GASTROINTESTINAL PROCESSES Beyond probiotics: Small Molecules

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OUTLINE, HIGHLIGHTS

- FINAL OUTCOME – SUPERB HEALTH
- Interactions
- Saliva – hidden secret of good digestion
- Drinking/Eating habits that can drastically change your health
- Genetics vs secret world of "small molecules"
- Microbiome – Alien world in your body
- Products and protocols

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20th CENTURY MEDICINE

- Up to 1953, biological research focused on organismal perspective.
- 1953 – landmark discovery of the structure of DNA. Research shifted from an organismal to a molecular perspective - the role played by macromolecules—not only DNA, but also RNA and proteins
- Discovering genomes was believed to have capacity to usher a new era of eradicating most diseases
- When doctors are lost to find answers, they dig into genetic testing.

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21ST CENTURY MEDICINE

- Small molecules importance and interactions
- Finding ways to stimulate or shut off GENE EXPRESSION
- NF KAPPA B – prime example

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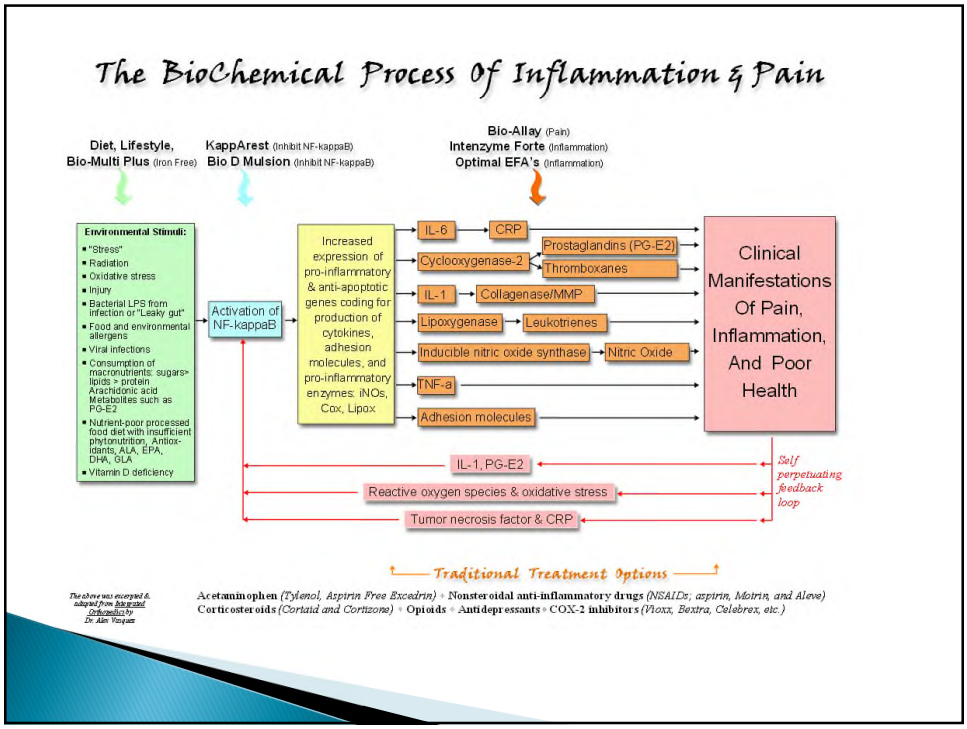
The BioChemical Process Of Inflammation & Pain
Diet, Lifestyle, Bio-Multi Plus (Iron Free)
KappArest (Inhibit NF-kappaB) Bio D Mulsion (Inhibit NF-kappaB)
Bio-Allay (Pain) Intenzyme Forte (Inflammation) Optimal EFA's (Inflammation)
Environmental Stimuli:
"Stress"
Radiation
Oxidative stress
Injury
Bacterial LPS from infection or "Leaky gut"
Food and environmental allergens
Viral infections
Consumption of macronutrients: sugars> lipids > protein Arachidonic acid Metabolites such as PG-E2
Nutrient-poor processed food diet with insufficient phytonutrition, Antiox-idants, ALA, EPA, DHA, GLA
Vitamin D deficiency
Activation of NF-kappaB
Increased expression of pro-inflammatory & anti-apoptotic genes coding for production of cytokines, adhesion molecules, and pro-inflammatory enzymes: iNOs, Cox, Lipox
IL-6
CRP
Cyclooxygenase-2
Prostaglandins (PG-E2)
Thromboxanes
IL-1
Collagenase/MMP
Lipoxygenase
Leukotrienes
Inducible nitric oxide synthase
Nitric Oxide
TNF-a
Adhesion molecules
Clinical Manifestations Of Pain, Inflammation, And Poor Health
IL-1, PG-E2
Reactive oxygen species & oxidative stress
Tumor necrosis factor & CRP
Self perpetuating feedback loop
Traditional Treatment Options
Acetaminophen (Tylenol, Aspirin Free Excedrin) • Nonsteroidal anti-inflammatory drugs (NSAIDs; aspirin, Motrin, and Aleve)
Corticosteroids (Cortaid and Cortizone) • Opioids • Antidepressants • COX-2 inhibitors (Vioxx, Bextra, Celebrex, etc.)

