogen-free NOD mice

deleted individually, in contrast to the effect of complete protection from diabetes associated with loss of MyD88 (Fig. 1).

These findings suggested that signalling through receptors that use the MyD88 adaptor is critical for T1D development, and that the autoimmune T cells would probably be affected systemically in $MyD88^{KO}$ NOD mice. Two types of experiments were performed to examine this hypothesis. First, splenocytes from pre-diabetic MyD88-sufficient and $MyD88^{KO}$ NOD mice were transferred into immunodeficient NOD/SCID (severe combined immunodeficient) animals. All recipients of control MyD88-sufficient splenocytes

"These findings indicate that interaction of the intestinal microbes with the immune system is a critical epigenetic factor modifying type 1 diabetes predisposition."

Proposed causes of dysbiosis of the microbiota



- We and our microbiota (bacteria, viruses, parasites) constitute an integrated superorganism, which is the result of millions of years of mutual adaptation and with significant advantages to both parts.

- The prospects for significant changes in the life style of the arctic population conceivably will have a significant impact on their commensal microbiota and ensuing disease predilections.