The human gut microbiome
- role of gut microbiota in health and disease

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Incidence of infectious and immune disorders

A

Incidence of Infectious Diseases (%)


Rheumatic fever
Hepatitis A
Tuberculosis
Mumps
Measles

B

Incidence of Immune Disorders (%)


Crohn’s disease
Multiple sclerosis
Type 1 diabetes
Asthma

Bach NEJM 2002
Animalcules (microbiota in 1683)

Leeuwenhoek
Spatial distributions of microbial phyla in healthy humans

*Microbiota*: the set of microbial species living in a given environment (gut)

*Microbiome*: the collection of genes contained in a microbiota
The human gut microbial gene catalogue

Metagenomics of the Human Intestinal Tract (MetaHIT) project

124 individuals (85 Danes, 39 Spaniards)

- 1000-1150 bacterial species, at least 160 prevalent species in each individual

<table>
<thead>
<tr>
<th>Individuals</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 124</td>
<td>18</td>
</tr>
<tr>
<td>&gt;90%</td>
<td>57</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>75</td>
</tr>
</tbody>
</table>

Abundance of a bacterial species varies 12-2200 fold in individuals

Qin Nature 2010
Conserved microbial functions between individuals

A. Bacterial phylum

B. COG categories

The Sahlgrenska Academy

Turnbaugh Nature 2009
The gut microbiota differs along the length of the gut

Kovatcheva et al., The Prokaryotes
The normal gut microbiota

Trophic
Development and homoeostasis of the immune system
Control of epithelial cell proliferation and differentiation
Bone mass
Promote intestinal angiogenesis

Protective
Protection against pathogens

Metabolic
Fermentation of non-digestible dietary polysaccharides and endogenous mucus
Cholesterol metabolism
Production of vitamin K
Xenobiotic metabolism

• $10^{13}$ bacterial cells in the gut (>10x total ensemble of human cells)
• 3-4 million genes (150x human genome)
• >1,000 bacterial species

The normal gut microbiota

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- Development and homoeostasis of the immune system
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*Bone mass*
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*Nature 444, 21 December 2006.*
Isolators for maintaining gnotobiotic mice
Germ-free mice have increased bone mass

Sjögren et al., J. Bone Miner. 2012
The normal gut microbiota

**Trophic**

- Development and homoeostasis of the immune system
- Control of epithelial cell proliferation and differentiation
- Bone mass
- Promote intestinal angiogenesis

**Protective**

- Protection against pathogens

**Metabolic**

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*10^13* bacterial cells in the gut (>10x total ensemble of human cells)

*3-4* million genes (150x human genome)

>1,000 bacterial species

Gut microbiota promotes intestinal angiogenesis

Reinhardt et al., Nature 2012
Gut microbiota is associated with obesity

MICROBIAL ECOLOGY

Human gut microbes associated with obesity

The gut microbiota as an environmental factor that regulates fat storage

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Contributed by Jeffrey I. Gordon, September 24, 2004

An obesity-associated gut microbiome with increased capacity for energy harvest

Mechanisms underlying the resistance to diet-induced obesity in germ-free mice

Fredrik Bäckhed*, Jill K. Manchester*, Clay F. Semenovitch*, and Jeffrey I. Gordon**

*Center for Genome Sciences and **Department of Medicine, Washington University School of Medicine, St. Louis, MO 63108

Edited by John J. Mekalanos, Harvard Medical School, Boston, MA, and approved November 22, 2006 (received for review June 27, 2006)

A core gut microbiome in obese and lean twins

Peter J. Turnbaugh†, Micah Hamady†, Tanya Yatsunenko†, Brandi L. Cantarel†, Alexis Duncan†, Ruth E. Ley†, Mitchell L. Sogin†, William J. Jones†, Bruce A. Roe†, Jason P. Affourtit†, Michael Egholm†, Bernard Henrissat†, Andrew C. Heath†, Rob Knight† & Jeffrey I. Gordon†
Obese mice have fewer Bacteroidetes, more Firmicutes

