GUT MICROBIOME DEFINED

- Collective microbial community of a certain environment (gut)
  - *2,000 distinct species of bacteria*
  - 100 trillion bacteria
  - Genome 150 times greater than the human host
- “The most densely colonized organ is the gastrointestinal tract: the colon alone contains > 70% of microbiota.”

EUBIOSIS

- Bacteria are in the right place and well-fed
  - Well-fed = fermentable, dietary fiber
- Bacteria are producing health-promoting products (Short Chain Fatty Acids – SCFA)
- Intestinal barrier is strong
  - Mucus Layer
  - Tight junction proteins
  - Antimicrobial peptides
  - Intestinal alkaline phosphatase
- Enteroendocrine cells homeostatic
- Goblet cells are making mucin
- Vagal inputs result in high parasympathetic tone
- Immune system is kept in check

PATTERN RECOGNITION

- We can recognize conserved molecular patterns associated with harmful forms of non-self.
  - Example – Lipopolysaccharide (LPS)
    - LPS is a highly conserved molecule on gram negative bacteria which serves as a potent influencer of inflammation.
- Recognition of harmful forms of non-self leads to an inflammatory cascade
- LPS migration beyond the lumen of the small intestine modulates the immune system and susceptibility to disease. It is incredibly important to maintain the gut barrier.

VAGUS NERVE AND THE GUT

- *Innervates all the digestive tract* (all layers of the digestive wall) but does not cross the epithelial layer.
- *Not in direct contact* with the gut luminal microbiota
- Senses (afferent signaling) only indirect signals through the diffusion of bacterial compounds or metabolites.
  - Chemoreceptors (Butyrate)
  - Hormone Receptors
  - Toll-like receptors (LPS)
- Parasympathetic efferent signals, via $\alpha_7$ Nicotinic Acetylcholine Receptors, limit inflammation.
- Eubiosis increases parasympathetic tone, while dysbiosis promotes inflammation and decreased parasympathetic tone.

**INTESTINAL BARRIER**

“The GI tract is subjected daily to thousands of microorganisms and nutrient components via the ingested diet.”

- Eubiosis requires the microorganisms and bacteria-derived endotoxins stay in the lumen.
  - Harmful paracellular transport must be prevented.
- The intestinal barrier is comprised of:
  - Mucus Layer
  - Tight Junctions
  - Antibacterial Proteins
  - Luminal Intestinal Alkaline Phosphatase (IAP)

**PREBIOTICS**

Prebiotics are the food for the microorganisms
- Carbohydrates (oligosaccharides, disaccharides, polysaccharides)
- Phytochemicals (polyphenols)
- Others (proteins, FUFAs, organic acids, etc.)

**FIBER**

- Edible carbohydrate polymers that we (humans) cannot digest.
  - **Soluble fiber**: Dissolves in water
    - Lowers blood glucose and cholesterol.
  - **Insoluble fiber**: Does not dissolve in water
    - Helps food move through your digestive track.
  - **Fermentable**: broken down by bacteria
  - **Non-Fermentable**: not broken down by bacteria

**SHORT CHAIN FATTY ACIDS (SCFA)**

- **Bacteria create SCFA by fermenting fiber**
- SCFA
  - Increase goblet cells
  - Increase mucus production
  - Increase IAP
  - Increase IgA
  - Increase antimicrobial peptides
  - Decrease neutrophil recruitment
  - Increase production of T regulatory cells
  - Inhibit histone deacetylases
- Butyrate is produced mainly by the firmicutes phylum (gram positive).
PROBIOTICS

Probiotics are the living microorganisms

Successful probiotic supplements:
- ✓ Resist gastric acidity
- ✓ Resist enzymatic breakdown
- ✓ Cannot be absorbed in the upper GI tract
- ✓ Can be fermented by intestinal bacteria
- ✓ Can stimulate bacterial growth

Effect of probiotic consumption is closely related to the composition of the individual’s basal gut microbiota. Abundance tends to return to levels prior to supplementation when intake ceases.

SPORES

“Bacterial spores are small oval or spherical structures that are very resistant to high temperatures, radiation, desiccation, and chemical agents.”
- Formed in response to adverse conditions
- Contain genetic material
- Protective shell that can survive for centuries
- Germinate to produce a new cell (bacteria) identical to the original - good conditions
- Some Gram-positive, never gram-negative are spore formers (e.g. genera Bacillus)
  - Firmicutes are G-positive and butyrate producers.

IDEAL COMPOSITION

There is no ideal composition
Composition varies from stomach, duodenum, jejunum, ileum, to colon
Prebiotics (diet) and lifestyle are primary determinants

Colon: 70% of the microbiome
- Two primary phyla: Firmicutes (G-positive) and Bacteroidetes (G-negative)

CHALLENGES TO GUT HOMEOSTASIS

ANTIBIOTICS
- Reduction in microbial diversity
- Reduction in the number of protective species
- Colonization of opportunistic pathogens
- Disrupted microbial metabolites (decreased SCFA)

NSAIDS
- Reduced prostaglandins (NSAIDS inhibit cyclooxygenase)
- Uncoupled oxidative phosphorylation
Dan Weinert DC, PhD

- Decreased ATP
- Increased reactive oxygen species (ROS) and oxidative stress
- Proliferation of Gram-negative bacteria (LPS)

- Probiotics restore microbiota and reduce NSAID-induced enteric damages
- Proton Pump Inhibitors (PPI) significantly worsen NSAID enteropathy.

**INTERMITTENT FASTING**

- Increased microbial diversity
- Decreased inflammation
- Increased villi length and the muscularis thickness
- Increased expression of tight junction proteins
- Decreased leaky gut

**CONCLUSIONS**

- The gut, especially the colon, represent a massive interface with the external environment.
- Gut microbiome has far-reaching health implications.
- Diet (prebiotics) is incredibly important.
- There are factors that challenge homeostasis.
- Probiotics affect microbiota composition and function.
REFERENCES

- Duca, FA and Lam, KT. (2014). Gut microbiota, nutrient sensing and energy balance. Diabetes, Obesity and Metabolism. 16(1); 68-76.


• Jean-Paul Lallès, Recent advances in intestinal alkaline phosphatase, inflammation, and nutrition, Nutrition Reviews, Volume 77, Issue 10, October 2019, Pages 710–724, https://doi.org/10.1093/nutrit/nuz015