

The gut flora as a forgotten organ

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Microbiota vs microbiome

- Diet and nutritional status are among the most important, modifiable determinants of human health. The nutritional value of food is influenced in part by a person's gut microbial community (microbiota) and its component genes (microbiome)

- Sci Transl Med. 2009 November 11; 1(6): 6ra14. doi:10.1126/scitranslmed.3000322.

- "Bacteria within the gut are manipulative," said Carlo Maley, PhD, director of the UC San Francisco Center for Evolution and Cancer. "There is a diversity of interests represented in the microbiome, some aligned with our own dietary goals, and others not."

- DiSalvo, David "Gut Feeling: How Intestinal Bacteria Could Manipulate Your Brain" *Forbes* August 17, 2014, online access September 7, 2014



What is the microbiome?

- Housed in approx 400 square meters.
- According to the Human Microbiome Project, the microbiome is the collective genomes of the microbes (composed of bacteria, bacteriophage, fungi, protozoa and viruses) that live inside and on the human body. We have about 10 times as many microbial cells as human cells.

- <https://www.genome.gov/27549400>

Outline

- Defining the gut biome
- How diet can change the gut flora
- Gut diversity and health
- Antibiotics in food producing animals
- How we can promote gut diversity in diet

What does this mean?

- An analysis of the full gene content and composition of these microbiomes (i.e. the metagenome) predicts that there may be more than 8 million unique microbial genes associated with the microbiomes across the human body of healthy adults.

- When compared to the total number of human genes, this suggests that the genetic contribution of the microbiome to the human supraorganism may be many hundreds of times greater than the genetic contribution from the human genome.

Diet changes in the gut flora

- Within hours of a dietary change the population of gut flora will change and adapt to the new diet.
- Researchers assigned volunteers to two diets—one based on animal products such as meat, eggs and cheese and one based on vegetables. Almost immediately the gut microbiome responded. The animal diet, curbed the numbers of microbes that break down carbohydrates from plants and boosted levels of organisms that can tolerate bile, which helps to digest fats.
- Feltman, Rachel. **Gut Microbes Respond within Days to Major Diet Changes**, *Scientific American* Mar 1, 2014

Bacterial species in the gut

- Firmicutes (gram positive)
- Bacteroidetes (gram negative)
- Actinobacteria (gram positive)
- Zoetendal EG, Vaughan EE, de Vos WM.
- *A microbial world within us. Mol Microbiol* 2006;59:1639–1650

So.. What does this mean?

- One interesting note from the study...
- Increases in the abundance and activity of *Bilophila wadsworthia* on the animal-based diet support a link between dietary fat, bile acids and the outgrowth of microorganisms capable of triggering inflammatory bowel disease
- David, Lawrence A, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature*, 505, 559–563 (23 January 2014) doi:10.1038/nature12820

Modifiable vs non-modifiable ways to manipulate gut flora

- | | |
|---|---|
| <ul style="list-style-type: none"> ■ Diet ■ Stress ■ Exercise ■ Lifestyle choices ■ Medications | <ul style="list-style-type: none"> ■ Birth (in 2012 32.8% US Births were C-Sections) CDC data) ■ Early feeding (formula vs mothers milk) ■ Pregnancy <ul style="list-style-type: none"> ■ When gut flora from third trimester women was transplanted into sterile mice they became heavier and increased insulin resistance than mice transplanted with gut flora in first trimester women <i>Cell</i> 150, 470–480 (2012) |
|---|---|



- Microbes in the gastrointestinal tract are under selective pressure to manipulate host eating behavior to increase their fitness, sometimes at the expense of host fitness. Microbes may do this through two potential strategies: (i) generating cravings for foods that they specialize on or foods that suppress their competitors

Alcock JI, Maley CC, Aktipis CA. Is eating behavior manipulated by the gastrointestinal microbiota? Evolutionary pressures and potential mechanisms. *Bioessays*. 2014 Aug 8. doi: 10.1002/bies.201400071.

Functions of gut bacteria

- Synthesis of vitamins (K, B12, biotin, folic acid, pantothenate)
- Biotransformation of steroid hormones, bile acids, drugs, and dietary carcinogens
- Modulation of epithelial tight junctions and gut motility
- Production of n-butyrate as a fuel source for colonocytes

- (ii) inducing dysphoria until we eat foods that enhance *their* fitness. Because microbiota are easily manipulatable by prebiotics, probiotics, antibiotics, and dietary changes, altering our microbiota offers a tractable approach to otherwise intractable problems of obesity and unhealthy eating.

