Microbe-Host Interactions in Inflammatory Bowel Diseases

Hera Vlamakis
Oct 3, 2018
Most of the bacteria in your body are in your gut

**HEALTH BENEFITS**
- Breakdown of polysaccharides
- Synthesis of vitamins
- Colonization resistance
- Maturation of our immune system

**DISEASE**
- Inflammatory bowel diseases
- Specific microbes enriched or depleted

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Stool is proxy for gut microbes

Mowat & Agace 2014 doi:10.1038/nri3738
Today’s Questions:

• Do infants acquire bacterial strains from their mother?

• Are different bacterial strains present in disease?

• Are microbial species associated with response to treatment or disease severity?
Early life events shape the microbiome

Delivery mode affects the newborn’s gut microbiome.

By age 3 years, the gut microbiome is adult-like.

Vertical transmission of microbes from mother to infants.

Large-scale paired longitudinal study of both mother and child samples

References:

- Koenig et al., PNAS 2011
- Yatsunenko et al., Nature 2012
- Dominguez-Bello et al. PNAS 2010
- Bäckhed et al., Cell Host & Microbe, 2015
- Asnicar et al. mBio 2017
- Koenig et al, PNAS 2011
Longitudinal mother-infant cohort design

33 families in total = metagenomic sequencing for 264 samples.

How similar are samples from the same family?

Yassour, Jason, Hogstrom et al. 2018 Cell Host and Microbe
Phylum-level microbial trajectories

Can we find distinctive species that were inherited by the child from the mother?
Do mother and child share their strains?

We are limited to species for which we have enough coverage for both mother and child samples.

*Yassour, Jason, Hogstrom et al. 2018 Cell Host and Microbe*
Do mother and child share their strains?

Yassour, Jason, Hogstrom et al. 2018 Cell Host and Microbe
Do mother and child share their strains?

Yassour, Jason, Hogstrom et al. 2018 Cell Host and Microbe
Transmission pattern varies across species

- **Bifidobacterium longum**: Mostly secondary strain transmissions
- **Bacteroides vulgatus**: Mostly dominant strain transmissions
- **Bacteroides dorei**: Mostly secondary strain transmissions
- **Bifidobacterium adolescentis**: z-score for dominant strain transfer
Functional differences in maternal strains may elicit inheritance mode

Bacteroides uniformis

Yassour, Jason, Hogstrom et al. 2018 Cell Host and Microbe
Functional differences in maternal strains may elicit inheritance mode.

Bacteroides uniformis

Yassour, Jason, Hogstrom et al. 2018 Cell Host and Microbe
Functional differences in maternal strains may elicit inheritance mode. Maternal strains that can utilize human milk oligosaccharides may be more likely to colonize the infant gut.
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Factors that influence development of inflammatory bowel diseases

IBD is caused by dysfunction in the \textit{composition of and interactions} between microbes, intestinal epithelium, and the immune system.
Differentially abundant species in IBD

Up in IBD species
- Ruminococcus gnavus
- Escherichia coli
- Streptococcus salivarius
- Streptococcus parasanguinis
- Haemophilus parainfluenzae
- Enterococcus faecium

Down in IBD species
- Faecalibacterium prausnitzii
- Eubacterium rectale
- Ruminococcus bromii
- Alistipes finegoldii
- Clostridium leptum
- Odoribacter splanchnicus

Hypothesis: Increased production of reactive oxygen species in IBD causes a decrease in obligate anaerobes and replacement by facultative anaerobes that can tolerate ROS

Morgan et al. 2012 (Huttenhower)
Lewis et al. 2015 (Wu)
Ballal et al. 2015 (Garrett)

Hall, Yassour et al. 2017 Genome Medicine
Transiently increased abundance of *R. gnnavus* in IBD

*Hall, Yassour et al. 2017 Genome Medicine*
Pangenome analysis of *R. gnavus*
Clade 2 is only found in adults with IBD

