New Insights on the Structure of the Human Gut Microbiota

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HUMAN GUT MICROBIOTA

“WE ARE BORN 100 % HUMAN AND WE DIE 90% MICROBES”
COMPLEXITY OF MICROBIAL COMMUNITIES

Complex community

Microbial Culture
HUMAN MICROBIOME – EVOLUTION OF THE TECHNIQUES
From culture to High-throughput sequencing

Microbial Culture before the 90s

DNA cloning - sequencing
Functional genes
16s rRNA gene
2000

Sanger

454 FLX Titanium
Illumina (GAIIx)
AB SOLiD

Next generation Sequencing
2005-2013
10 YEARS BACK…

Figure 1 | Timeline of sequence-based metagenomic projects showing the variety of environments sampled since 2002. The oceanic viromes (all viruses in a habitat) (August 2006) were from the Sargasso Sea, Gulf of Mexico, coastal British Columbia and the Arctic Ocean. The nine biomes (March 2008) were stromatolites, fish gut, fish ponds, mosquito virome, human-lung virome, chicken gut, bovine gut and marine virome. The different technologies used are dye-terminator shotgun sequencing (black), fosmid library sequencing (pink) and pyrosequencing (green). (Graphic based on data sets represented at www.genomesonline.org.)
COST OF DNA SEQUENCING

Search in PubMed: “human gut microbiome” --> 2700 hits
The Human Microbiome Project

Peter J. Turnbaugh, Ruth E. Ley, Micah Hamady, Claire M. Fraser-Liggett, Rob Knight & Jeffrey I. Gordon

A strategy to understand the microbial components of the human genetic and metabolic landscape and how they contribute to normal physiology and predisposition to disease.
Manichanh et al., Nature Rev Gastro Hepato 2012
WHO ARE THEY?

Oceans: 12 phylas

Soil: 20 phylas

Human Gut: 10 phylas

1000 species
7000 strains

HUMAN MICROBIOME

160 species / individual
18 common species in all individuals (N=124)
57 species in > 90%
75 species in > 75%

3.3 millions non-redundant genes
500 000 prevalent genes/individual
38% are shared

Qin et al., Nature 2010
WHAT ARE THEY DOING?

Diversity

Functions

METABOLIC PATHWAYS
- Central carbohydrate metabolism
- Cofactor and vitamin biosynthesis
- Oligosaccharide and polyol transport system
- Purine metabolism
- ATP synthesis
- Phosphate and amino acid transport system
- Aminoacyl tRNA
- Pyrimidine metabolism
- Ribosome
- Aromatic amino acid metabolism

Human Microbiome Project 2012
FUNCTIONS

Minimal Gut Metagenome: 6000 functions (2000 were annotated)

Housekeeping functions (carbon metabolism and amino acid synthesis)

Gut specific functions (adhesion and sugar harvesting)

Qin et al., Nature 2010
FUNCTIONAL BIOMARKERS FOR HOST PROPERTIES

Functions that correlate with:

- **Age** (12 OGs: starch degradation enzymes increase)
- **Gender** (5 OGs: enriched aspartate biosynthesis modules in males)
- **Nations** (10 OGs, varies more between than within nationalities)

Arumugam et al., Nature 2011
We acquire the gut microbiota during delivery.

Depending on the delivery mode via the vagina or by c-section, our first microbiota will resemble more to the skin or the vagina population of our mom.
COLONIZATION AND EVOLUTION
OF THE MICROBIOTA

Succession of microbial consortia in the developing infant gut microbiome

Jeremy E. Koenig, Aymé Spor, Nicholas Scalfone, Ashwana D. Fricker, Jesse Stombaugh, Rob Knight, Largus T. Angenent, and Ruth E. Ley

PNAS

Edited by Todd R. Klaenhammer, North Carolina State University, Raleigh, NC, and approved June 24, 2010 (received for review March 2, 2010)
Comparison between different regions of the world and different culture
Great difference between children and adult microbiota during the 3 first years period
After that, the bacterial community evolves towards an adult-like configuration

Yatsunenko et al., Nature 2012
Difference in the phylogenetic microbial composition between individuals living in different countries

Yatsunenko et al., Nature 2012
MICROBIOME OF THE ELDERLY

160 elderly subjects (> 65 y) vs 9 adults

Claesson et al., PNAS 2010
GUT MICROBIOTA
ENTEROTYPES

Arumugam et al., Nature 2011
DISEASES ASSOCIATED MICROBIOTA
DYSBIOSIS

- Obesity
- Complication of cirrhosis
- IBD: Inflammatory Bowel Disease
  - Crohn’s disease
  - Ulcerative colitis
- IBS: Irritable Bowel syndrome
- Type 1 diabetes
“the same bacterial phyla predominate in the stomach, small intestine, and colon, although their relative abundance and details of the component species vary as a function of position along the gut”

Peterson et al., Cell Host Microbe 2008

Diet challenge uncovers a more unstable microbiota in patients

Dysbiosis at the species level

*Bilophila wadsworthia* was found positively correlated with volume of gas evacuated in patients at basal diet, $r = 0.64$; FDR = 0.12
- Lean and obese mice are differentiated by their relative abundance of the 2 dominant bacterial divisions: Bacteroidetes and Firmicutes
- Obese microbiome has an increase capacity to harvest energy from diet
- Transfer of the “obese microbiota” to germ-free mice increase body fat
STUDIES IN HUMAN
Turnbaugh et al., 2006; 2009

- Lower proportion of Bacteroidetes and a higher proportion of Actinobacteria in obese compared with lean individuals
- Bacteroidetes: enriched for several carbohydrate metabolism pathways
- Firmicutes: enriched for transport systems
- Obesity-associated genes: carbohydrate, lipid and amino-acid metabolism
- In obese subjects: a reduction of microbial diversity
Bimodal distribution of microbial genes

- Low gene count: < 480,000 genes
- High gene count: > 480,000 genes

- Species richness between groups of individuals with high and low gene counts
- 46 genera differed significantly in abundance between the HGC and LGC individuals

123 non-obese and 169 obese Danish individuals

Le Chatelier et al., Nature 2013
**Phenotypes of the HGC and LGC groups**

Le Chatelier et al., Nature 2013
58 species significantly different in abundance between LGC and HGC

Overall, this suggests that LGC individuals harbour an inflammation-associated microbiota

Le Chatelier et al., Nature 2013
Gut microbial composition of LGC (n=18) and HGC (n=27) subjects.

Baseline gene count

STUDIES IN HUMAN

Diet intervention

• Diet intervention: 49 obese and overweight subjects
• 6 weeks: high-protein diet and fibers
• 6 weeks: body weight stabilization period with 20% increase in total energy

Cotillard et al., Nature 2013
Gene richness may help to predict the efficacy of dietary intervention on inflammatory variables in overweight or obese individuals.

Cotillard et al., Nature 2013
Differences between LGC and HGC subjects in bioclinical variables

Cotillard et al., Nature 2013
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