- Italics mine

Gut diversity

- The diversity of microbes within a given body habitat can be defined as the number and abundance distribution of distinct types of organisms, which has been linked to several human diseases: low diversity in the gut to obesity and inflammatory bowel disease
- The Human Microbiome Project. Structure, function and diversity of the healthy human microbiome. *Nature* **486**, 207–214 (14 June 2012) doi:10.1038/nature11234

Functions of gut bacteria

- Competition with potential pathogens for space and resources
- Digestion of plant polysaccharides that would otherwise be unavailable
- Promotion of monosaccharide absorption and triglyceride storage
- Priming of immune effector cells
- Absorption of ions (Ca²⁺, Mg²⁺, Fe²⁺)

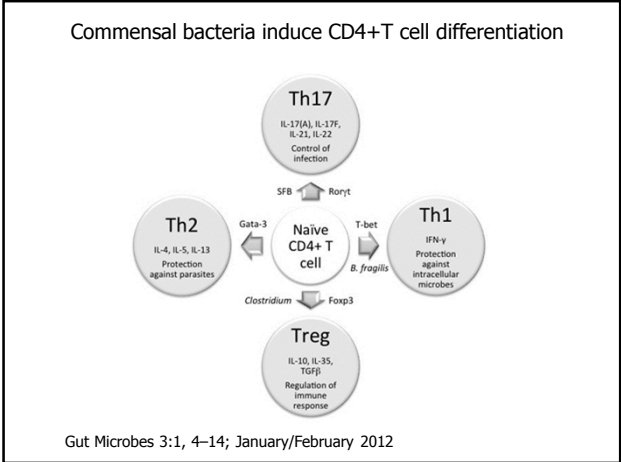
Diseases and disorders associated with human gut microbiome aberrations

- Celiac Disease
 - Pediatric celiac disease patients have significantly higher numbers of total bacteria, in particular Gram-negative organisms, compared with asymptomatic patients and healthy subjects
 - Bacteroides spp. and Escherichia coli were significantly higher in celiac disease compared with healthy subjects; abundance of these species returned to healthy levels in asymptomatic patients. The ratio of Lactobacillus–Bifidobacteria species to Bacteroides–E. coli was lower for celiac disease patients
 - Metabolomic study identifies signature metabolic pathways associated with celiac disease

Expert Rev Anti Infect Ther. 2010 April ; 8(4): 435–454. doi:10.1586/eri.10.14.

- **Obesity**
- **Type II diabetes**

- Obese patients may depend on interspecies transfer of H₂ between Archaea and Bacteria to increase energy uptake
- Obese individuals exhibit lower abundance of Bacteroidetes and a higher abundance of Firmicutes compared with lean people
- Ratio of Bacteroidetes and Firmicutes reverts back to a composition that resembles that of lean subjects following a diet and exercise regimen
- Absence or presence of specific functional groups and not bacterial species may be a more appropriate measure of the differences between obese and lean people
- Studies that examine the effects of the gut microbiota on Type II diabetes are often included in those that study the relationship between obesity and gut bacterial community
- Gut microbiota may contribute to insulin sensitivity, causing low-grade systemic inflammation, which may be independent of obesity



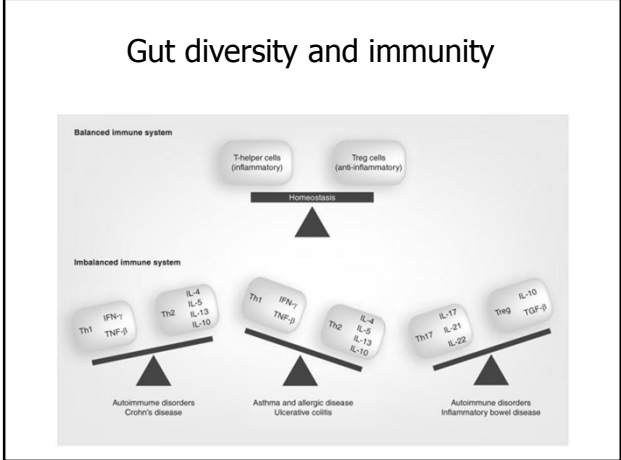
Gut microbiota and obesity

- Individuals with a low bacterial richness are characterized by more marked overall adiposity, insulin resistance and dyslipidemia and a more pronounced inflammatory phenotype when compared with high bacterial richness individuals. The obese individuals among the lower bacterial richness group also gain more weight over time
- Le Chatelier E, et al. Richness of human gut microbiome correlates with metabolic markers. *Nature*. 2013 Aug 29;500(7464):541-6. doi: 10.1038/nature12506.

