The Gut Microbiome in Health and Disease

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Comprised of Bacteria, Viruses, others (Archaea, Eukaryotes)

Distinctive microbiomes at each body site (gut, lung, skin, mucosa etc.)

The Gut Microbiome
- Human gut is home to ~100 trillion bacterial cells
- Density of $10^{11}$ to $10^{12}$ per gram in the colon
- Genome size of microbiota at least 100-fold greater than human
- Large numbers species present, most uncultured

Host-Microbial Mutualism of the Gut

Host benefits to the bacteria
• Provides a unique niche
• Intestinal mucus provides a source of nutrition

Bacteria benefits to the host
• Fermentation of indigestible carbohydrates to assist digestion
• Biotransformation of conjugated bile acids
• Urease activity participates in nitrogen balance
• Synthesis of certain vitamins
• Metabolize drugs
• Education of the mucosal immune system
Gut Microbiome Development

Colonization of the gut begins at birth

Transition to the highly distinct, highly differentiated adult microbiota
Community Evolves Towards an Adult-like Configuration by the Toddler years

Factors that affect gut microbiome composition

- Environment
- Genetics
- Other Host Factors
- Antibiotics
- Inflammation
- Diet

Science. 2011 May 20;332(6032):970-4
Science. 2011 Jul 1;333(6038):101-4
Science. 2011 Oct 7;334(6052):105-8
Elements of Modern Lifestyle Lead to Changes in Gut Microbiota

- Improved sanitation
- Less crowded living conditions
- Decline in parasite and *H. pylori* infections
- Vaccinations
- Increased antibiotic use
- Sedentary lifestyles
- Caesarean section
- Refrigeration
- Food processing
- Diet changes
Diet and the Gut Microbiota
Greatest change occurs with introduction of solid foods

Clustering of Gut Microbiome into Enterotypes is Associated with Long-term Diet

The *Bacteroides* enterotype,
Highly associated with animal protein and saturated fats which suggests that meat consumption is associated with a Western diet

The *Prevotella* enterotype,
High values for carbohydrates and simple sugars indicating association with a carbohydrate-based diet more typical of agrarian societies
Impact of Diet in Shaping Gut Microbiota Revealed by a Comparative Study in Children from Europe and Rural Africa

African Diet: High Fiber and carbohydrate, low animal fat and protein

European Diet: High animal fat and protein, low fiber

De Filippo C, et al. PNAS 2010: 14691-96
HUP/CHOP Microbiome Project: Longitudinal analysis of microbiome under controlled feeding

Changes detectable within 24 hours!

Each color represents a different subject

Methods
454 pyrosequencing of 16S rDNA

Day 1 is different than all other days!!
The Gut Microbiota in Health and Disease

Cerf-Bensussan N, Gaboriau-Routhiau V, Nature Reviews Immunology 10, 735-744 (October 2010)
Gut Microbiome and Disease

- **Diabetes:** Type 1 DM and Type 2 DM
- **Obesity:** dysbiosis?
- **Atherosclerosis:** Oral, gut and plaque microbiota; Microbial metabolism of choline to TMA
- **Asthma:** Sanitized environment
- **Colon Cancer:** Enterotoxigenic *Bacteroides fragilis* and *Fusobacterium*
- **Inflammatory Bowel Disease:** Dysbiosis
- **Clostridium difficile:** dysbiosis
C. Difficile and Dysbiosis of Gut microbiota

- Gram positive, anaerobic, spore forming bacterium
- Infection is due to:
  - toxins TcdA and TcDB
  - NAP1/027/B1 strain: increased virulence
- Frequently secondary to antibx use that result in a dysbiotic gut microbiota
  - Decrease in abundance of members of the Bacteroidetes and Firmicutes phyla, increase in Proteobacteria (enterobacteraceae)
Reset of Disturbed Microbiota

Fuentes et al, ISME journal 2014
Environment + Host Genotype = Disease

• Increased Incidence

• Geographic distribution
  – Clustering in industrialized nations

• Immigration studies
  – Adoption of disease risk of the host country within 1 or 2 generations

• Genomic advances
  – Contribution of host genetics to the risk of disease development is significantly less than 50%
IBD and the Gut Microbiome
Associations of Environmental Factors with New Onset IBD

- Infectious gastroenteritis
- Early antibiotic use has been associated with IBD
  - Tetracycline
  - Oral antibiotics for ear infection
Trends in Incidence of IBD

N. America/Europe

Immigrants from low incidence region have rates comparable to high incidence natives.

