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Learning Objectives

Understand how gut microbiome affects health

Learn how diets affect microbiome composition and function

Understand the pathogenesis of IBD and role of diets
The Intestinal Microbiome – an “organ” of its own

Human gut contains more than 1000 species with 99% belonging to about 40 species 10-fold the number of human cells, and predicted to encode 100-fold more unique genes than our own genome.
Beneficial role of microflora

- Harvest of energy from food not digested by the host
- Production of vitamin K
- Production of short chain fatty acids
- Trophic effects on the intestinal epithelium
- Maturation of the host’s innate and adaptive immune responses
Dominant fecal microbiota remains stable at intra-individual level but is unique for each individual – data from β-fructans (oligofructose enriched-inulin) interventional study in active UC.
How to analyze the gut microbiome and use them in clinical medicine?

Who is there – species/strains – 16s rRNA gene sequencing

What is their function? Metagenomics

What are they doing? Metabolomics
Host-microbe interactions in the GI tract maintain health

Role in Disease
- Complex immune disorders
  - IBD
  - Allergic disorders
  - RA
  - T1 diabetes
- Metabolism
  - T2 diabetes
  - Obesity
- Cancer
- Development
- Infectious diseases
- Neurological/motor disorders
There is evidence for an involvement of intestinal dysbiosis in chronic diseases, with inflammation as one of the mechanistic links.
Gut microbial dysbiosis associated with human disease
Intestinal microbiota dysbiosis and chronic inflammation

Abnormal gut barrier, pro-inflammatory immune response

Obesity  Nonalcoholic Fatty Liver  Type 2 Diabetes  Inflammatory Bowel Disease

↓

Bacteroidetes  Fecalibacterium prausnitzii  Butyrate-producing Enterobacteriaceae

↑

Firmicutes  Akkermansia municiphila

↓

γ-Proteobacteria  Enterobacteriaceae

↑

Intestinal microbiota dysbiosis and chronic inflammation
We can modulate composition of the human gut microbiota and induce changes that are predicted to be beneficial

- Diverse and abundant microbiota
- Firmicutes, Bacteroidetes and Actinobacteria dominant
- Healthy levels of SCFA production
- Intact mucosal barrier
- No overt inflammation

**Health**

**Therapeutic disruption of dysbiosis**
- Antibiotics
- Probiotics
- Dietary intervention/Prebiotics
- Faecal transplantation

**Dysbiosis-related diseases**
- Chronic gastrointestinal infections
- Antibiotic-associated diarrhoea
- Pseudomembranous colitis
- Inflammatory bowel disease
- Necrotizing enterocolitis

**Dysbiosis**

- Microbiota diversity reduced
- Elevated *Enterobacteriaceae*/opportunistic pathogens
- Skewed SCFA profile
- Disruption of mucosal barrier
- Host inflammatory response initiated

Invited review

**Therapeutic modulation of intestinal dysbiosis**

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Pharmacological Research 59 (2013) 75–86
Crohn’s disease and ulcerative colitis have unique geographic features.
IBD has been increasing over the past half century.
Model of the Etiopathogenesis of IBD

Genetics
- Nod2
- TLR, TNF
- Autophagy
- IL23R

Immune imbalance
Defective Host defense

Environment
- Microbes
- Diet
- Smoking

IBD
Diets in the US have changed dramatically over the past century
Dietary Changes in Western Society

Increase
- Animal protein
- Fat
- Refined Carbohydrates

Decrease
- Whole grains
- Fruits and vegetables
Impact of diet in shaping gut (fecal) microbiota – a study of modern versus rural diet

Enterotypes of the human gut microbiome

Enterotypes are strongly associated with long term diets:
- *Bacteroides* enterotype – protein and animal fat
- *Prevotella* enterotype - carbohydrates

Short-term effect of diet on the gut microbiota composition

Animal-based diet showed greater impact on the gut microbiota than the plant-based diet.

Western Diet changed the composition of the gut microflora
Western Diet decreased microbial diversity
Can diet affect the enteric microbiome?

C57Bl/6 mice fed different diets; Cecal samples harvested 21 days later

16S rRNA gene sequences were determined by Sanger-based clone library sequencing
Bilophila wadsworthia is a sulfite-reducing microbe that is uncommon in gut microbiota

- Discovered in 1988
- Often recovered from a variety of infections (pathobiont)
- Bilophila = “bile-loving”
- Sulfite-reducing bacteria (SRB- dsrA)
- Production of H₂S

B. wadsworthia colonizes only when mice are on MF diet
Could differences in dietary fat-induced bile acid conjugation promote *B. wadsworthia* growth?
B. wadsworthia induces TH1-mediated colitis (Bw monoassociation of GF mice)
Dietary strategies to modulate the gut microbiota and redress disease associated dysbioses.

- Bifidobacteria
- Functional targets
- SCFAs and Butyrate producers
- Community diversity

**Therapeutic:**
- Fecal transplantation
- Antimicrobials (Bacteriophages)
- Probiotics

**Nutritional:**
- Probiotics
- Prebiotics
- Fibers, resistant starches, and whole grain

- Microbiota diversity reduced
- Elevated *Enterobacteriaceae* opportunistic pathogens
- Skewed SCFA profile
- Disruption of mucosal barrier
- Host inflammatory response initiated
Dose-dependent clinical response in active UC by adjunct prebiotic inulin-enriched oligofructans

- 15g/day (10/23 patients)
  - Remission: 50%
  - Response: 10%
  - No response: 0%
  - Worsened: 0%

- 7.5g/day (13/23 patients)
  - Remission: 39%
  - Response: 3%
  - No response: 38%
  - Worsened: 23%
Prebiotics inulin plus oligofructose alter fecal microbiota

Change in log₁₀ bacterial abundance in fecal samples

-7.5 g dose
-15 g dose

Actinobacteria  Firmicutes  Bacteroidetes  Proteobacteria
Criterium 2: Prebiotics are FERMENTED BY the (endogenous) INTESTINAL MICROBIOTA

Exhalation and Flatulence

INULIN & OLIGOFRUCTOSE

GASES: CO₂, H₂, CH₄

FERMENTED BY INTESTINAL BACTERIA

Excretion

BACTERIAL BIOMASS

ACETIC ACID
PROPIONIC ACID
BUTYRIC ACID
LACTIC ACID
Feed Your T_{reg} More Fiber

Microbes that metabolize dietary fiber can generate key fatty acids that enforce regulatory T cells in the gut.
Correlations between colitis and mucosa-associated bacterial taxa
Diet alters β-fructans protective effect in rodent colitis model

FOS – fructooligosaccharides
IMO – iso-maltooligosaccharides

Values in the same panel that do not share a common superscript differ significantly ($P<0.05$, Bonferroni adjustment)
Diet rich in refined sugars changes the function of colonic bacteria

Diet rich in refined sugars and milk protein, but deficient in complex fiber and polyphenol, sources promotes protein fermentation versus carbohydrate (fiber) fermentation in cecum and colon of a rat colitis model.
The “Omics” Cascade

What can happen

What appears to be happening

What makes it happen

What has happened and is happening
Dietary and bacterial-derived metabolites in serum and urine of UC patients predict future relapse
Take Home Points

• Diets as well the prevalence of certain “western GI disorders” have drastically changed in the last 50 years

• Diets affect the composition and function of the human microbiome

• Dietary therapy may be the solution to prevent and possibly cure these disorders