What Have We Learned About the Microbiome in Pediatric IBD?

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Objectives

• Microbial shifts and associated host gene expression programs in pediatric IBD

• Mechanistic insights from murine ileitis and colitis

• Next steps for epigenomic studies and clinical trials
Increasing Trend of Pediatric IBD Suggests Growing Environmental Influences

Most rapid increased incidence in prevalent regions was for children under 10 & now under 6
Effects of Microbial Metabolites on the Host in Health & Disease

A

Health:

IBD:

Sartor & Wu Gastro 2017
Development of the Intestinal Microbiome is Influenced by Mode of Delivery and Antibiotic Exposure

Xavier et al Sci Transl Med 2016
Antibiotic Treatment Suppresses Beneficial Microbes in Infants
Are Specific Genes & Microbes Associated with Disease Severity and Treatment Responses?

Normal ileum (Peyer’s patches)

Crohn’s Ileitis (linear ulcers, exudate)

16S DNA Sequencing: Mucosal Microbes

RNA Sequencing: Patient Gene Expression

Identified Biologic Pathways associated with Clinical Severity and Outcomes

2 mm Ileal Biopsy
NIH/CCF Sponsored Pediatric Clinical Research Network: RISK & PROTECT Studies

1112 children with CD at diagnosis between 2008-2012
432 children with UC at diagnosis between 2013-2015
Follow-up to 2017

Clinical & Demographic
Genotype
Environmental Exposures
Immune Serology
Microbial Community/Gene Expression

Patient outcomes:
Steroid-free remission
Surgeries
PRO-KIIDS

CCHMC - GI
• Lee Denson
• Yael Haberman

CCHMC Bioinformatics core
• Bruce J Aronow
• Phillip Dexheimer

CROHN'S & COLITIS FOUNDATION OF AMERICA

PRO-KIIDS

• Enrolling sites
• Thomas D. Walters, SickKids, Toronto, Canada
• Subra Kugathasan, Emory-Children’s Center, Atlanta, GA
• Greg Gibson &
• Urko Marigorta, Georgia Tech

Cincinnati Children’s

HARVARD SCHOOL OF PUBLIC HEALTH

Curtis Huttenhower
Timothy L Tickle

BROAD INSTITUTE

Ramnik J Xavier
Dirk Gevers
Melanie Shirmer
Antibiotics Exacerbate the Mucosal Dysbiosis in Newly Diagnosed Pediatric Crohn Disease

Gevers et al Cell Host Microbe 2014
Specific Bacterial Shifts are Associated with Symptoms

A) Co-occurring

B) Inflammatory vs. Non-inflammatory
Core Ileal Gene Co-Expression Modules are Associated with Mucosal Injury

**DUOX2 Co-Expression Module**

- Response to wounding
- Abnormal adaptive immunity
- Myeloid Cells, DC
- Response to lipid
- Decreased susceptibility to endotoxin
- Shock
- Response to oxygen-containing compound
- Lipopolysaccharide

**APOA1 Co-Expression Module**

- Abnormal lipid homeostasis
- Fatty acid binding
- PPARG
- HNF4A
- Lipid transporter activity
- Intestinal absorption
- Response to oxygen-containing compound
- Response to nitrogen compound

Haberman et al JCI 2014
Covariation of the Ileal Microbial Community Structure with Ileal Gene Expression and Clinical Subgroup and Severity

NMDS stress = 0.168249780620643

Haberman et al JCI 2014
DUOX2 is a Mucosal Sensor for Dysbiosis

Grasberger et al. Gastroenterology 2015
Deficiency in Duox2 Activity Alleviates Ileitis in Glutathione Peroxidase-Knockout mice

Chu et al. Redox Biol 2017
Induction of an Antimicrobial Epithelial DUOX2 ROS Production Gene Signature is Associated with Proteobacteria Expansion and Ileal Ulceration in CD

Haberman et al JCI 2014
Increased hydrogen sulfide production
Mucin degradation
Associated with suppression of host mitochondrial proteins

Decreased butyrate production

Butyrate induces host mitochondrial proteins for hydrogen sulfide detoxification

Stintzi et al Nature Comm 2016
Induction of A. parvulum-associated Colitis Requires Hydrogen Sulfide
Reduced Butyrate-Producing Microbes are Associated with Pediatric Ulcerative Colitis Severity

Shirmer et al DDW 2017
Reduced Mucosal PGC1A Expression and Mitochondrial Function in Pediatric Ulcerative Colitis

Haberman et al DDW 2017
Intestinal Epithelium-specific PGC1α Knock-out Mice Develop Severe DSS Colitis

Cunningham et al. JBC 2016
Mitochondrial Dysfunction in Colitis Secondary to Microbial and Inflammatory Mechanisms

Butyrate

Butyrate Receptor

Butyrate Transport

Butyrate Oxidation

Mitochondrial Biogenesis

PGC1A

Active Inflammation

Combined Therapy

Bifidobacterium

Dietary Fiber

2′-0-fucosyllactose (2′-FL)

Acetate

Butyrate

F. Prausnitzii

Anti-TNF
Epigenomic Regulation of Microbiota-dependent Intestinal Homeostasis via Short Chain Fatty Acids & Histone Deacetylases
The Microbiota Shifts Towards Health but Does not Normalize with Suppression of Inflammation by Exclusive Enteral Nutrition or Anti-TNF Therapy

• Anti-TNF-treated responders: 11 taxa differed in abundance from healthy controls at baseline (q < 0.05).

• At week 8, six taxa (55%) were significant at a q < 0.05 (*Klebsiella, Prevotella, Escherichia, Odoribacter, Enterococcus, and Fusobacterium*).
Treatment of IBD by Altering Microbial Composition or Function

**Correct dysbiosis/microbial function**

**Traditional**
- Antibiotics
- Probiotics
- Prebiotics
- Synbiotics (combination probiotics/prebiotics)

**Developing**
- FMT
  - Random donor
  - Matched donor/recipient
  - Optimized donor
  - Prepared donor
- Synthetic Mixtures
  - For all patients
  - Targeted for individual recipient
- Dietary
  - Complex foods
  - Simplified (synthetic)
  - Improved prebiotics
- Bacteriophage targeting aggressive bacteria
- Block attachment/invasion AIEC
- ↑ Anaerobic environment-sequester O₂

**Normalize mucosal barrier function**
- ↑ SCFAs
  - Clostridium spp., XIVA
  - F. prausnitzii
  - Reubena
- ↓ Mucolytic spp (E. faecalis)
- Block attachment/invasion E.coli
- Agonists EGFR
- Agonists FXR (i.e., bile acids)

**Reverse immune dysfunction**

**Diet**
- ↑ SCFA substrates
- ↓ HS substrates
- ↑ Omega 3 FAs
- ↓ milk fat
- Selected Commensal Bacteria
  - Clostridium groups IV, XIVA
  - Faecalibacterium prausnitzii
  - Bacteroides fragilis
- Novel Synthetic
  - Bacterial Metabolites
    - F. prausnitzii 15kDa
    - Bacteroides fragilis OMV
- Selected Bacteria
  - SFB Bilophila wadsworthia
  - Adherent/invasive E.coli
- Recombinant Bacteria
  - IL10 producing

**Induce remission with corticosteroids or biologics**