Trend not explained by genetics, but environmental changes (Westernized diet, gut microbiome)

Asia
Clinical Evidence Implicating a Role of Bacteria in the Pathogenesis of IBD in Humans

• Inflammation occurs predominantly in the terminal ileum and colon, where the greatest concentrations of bacteria are found

• Antibiotics can be a modestly effective treatment for Crohn disease

• Surgical diversion of the fecal stream is an effective treatment for Crohn disease
  • Inflammation is known to recur upon restoration of the fecal flow
Dysbiosis of Gut Microbiota

Potentially injurious species in susceptible hosts

- *Bacteroides vulgatus*, *B. thetaiotaomicron*
- *Escherichia coli* (adherent/invasive)
- *Enterococcus faecalis* (nonpathogenic)
- *Klebsiella pneumoniae*
- *Fusobacterium varium*
- *Helicobacter hepaticus* and other intestinal species
- *Bifidobacterium animalis*

Protective species

- *Lactobacillus* species
- *Bifidobacterium* species
- *Escherichia coli*
- *Bacteroides thetaiotaomicron*
- *Faecalibacterium prausnitzii*

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Identification of Disease Associated Pathways

Epithelial barrier
- GNA12*, HNF4A, CDH1, ERRF1, MUC19, ITLN1*

Restitution
- REL, PTGER4, NKK2-3, STAT3, ERRF1, HNF4A, PLA2G2A/E

Solute transport
- SLC9A4, SLC22A5, SLC22A4*, AQP12A/B, SLC9A3, SLC26A3

Paneth cells
- ITLN1*, NOD2*, ATG16L1*, XBPI*

Innate mucosal defence
- NOD2*, ITLN1*, CARD9*, REL, SLC11A1, FCGR2A/B

Immune cell recruitment
- CCL11/CCL2/CCL7/CCL8, CCR6, IL8RA/IL8RB, MST1*

Antigen presentation
- ERAP2*, LNP6P, DENND1B

IL-23/T_H17
- IL23R*, JAK2, TYK2*, STAT3, ICOSLG, IL21, TNFSF15*

T-cell regulation
- NDFIP1, TNFSF8, TAGAP, IL2, IL2Rv, TNFRSF9, PIM3, IL7R*, IL12R, IL23PRD1, ICOSLG, TNFSF8, IFNG, IL12

B-cell regulation
- IL5, IKZF1, BACH2, IL7R*, IRF5

Immune tolerance
- IL10, IL27*, SBN02, CREM, IL1R1/IL1R2, NOD2*

**Cellular responses**

**Autophagy**
- ATG16L1*, IRGM, NOD2*, LRRK2, CUL2, PARK7, DAP

**Apoptosis/necroptosis**
- FASLG, THADA*, DAP, PUS10, MST1*

**ER stress**
- CPEB4, ORMEL3, SERINC3, XBPI*

**Carbohydrate metabolism**
- GCKR*, SLC2A4RG

**Intracellular logistics**
- VAMP3, KIF21B, TTL8, FGFR1OP, CEP72, TPP1

**Oxidative stress**
- PRDX5, BACH2, ADO, GPX4, GPX1*, SLC22A4, LRRK2, NOD2*, CARD9*, HSPA6, DLD, PARK7, UTS2*, PEX13

**Cell migration**
- ARPC2, LSP1, AAMP

**IBD-related processes**

- Microbial sensors
- Recruitment of mediators
- Signal amplification
- Transducers and effectors

Microbiota, diet

Microbiota, diet

Plasma cell

B cell

T_H17

T_reg cell

IgA

Xavier 2011
“Bacterially”-Generated Phenotypes

Germ-Free

Commensal Bacteria

E. faecalis

E. coli

Genomics and IBD

Primary Immunodeficiencies

Kugathasan, *IBD* 2014
Very Early-Onset IBD

• Diagnosed ≤5 years of age
• Frequently different phenotype and more severe disease presentation
• Often unresponsive to conventional therapy
• No standard guidelines:
  – evaluation and treatment

Candidate Pathways for VEO-IBD?
Whole Exome Sequencing
Gut Microbiota Development

Factors affecting the microbiome
- Genetics
- Birth route
- Geography
- Hygiene
- Stress
- Diet/nutrition
- Drugs

Microbiome complexity and stability

Disease

Healthy

Perturbation

Infectious diseases, metabolic diseases, and inflammatory disorders

- Protect against pathogens
- Train/stimulate immune function
- Supply nutrients, energy, vitamins, SCFA

- Inflammation (local > systemic)
- Oxidative stress
- Increase in Gram negative bacteria
- Infection (opportunistic/pathogenic)
- Altered metabolite production

Early onset

Adult onset

Late onset

Birth 3 years Adult Elderly

Kostick et al, Gastro 2014
The microbiome shapes the innate immune response and vice versa.