Age: the microbiome through life and its impact on host

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Host-microbiome states change with age: Impact on human health and disease

Assembly
Maternal, environmental, dietary influences

‘Stability’
compositional stability variable metabolic activity

Instability
loss of key species gain of pathobionts

Slide adapted from one provided by Fergus Shanahan
Potential insights gained through a combination of human and experimental models
Crohn’s disease and ulcerative colitis are **clinical phenotypes** of inflammatory bowel diseases.

**Crohn’s disease**

**Ulcerative Colitis**
Inflammatory Bowel Diseases (IBD): prototypes of complex immune disorders

- Gut Microbes
- Environment
- Host Genetics, other Factors

IBD
Our gut microbial organ up close

Colonic Mucosa

Gut Microbes

Mucus
The Treatment-Naive Microbiome in New-Onset Crohn’s Disease

Dirk Gevers,1 Subra Kugathasan,4,24 Lee A. Denson,5,24 Yoshiki Vázquez-Baeza,6 Will Van Treuren,7 Boyu Ren,8 Emma Schwager,8 Dan Knights,9,10 Se Jin Song,7 Moran Yassour,1 Xochiti C. Morgan,8 Aleksandar D. Kostic,1 Chengwei Luo,1 Antonio González,7 Daniel McDonald,7 Yael Haberman,5 Thomas Walters,11 Susan Baker,12 Joel Rosh,13 Michael Stephens,14 Melvin Heyman,15 James Markowitz,16 Robert Baldassano,17 Anne Griffiths,18 Francisco Sylvester,19 David Mack,20 Sandra Kim,21 Wallace Crandall,21 Jeffrey Hyams,19 Curtis Huttenhower,1,8 Rob Knight,7,22,23 and Ramnik J. Xavier1,2,3,*
Peripartum antibiotics are commonly used in mothers and infants

Facts:

• ~ 40% of pregnant women at term
• In developed countries, broad-spectrum antibiotics are prescribed more frequently during pregnancy. (Petersen et al., 2010)
• >30% of neonates are exposed to antibiotics. (Broe et al., 2014; Stokholm et al., 2013)
• In most cases, indications for antibiotic use during the peripartum period are unclear
Early-in-life antibiotics, altered immune states, disease risk

Peripartum Antibiotics Promote Gut Dysbiosis, Loss of Immune Tolerance, and Inflammatory Bowel Disease in Genetically Prone Offspring

Jun Miyoshi,1,2 Alexandria M. Bobe,1,2 Sawako Miyoshi,1 Yong Huang,1 Nathaniel Hubert,1 Tom O. Delmont,1 A. Murat Eren,1 Vanessa Leone,1 and Eugene B. Chang1,3,7

Intergenerational transfer of antibiotic-perturbed microbiota enhances colitis in susceptible mice

Anjelique F. Schulfer1,2, Thomas Battaglia3, Yelina Alvarez3, Luc Bijnens4, Victoria E. Ruiz3,5, Melody Ho3, Serina Robinson6, Tonya Ward7, Laura M. Cox3,8, Arlin B. Rogers9, Dan Knights10, R. Balfour Sartor11 and Martin J. Blaser1,3,12*
Does early life exposure to antibiotics cause gut dysbiosis, skewed immune development and increase risk for IBD in genetically prone subjects?
Peripartum antibiotic exposure increases the risk for spontaneous colitis in IL-10 KO offspring

Miyoshi, et al. Cell Reports 2017
IL10KO offspring without frank colitis after exposure to peripartum CPZ are more susceptible to DSS-induced colitis.

IL-10 KO mice exposed to CPZ during a critical window of development exhibit increased susceptibility to developing both spontaneous and chemically-induced colitis later in life.
Peripartum CPZ treatment induces persistent and significant gut dysbiosis in IL-10 KO offspring

Miyoshi, et al Cell Reports 2017
Gain or loss of microbiota function?

10 female pups in each group

10 male pups in each group

Miyoshi, et al Cell Reports 2017
Host-immune states with aging: Impact on human health and disease

Host

Gut Microbiome

Immune response, development, diversity

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Inflammation
Immune aging

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Limitations of cross-sectional studies in IBD

**Curve 1:** Remission or mild severity of intestinal symptoms after initial high activity

**Curve 2:** Increase in the severity of intestinal symptoms after initial low activity

**Curve 3:** Chronic continuous symptoms

**Curve 4:** Chronic intermittent symptoms

Source: © 2011 BMJ Publishing Group Ltd & British Society of Gastroenterology
Why study ulcerative colitis with total colectomy and ileal pouch anal anastomosis (IPAA)?

- ~50% pts will develop it in <2y
- Incidence in UC >> FAP
- Microbe-dependent
- Prospective design
- Easy to sample (unprepped)
- Pts as their own controls
- Control group (FAP)

Fig. 1: Anatomy of an ileal pouch anal anastomosis. Following colectomy, the terminal ileum is fashioned into a “J-pouch” connected to the anal canal (from www.mayoclinic.com).