Ley et al. PNAS 2005
Increased efficiency of the gut microbiota in obese mice

Turnbaugh et al. Nature 2006
Reduced diversity of the gut microbiota in obese individuals

Ley et al. Nature 2006
Turnabugh et al. Nature 2009
Gut microbiota is associated with CVD

Symptomatic atherosclerosis is associated with an altered gut metagenome

Fredrik H. Karlsson¹, Frida Fäk²,³,*, Intawat Nookaew¹,*, Valentina Tremaroli²,³, Björn Fagerberg²,³, Dina Petranovic¹, Fredrik Backhed²,³ & Jens Nielsen¹
Altered gut metagenome in CVD patients

Karlsson et al, Nat Commun 2012
Gut microbiota is associated with T2D in a Chinese population

A metagenome-wide association study of gut microbiota in type 2 diabetes

Junjie Qin, Yingrui Li, Zhiming Cai, Shenghui Li, Jianfeng Zhu, Fan Zhang, Suisha Liang, Wenwei Zhang, Yuanlin Guan, Dongqian Shen, Yangqing Peng, Dongya Zhang, Zhuye Jie, Wenxian Wu, Youwen Qin, Wenbin Xue, Junhua Li, Lingchuan Han, Donghui Lu, Peixian Wu, Yali Dai, Xiaojuan Sun, Zesong Li, Aifa Tang, Shilong Zhong, Xiaoping Li, Weineng Chen, Ran Xu, Mingbang Wang, Qiang Feng, Meihua Gong, Jing Yu, Yanyan Zhang, Ming Zhang, Torben Hansen, Gaston Sanchez, Jeroen Raes, Gwen Falony, Shuiro Okuda, Mathieu Almeida, Emmanuelle Le Chatelier, Pierre Renault, Nicolas Pons, Jean-Michel Batto, Zhaoxi Zhang, Hua Chen, Ruifu Yang, Weimou Zheng, Songgang Li, Huanming Yang, Jian Wang, S. Dusko Ehrlich, Rasmus Nielsen, Oluf Pedersen, Karsten Kristiansen, & Jun Wang
Causative?
Mechanism?
Germ-free mice are leaner than conventionally raised mice

Bäckhed et al. PNAS 2004
Germ-free mice are protected against diet induced obesity

Bäckhed et al. PNAS 2007
Rabot et al. FASEB J 2010
Ding et al PLoS one 2010
Fleissner et al Br J Nutr 2010
Bacterial modulation of host metabolism
Impaired glucose signaling in colonized mice

Caesar et al Gut 2012
Fewer crown-like structures in germ-free mice

Caesar et al. Gut 2012
Metabolism of food components

Independent effects
- Lipopolysaccharide
  - CD14/TLR4
  - Insulin resistance
- Peptidoglycan
  - NOD1

Dependent effects
- Choline
  - TMA
    - FMO host
    - TMAO
    - Cardiovascular disease
- Cholesterol
  - Primary bile acids
  - Secondary bile acids
- Polysaccharides
  - Short-chain fatty acids
  - Energy source
    - GPR41 and GPR43
    - Regulation of PYY and GLP-1
    - Modulation of inflammation

Tremaroli & Bäckhed, Nature 2012
Transcriptional responses by the gut microbiota and the innate immune system

Conventionally raised (CONV-R)
- C57Bl/6
- Myd88-/-
  - n = 5
  - n = 5

Germ-free (GF)
- C57Bl/6
- Myd88-/-
  - n = 4
  - n = 6

- 12 w old males
- Duodenum, jejunum, ileum, colon
- Liver
- Subcutaneous and epididymal adipose tissue
- In total 140 microarrays
Transcriptional responses by the gut microbiota and the innate immune system

http://microbiota.wall.gu.se

Larsson et al. Gut In Press
LCM of GF and CONV-R tip/crypt from ileum and colon
Harvest specific cell populations using LCM
Harvest specific cell populations using LCM
Harvest specific cell populations using LCM

Relative expression

- Alpi
- Apoa4
- Lyz1
- Defa5
- Duox2

- Alpi
- Krt20
- Ki67
- Ephb2
- Duox2

Tissue
Tip
Crypt
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