Metagenomic data from
- IBD: LSS, Lewis et al.
- Healthy: HMP, 500FG

*R. gnavus* clade 2 found in IBD patients from 3 clinical centers

199 Clade 2 specific genes
- Responses to oxidative stress
- Mucus utilization
- Adherence
- Iron acquisition

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Hall, Yassour et al. 2017 Genome Medicine
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Study overview: PROTECT

405 pediatric, treatment-naive cohort with new-onset UC

2 treatment strategies

Strategy 1: mesalamine

Strategy 2: corticosteroids → mesalamine

Sample collection weeks:

- 263 rectal biopsies
- 949 stool samples

1,212 samples

Pediatric patients often exhibit a more severe clinical phenotype compared to adults

Schirmer et al. 2018 Cell Host and Microbe
While disease severity improved for many patients, only 34% achieved week 12 remission and 37% achieved week 52 remission.

Schirmer et al. 2018 Cell Host and Microbe
Samples cluster by disease severity

Changes in microbial community composition are associated with disease severity

Fecal calprotectin significantly increases with disease severity

Schirmer et al. 2018 Cell Host and Microbe
Microbial factors are associated with disease severity

- Heatmap shows 30/91 most significant OTUs (1,212 samples, FDR < 10^{-11})
- 75% of severity-decreased OTUs (54) were from the order Clostridiales
- Increase in oral taxa associated with severe disease

Schirmer et al. 2018 Cell Host and Microbe
**Severe patients** achieving **week 52 remission** started with high levels and displayed a **continuous decrease** of *H. parainfluenzae*

**Mild patients** that **failed to achieve week 52 remission** started with lower levels but displayed a **substantial increase** by week 52.
Human Microbiome Project 2: Goals and Objectives of this Study

132 subjects; sampled every 2 weeks; 1 year

Ramnik Xavier and Curtis Huttenhower
The IBD Multi’omics DataBase

The Inflammatory Bowel Disease Multi'omics Database

The cells of the human body are outnumbered ten to one by bacteria, but large-scale surveys of the human microbiome were not feasible until the advent of next-generation sequencing. The first stage of the Human Microbiome Project sampled 300 healthy subjects to determine normal microbial composition of healthy Americans (which microbial species were there), their biochemical function (what the microbes were doing), and microbial variation both between individuals and over time. Now that we have determined the healthy human microbiome, the next stage of the Human Microbiome Project is to understand how the microbiome changes in and contributes toward disease.

Inflammatory bowel disease (IBD), which includes both Crohn’s Disease (CD) and ulcerative colitis (UC), affects approximately 1.5 million Americans and is one of the most-studied imbalances between microbes and the immune system. Genetic and environmental risk factors exist but are not associated with IBD; however, they are inadequate to explain the dramatic (more than 1000-fold) increase in microbiota diversity in IBD patients compared with non-IBD individuals. For better insight into the role of the microbiota in IBD disease, the project seeks to improve the understanding of the microbial community dynamics and to provide many useful data on genetic and metabolic differences.

Results

This page shows the high-level results across all of the HMP2 pipelines. Each run is comprised of a set of data that has been uploaded to the HMP2 servers. Once there, it is filtered for quality and error checked for completeness and saved under the raw files page. After the QC phase, the data is run on a specific Andromeda pipeline, producing several types of data products. Each data product for a project is saved on the products page. For contact information regarding the results and the workflow process, please search here.

Available Studies

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Containers

- Virionics Protocol
- Clinical Protocol
- Metabolomic Protocol

Objects

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http://ibdmdb.org
Thank you!

Ramnik Xavier  Curtis Huttenhower
...and the labs!

Human Microbiome Project 2
Lita Procter
Jon Braun
Dermot McGovern
Subra Kugathasan
Ted Denson
Janet Jansson
Owen White
Bruce Birren
Chad Nusbaum
Clary Clish
Joe Petrosino
Thad Stappenbeck

ibdmdb.org

We are now hiring postdocs
contact us if interested