Highlights

- Incidence in UC >> FAP
- Microbe-dependent
- Prospective design
- Easy to sample (unprepped)
- Pts as their own controls
- Control group (FAP)
Study design and sampling points

Mucosal biopsy and luminal aspirate

FAP patients – studied only at one time point > 2 yrs after IPAA

Sample analysis
- **Patient**
  - Histology
  - Gene Expression
  - Clinical metadata
- **Microbiome**
  - Membership (16S)
  - Function profile
  - Cultivars

Pouchoscopy and biospecimen collections

TC-IPAA 4 8 12

Track outcome
UC patients exhibit differences in tissue response to gut microbiota (coding and nc RNA)

Non-UC (FAP) patients

No significant differences in genes in transcriptomes

UC patients

>6000 genes different
Pathways represented in the UC pouch transcriptome

• Colonic metaplasia
• Changes in the extracellular matrix and growth factors
• Enhanced immune activation
• Suppressed xenobiotic metabolism and P450 signaling
Aberrant gene expression profiles of the UC pouch are evident at 4 months after pouch functionalization (Illumina HiSeq 75bp, PE)

Upregulated DEGs

Pre-Pouch  12 mo  Pouch

Downregulated DEGs

Pre-Pouch  12 mo  Pouch

4mo Pouch - UP genes

4mo Pouch - DN genes
What about the role of gut microbes in the development of UC pouchitis?
B. fragilis blooms before and during pouchitis in some, but not all patients
Capsular polysaccharide (CPS) genes
Mucosa metagenome
Lumen metagenome

Analysis performed by Alon Shaiber using Anvi’o

The *B. fragilis* genome
4,296 genes (ordered by synteny)

A. Murat Eren (Meren)
Assistant Professor
University of Chicago
Genomic hot spots: Capsular polysaccharides
Proposed three stage model for the development of pouchitis

Stage I
- Colonic-like microbiota
- FAP
- ~50%

Stage II
- UC
- Stage III
- Pathobiont(s)
- ~50%

Stage III
- Compensated state of immune activation and inflammation
- COLONization

Healthy

Pouchitis

Intestinal continuity restored

Seal pouch

The University of Chicago
Argonne National Laboratory
MBL Biological Discovery in Woods Hole
Mayo Clinic
IBD pathobionts – what should we be looking for?
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Gut Microbiome

Host

Immune response, development, diversity

Metabolic demands

Inflammation Immune aging

Metabolic decline

Slide adapted from one provided by Fergus Shanahan
Diversity as staple not spice of life

Dietary diversity

Microbial diversity

Inflammation

CRP
IL-6
TNF-α

Frailty

Shanahan et al. Gut 2017
Claesson et al. Nature 2012
Gut bacteria vary with where you live

Claesson et al., 2012 Nature
Microbiota & diet correlation by duration in long-stay care

Claesson et al., 2012 Nature
Potential impact of the aging gut microbiome on human health

**Fig. 2** a Prominent health conditions with both biologic age and chronic inflammation as central risk factors. b Prominent health conditions with evidence linking them to gut dysbiosis. Note the similarities between the conditions associated with aging and inflammation and those associated with gut dysbiosis.
Key questions posed for this workshop

- Many factors can influence responses such as genetics of the individual/subpopulation, diet, concomitant disease and drugs, etc. Maybe. What evidence do we have on these factors playing a role in the microbiome particularly as it affects human susceptibility? Shown

- Are there groups of bacteria that signal impact on the microbiome? How would you go about ranking or prioritizing the bacterial subgroups? (1) Building next generation of functional tools to study microbial strains and consortia in context. (2) Combination of human and experimental models, (3) longitudinal and interventional study designs

- How do we account for different functioning capacities when we think of species level diversity? (combine with second question?) Species-level is insufficient resolution

- What would the most impactful work that a public-private consortium could contribute to this area? Promoting and funding innovative team science that goes beyond description and observation; Focus on bold, transformative agendas. Use both human and experimental approaches.

- How do changes in the gut microbiome produce adverse effects that can impact the health of the host and result in the presence of biomarkers? What approaches have been successful? What have failed? Too early to tell

- What would the most impactful work that a public-private consortium like HESI could contribute to this area? See above
Metagenomic-assembled genomes (MAGs) selected for further study
Tay Lab – Microfluidics for Life Sciences
Microfluidic separation of Microbes

Poisson Distribution

\[ P(X = x) = \frac{e^{-\lambda}}{x!} \lambda^x \]

\( x \): number of bacteria in a single droplet
\( \lambda = \frac{\text{Number of cells/mL}}{\text{Number of drops/mL}} \)
Perinatal Antibiotics and Immune Tolerance Team

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