Probiotics: Yes, They Work

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Importance of Microbiome

• *All Disease Begins in the Gut*
• Hippocrates 3rd Century BCE

• *Death begins in the colon*
• Elie Mechnikov (1845-1916)
Importance

• NIH $190 million over 5 years
  • How MB influences gene expression
• White house $500 million
  • To study MB communities of earth
Overview

• Explosion of Autoimmune Conditions
• What is the Microbiome?
• What is Dysbiosis?
• MB and Autoimmunity
• What can we do?
Autoimmune Conditions

- 1 in 12 Americans, 1 in 9 women
- Increasing prevalence
  - 23-50 million Americans affected
- Cancer 9 million, Heart dz 22 million
- 120-140 different autoimmune conditions
- ITP, IMHA, IBD, polyarthritis, etc.
Autoimmune Conditions

• What is driving the increase?
• Chronic inflammation
• What drives this?
• Leaky gut!
• What drives leaky gut....
The Microbiome - History

- War on bacteria
- Began ~1300’s
- When Bubonic plague wiped out
- 1/3 European population
- Antibiotics, chlorinated water, etc.
What is the Microbiome?

- Microbes inhabit niches in/on mammals
- On earth too
- Microbes in ocean make 50%
- Of oxygen we breathe
- Coral reefs – loss of microbes detrimental
What is the Microbiome?

- Microbes in/on mammals
- Bacteria, fungi, archaea, viruses, parasites
- Each niche has own MB
- Skin, mouth, ears, nose, lungs, eyes, etc.
- Importantly, these are functional!
Skin Microbiome

- Atopic dermatitis affects
- 10-15% canine population
- During flare ups
  - Decreased diversity in skin bacteria
- Decreased protective barrier

- Grice; J Invest Derm 2016
Oral Microbiome
Ear, Nose, Lungs, etc.
Gut Microbiome

• ~100 trillion microbes human gut
• ~10X more than # of human cells
• ~100X more genes than human genome
• ~90% of human illness attributed to MB
  • To some degree
Gut Microbiome

• ~99% genetic material in humans
• Bacterial or viral
• We can change our DNA!
  • Rapidly, 3-4 days
Formation of Microbiome

- At birth neonate is inoculated
- Microbes from vaginal canal
- C-section microbes from skin
- Very different microbiome
- Higher rates asthma, autism??
Formation of Microbiome

- Many centers “inoculate”
- C-Section baby
- With mother’s vaginal microbiome
- Bulb syringe secretions
- Then swab oral cavity
Structure of Microbiome

- Mucus lines intestines
- Particularly colon
- Mucus layer very important!
- Renews every hour
- Critical to protect gut lining
Structure of Microbiome

- Layers of microbes in lumen
- On outer and inner mucus layer
- Bilayered – luminal layer exits with feces
- Lubrication
- And escorts microbes out
- 50% stool weight = bacteria!
Structure of Microbiome

- Eat pathogenic bacteria
- Sensed by MB
- Increased peristalsis
- Remove with mucous
Structure of Microbiome

- Mucus protects epithelium of colon
- Bacteria attach to luminal most mucus
- Bacteria munch on fiber
- Fiber essential for bacteria survival
- And formation of SCFAs
Structure of Microbiome

- All carbohydrates absorbed in SI
- High carbohydrate diets
- Sugar loving bacteria communicate
- With brain via vagus
- MORE, MORE, MORE...
- Are we starving our colon?
Structure of Microbiome

- If insufficient fiber
- Bacteria eat mucus!
- After mucus, bacteria eat epithelium
- Esophagus to anus – single layer epi
- Bacterial translocation
- Chronic inflammation
Structure of Microbiome

• What is enough fiber?
• Avg American consumes 5g prebiotic fiber
• Hunter-gather ancestors ~120g/d
• If insufficient fiber
• Bacteria do not make SCFAs
Short Chain Fatty Acids

- Regulate sodium, water absorption
- Increase mineral absorption
- Lower pH in gut
  - Inhibits pathogens
- Increase immune function
- Signal to brain – enough food
Short Chain Fatty Acids

• Dysbiosis = decreased diversity
• Of microbiome
• Decreased % of bacteria
  • That produce SCFAs
• SIBO – changes in MB
  • New term = dysbiosis
Dysbiosis

• Links between dysbiosis and...
• Autoimmune conditions
  • RA, Asthma, Atopy, ITP, IMHA
• Neurodevelopmental
  • Alzheimer’s, Parkinson’s, CDS?
• Obesity
Obesity

• Near Epidemic Levels
  • Humans and Pets

• Obese humans, mice – decreased bacteroidetes

• Transplant MB lean – obese mice

• Obese cats – decreased bacteroidetes
Function of Microbiome

• Gut associated lymphoid tissue
  • 70-80% of total immune system!
• Immune signals, Nutrient absorption
• Detoxification, Vitamin production
• Mental state – direct via vagus
• Gut neurons – 2nd brain
• 80-90% serotonin made in gut
Function of Microbiome

- Inflammation
- Two types of T cells
- Underneath epithelium
- Pro-inflammatory
- Anti-inflammatory – T regulatory cells
  - Tregs
Function of Microbiome

• Gut associated lymphoid tissue
• Microbes in lumen communicate with cells in/on/behind epithelium
• Immune cells are “told” to induce
• Inflammatory or anti-inflammatory state
Function of Microbiome

- Immune system also does surveillance
- Dendritic cells sit behind epithelium
- Send dendrites into lumen to sample
- Capture live bacteria
- Determine appropriate response
- Transport beneficial ones to breast milk
Function of Microbiome

- Bacteria can induce chronic inflammation
- Translocation – from too little fiber
- Pathogenic bacteria
- Chronic inflammation – can induce cancer
- Beneficial microbes = decreased cancer
- Due to decreased inflammation
How Does Damage Occur?