Antibiotics in food

In food animals, FDA has approved the use of antibiotics in addition to treating infection:

Growth promotion or increased feed efficiency in a herd or flock of animals to promote weight gain.



FDA 2011 report

- Starting in 2009 FDA started reporting on the use of antibiotics in food producing animals.
- Over 29 million pounds of antibiotics annually given to feed livestock in 2009-2011
- 300mg of antibiotics are used to provide every kilogram of meat and eggs
- **FDA Annual Report on Antimicrobials Sold or Distributed for Food-Producing Animals in 2011**
- *Nature* 486 Get Pigs off Antibiotics, 465-466, 28 June 2012

Antibiotic classes FDA approved for use

Aminocoumarins	Macrolides
Aminoglycosides	Penicillins
Amphenicols	Pleuromutilins
Cephalosporins	Tiamulin
Diaminopyrimidines	Polypeptides
Fluoroquinolones	Bacitracin
Ionophores	Quinoxalines
Lincosamides	Sulfas
	Tetracyclines

History of prebiotics in diet

- Analysis of well-preserved coprolites suggest that dietary intake of inulin was about 135 g/day for the typical adult male hunter-forager.

- Gibson G.R., Roberfroid M.B. Dietary modulation of the human colonic microbiota: Introducing the concept of prebiotics. *J. Nutr.* 1995;125:1401-1412.

CDC statement

- Food animals serve as a reservoir of resistant pathogens and resistance mechanisms that can directly or indirectly result in antibiotic resistant infections in humans. For example, resistant bacteria may be transmitted to humans through the foods we eat.
- Some bacteria have become resistant to more than one type of antibiotic, which makes it more difficult to treat the infections they cause.

- <http://www.cdc.gov/narms/animals.html>

Inulin and oligofructose in common foods, listed in g/100g

- **Banana**
- Raw **0.5/0.5**
- Raw-dried **1.4/1.4**
- **Asparagus**
- Raw **2.5/2.5**
- Boiled **1.7/1.7**
- **Chicory root 41.6/22.9**
- **Globe artichoke 4.4/0.4**
- **Jerusalem artichoke 18.0/13.5**
- **Leeks, Raw 6.5/5.2**
- **Onions, Raw 4.3/4.3**
- Raw-dried **18.3/18.3**
- Cooked **3.0/ 3.0**
- **Garlic, Raw 2.5/5.0**
- Dried **28.2/11.3**

J. Nutr. July 1, 1999 vol. 129 no. 14075-1411s

Prebiotics

- Classification of a food ingredient as a prebiotic requires scientific demonstration that the ingredient:
- Resists gastric acidity, hydrolysis by mammalian enzymes, and absorption in the upper gastrointestinal tract;
- Is fermented by the intestinal microflora;
- Selectively stimulates the growth and/or activity of intestinal bacteria potentially associated with health and well-being.

- Gibson G.R., Roberfroid M.B. Dietary modulation of the human colonic microbiota: Introducing the concept of prebiotics. *J. Nutr.* 1995;125:1401-1412.

Inulin and oligofructose in common foods, listed in g/100g

- **Wheat**
- Bran-raw **2.5/2.5**
- Flour-baked **2.4/2.4**
- Flour-boiled **0.4/0.4**
- **Barley**
- Raw **0.8/ 0.8**
- Cooked **0.2/0.2**
- **Rye, Baked 0.7/0.7**
- **Dandelion greens**
- Raw **13.5/ 10.8**
- Cooked **9.1/7.3**

Conclusions from the Human Microbiome Project

- This is only the beginning. We have learned that the bacteria living in and on us are not invaders but are beneficial colonizers. The hope is that, as research progresses, we will learn how to care for our microscopic colonizers so that they, in turn, can care for our health.

- <https://www.genome.gov/27549400>