THE MICROBIOME IN IBD

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The microbiota in health and disease
Rationale for a role of the microbiota in IBD
Manipulating the microbiota through diet or Fecal Microbiota Transplant, rationale and evidence
Autoimmune Disease in the US

Incidence of Immune Disorders (%)

- Crohn’s disease
- Multiple sclerosis
- Type 1 diabetes
- Asthma

Age & IBD

Loftus, Gastroenterology 2003; 124:abstract 278
IBD: Evolving concepts

Genes

Mucosal Immune System

Environment
Identified IBD genetic risks

10th anniversary:
- Nod2/CARD15 polymorphisms predispose to Crohn’s

163 distinct genetic risk loci (SNPs)
- Majority are shared: IL23R, IL12B, STAT3, and NKX2-3
- 23 UC
- 30 CD: NOD2, ATG16L1, and IRGM
- IBD associated SNPs shared between adults and children
- Variants correlate well with disease risk
  - modest odds ratios
IBD concordance in twins

Halme et al. World J Gastroenterol 2006;12:3668-72
IBD & Genetics: Evolving concepts

* No major cosmic event over the past 50 years
* Risk imposed by genetics does not account for the majority of the risk to an individual
* Specific genetic driven immune deficit can be restored
* Role of epigenetics
Environment

Internal-external
Microbiome
Diet Exposure
Non-diet Exposure
What is the microbiome/microbiota?

- **Microbiota:** "The ecological community of commensal, symbiotic and pathogenic microorganisms that literally share our body space"
  
  Joshua Lederberg

- **Microbiome:** The collective genome
- The gut (mac colon): largest reservoir
- $10^{11}$ or $10^{12}$ cells/g of luminal contents
Not Only Bacteria!

- Microbiota are based on 16S sequencing
- Flora is rich with fungi, viruses, archaea & bacteriopahges
Internal Environment: Microbiome in health & disease

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

Microbiome complexity & 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

Birth | 3 yrs | Adult | Elderly

EARLY ONSET | ADULT ONSET | LATE ONSET

Kostic et al. D. Gastroenterology. 2014 Feb 18
Microbiome & age

- 3 stages of microbiota diversity & stability

**Early**
- Low complexity
- Low stability
- Volatile
- Affected by birth route
- Fluctuates with diet (breastfeeding to solids), illness, and puberty

**Adulthood**
- Max stability
- Max complexity
- Improved resilience

**>60 years**
- Decreased stability
Evidence for Microbiome role in IBD
1: IBD models

IBD mouse model

NO BACTERIA = NO DISEASE

Norovirus infection is required for the development of CD in mouse model with mutated Atg16l1

Chamaillard M et al. Inflamm Bowel Dis. 2013 Dec 17
2. Fecal Exposure & Disease

Fecal diversion can result in inflammation

Fecal diversion can reduce inflammation in IBD
3. Microbiome is different in IBD

Dysbiosis

↓α-biodiversity
↓commensal bacteria

Dysbiosis

↑mucus or mucosal associated bacteria
↑mucolytic bacteria

Dysbiosis

• ↓ bacteria involved in butyrate & propionate metabolism

Rajilic-Stojanovic, et al Inflamm Bowel Dis 2013; 0: 1-8

Slide courtesy of Dr. David Suskind
4. IBD Genes relate to the Microbiome

- Monozygotic twins: more similar microbiomes
- Monozygotic twins who do not share IBD have different microbiomes
How do Genes Alter Microbiome

- **NOD2 mutations**
  - \(\uparrow\) mucosa-adherent bacteria
  - \(\downarrow\) IL-10 transcription

- **NOD2 & ATG16L1 risk alleles**
  - \(\downarrow\) Decreased levels of *Faecalibacterium*
  - \(\uparrow\) *Escherichia coli*

5. Antibiotic Exposure & IBD

Anaerobic antibiotics exposure associated with 84% relative risk increase. Earlier exposure & multiple courses = higher risk

Kronman et al. Pediatrics 2012;130:e794–e803
6. Diet Exposure & IBD

- Foods associated with ↓CD risk in children
  - Fruit, Vegetables, Fiber, Fish, ω-3 fatty acids
    - n=130 CD patients, 202 controls

- Regular contact with farm animals in infancy inversely associated with CD & UC
  - n= 444 CD, 304 UC, and 1481 controls
  - Questionnaire response rates 85% & 90%

K Radon et. al. Pediatrics 2007;120;354-361
7. TNFα & Microbiome

TNFα Negative mouse IBD model

Less inflammation

Better microbiome diversity

Manipulating the Microbiome in IBD
Antibiotics & IBD

- Short-term treatment with enteric antibiotics can reduce Crohn’s inflammation

- Antibiotics are the main treatment for pouchitis
IBD & Diet Therapy

Induction Therapy with Polymeric Diet vs. Steroids for Active CD

- Clinical improvement
  - Enteral nutrition: n=19
  - Corticosteroids: n=18
  - P<0.05

- Healing of GI tract

Other diet therapy: Specific Carbohydrate Diet

- 7 children with CD & no immunosuppression
- Dietary therapy 5-30 months (avg 14)
- All symptoms resolved at 3 months
- Albumin, CRP, HCT & stool calprotectin:
  - normalized or significantly improved during

IBD & Diet Therapy

Figure 2  C- Reactive Protein (mg/dL)

Figure 3  Albumin Level (g/dL)

Other diet therapy

- Diets shown to reduce symptoms in IBD
  - Vegetarian or vegan
  - Semi-vegetarian
Initiated Standard medical treatment prior to clinic visit

Initiated Standard medical treatment after 12 week clinic visit

IBD & Fecal Transplant

Suskind et al. Accepted Pediatr Gastroenterol Nutr. 2014
** Initiated Standard medical treatment prior to clinic visit

** Initiated Standard medical treatment after 12 week clinic visit

Normal <0.8 mg/dL

Are the Current Medical Therapies effective to achieve treatment goals?

**Remission**
- No symptoms
- Normal growth
- Normal labs
- Normal bone density
- Steroid free remission
- **Mucosal healing**
- Changing the natural history

**Modestly YES**
Impact of mucosal healing

- ↑ Steroid-free remission
- ↓ Hospitalization
- ↓ Surgery
- Children without mucosal healing:
  - more likely to receive treatment change
- Deep mucosal healing predicts sustained clinical remission after stopping anti-TNF ab

Allez M et al. World J Gastroenterol 2010;16:2626e32
Froslie et al. Gastroenterology 2007;133(2):412-422
Thakkar K et al. Am J Gastroenterol 2009;104:722e7
Louis E et al Gastroenterology 2012;142:63e70.e65
Where does the microbiome knowledge fit today and where is it going tomorrow?
Role of the microbiome in IBD is evolving
Manipulating the microbiome changes symptoms and inflammation
The depth of the inflammation reduction is not known yet (deep mucosal healing)
FMT and diet role in sustaining microbiome and inflammation change is evolving
Tomorrow

- Exact role played by microbiome to start, continue and end the inflammation
- Understanding how/why microbiome changes
- Better targeted diet and microbiome interventions
- The right change at the right time to establish deep mucosal healing

....... AND A CURE!