- Antibiotics
- 4/5 in US take antibiotic every year
- Single dose of ciprofloxacin
- Altered MB for >1 year
- #days antibiotic use = increased risk breast cancer
  - Increased fatality
  - JAMA 2004
How Does Damage Occur?

• Gluten – 2 main proteins
• Glutenin and gliadin
• Gliaden triggers zonulin production
• Zonulin breaks down tight junctions
• In epithelium of gut – in all mammals

• Dr. Alessio Fasano, Harvard
How Does Damage Occur?

- Most autoimmune conditions
- Show high levels of zonulin
- RA, MS, DM 1&2, IBD, Celiac
- Expose mice to zonulin – leaky gut
- Make antibodies to beta cells
**FAECALIBACTERIUM PRAUSNITZII**

Other benign bacteria

**DISRUPTED MICROBIOME**

When the mucous layer is reduced, opportunists can move close to the gut lining, inciting inflammation. Fermentation of fiber seems to keep the mucous layer intact. So does the presence of peacekeeping microbes, such as *F. prausnitzii*. Fiber may keep the peacekeepers healthy, the mucous layer thick and the immune system well calibrated.

**F. PRAUSNITZII**

AND/OR FIBER ABSENT

Opportunist microbes and toxins

Reduced mucous layer

**RESIDENT PEACEKEEPER**

*F. prausnitzii* colonizes the mucous layer and produces by-products such as butyrate via fermentation. These short-chain fatty acids seem to have an anti-inflammatory effect by inducing regulatory T cells (Tregs), which in turn control aggressive aspects of the immune system. The absence of *F. prausnitzii* and other microbes that perform similar functions often correlates with diseases, such as inflammatory bowel disease and obesity. Some of its relatives, called clostridial clusters, have similar properties.

**INFLAMMATION INHIBITORS**

Blocked inflammatory response

Leaky cell junctions

**Epithelial cell**

Primed immuno-suppressive cells (Tregs)

Illustration by AXS Biomedical Animation Studio

*Source: 'Feed Your Tregs More Fiber',* BY JULIA BOLLMANN AND POMA POWER. IN SCIENCE, VOL 344, AUGUST 2, 2019*
Investigators do not know every detail of how the immune system wreaks havoc with the intestinal lining of celiac patients, but they have identified a number of likely processes (below). Colored arrows indicate events that might be blocked by interventions now being investigated [see table on opposite page].

1. Indigestible fragments of gluten induce enterocytes to release the protein zonulin, which loosens tight junctions.

2. Gluten fragments cross the intestinal lining in abundance and accumulate under epithelial cells (enterocytes).

3. The gluten induces enterocytes to secrete interleukin-15 (IL-15), which arouses immune cells called intraepithelial lymphocytes (IEL) against enterocytes.

4. Tissue transglutaminase (TTG), an enzyme released by the damaged cells, modifies the gluten.

5. Antigen-presenting cells (APCs) of the immune system join the modified gluten to HLA molecules and display the resulting complexes to other immune cells: helper T lymphocytes.

6. Helper T cells that recognize the complexes secrete molecules that attract other immune cells and can directly damage enterocytes.

7. Helper T cells spur killer T cells to directly attack enterocytes.
Components of the intestinal barrier

- **Microbial barrier** (commensal bacteria)
- **Chemical barrier** (mucus layer)
- **Physical barrier** (the epithelium)
- **Immunological barrier** (immune cells of the lamina propria)
- **Muscle layers** (smooth muscle intestinal wall)

• What can we do?
• Low dose Naltrexone?
• 3.0-4.5 mg PO q24h at night
Options - Probiotics

- Foods rich in probiotics
- Fermented foods
- Kimchi, Sauerkraut, kefir, lassi
- Kombucha tea, tempeh, pickles
Options - Probiotics

• Supplements
Options - Prebiotics

- Prebiotic fiber
- Non-digestible
- Garlic, onion, leaks, jicama, chicory, Jerusalem artichoke, raw dandelion greens, raw asparagus
Options - Other

• Filter water
• Chlorine
Options - Enema

- Probiotic enema
- Dates back to ancient Egypt, Mayans
- Don’t use chlorinated water
- 3-6 probiotic capsules
- Bifidobacteria predominant in colon
Options - Enema

• Fecal microbial transplant
Parasites

- Double edged sword
- Co-evolutionary relationship
- Helminths promote anti-inflammatory
- They don’t want to be removed
- Anti-inflammatory effects associated
- Decreases Crohn’s, Colon cancer...
Parasites

• New way to treat chronic inflammation
• 1976 researcher infected himself
• With hookworms
• Remission from allergies
• Lancet 1976
• ~7,000 humans self treating...
Pre-biotics

- Prebiotic fiber acts like fertilizer
- For every 100g consumed
- 30 grams of bacteria produced
Questions???