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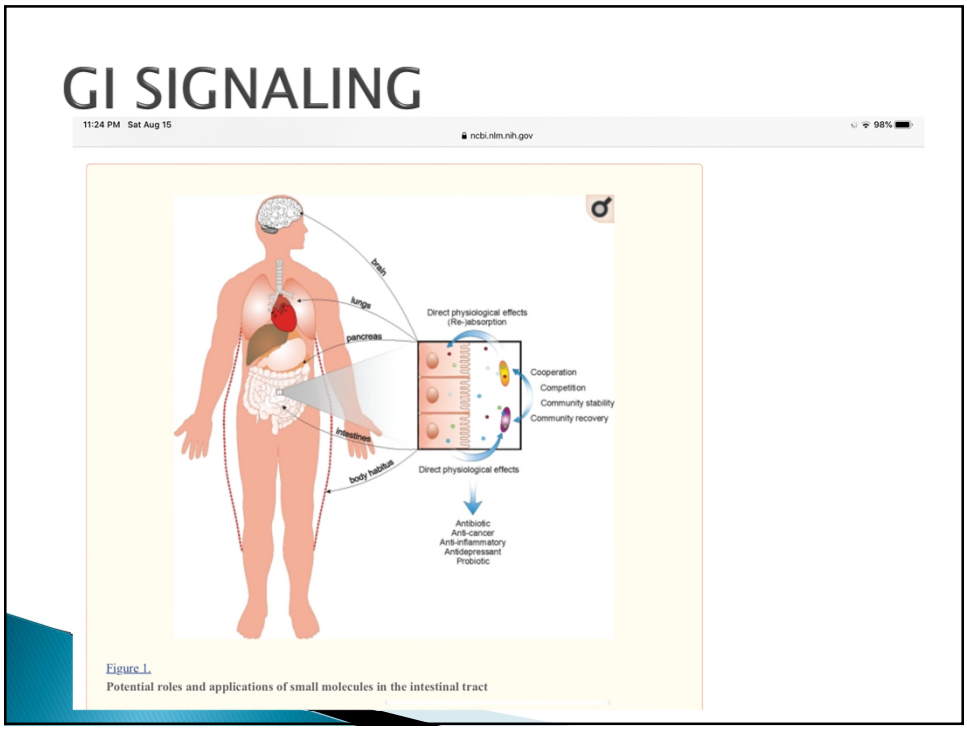
GI SIGNALING
11:24 PM Sat Aug 15
ncbi.nlm.nih.gov
98%
brain
lungs
pancreas
intestines
body habitus
Direct physiological effects (Re-)absorption
Cooperation
Competition
Community stability
Community recovery
Direct physiological effects
Antibiotic
Anti-cancer
Anti-inflammatory
Antidepressant
Probiotic
Figure 1.
Potential roles and applications of small molecules in the intestinal tract

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LIFE

- Three domain system
  1. Eukaryota
  2. Bacteria
  3. Archaea

EUKARYOTS – cells have a nucleus within a nuclear envelope

PROKARYOTS – lack cell nuclei

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- "Small molecules" - any compound of molecular weight around or under 3000 Da and with chemical characteristics that preclude their description as DNA, RNA, or proteins.
- Critical biological functions in humans:
  - control immune functions,
  - the development of sexual characteristics,
  - stress responses,
  - metabolism,
  - mineral balance, amongst others
- In higher organisms, these small molecules are called hormones—from the Greek for "excite" or "arouse"—a term coined in 1905 by Ernest Starling
- They are produced by one organ of the body and travel to distant organs to exert physiological effects.
- Hormones and hormone-like molecules

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SIGNALING

- Our knowledge on cellular chemical communication comes from studies of multicellular eukaryotes
- Bacteria can also communicate using sophisticated signaling systems
- There is a wealth of **unidentified bioactive small molecules** in the human body, originating from both microbial and human cells and that have important biological functions.

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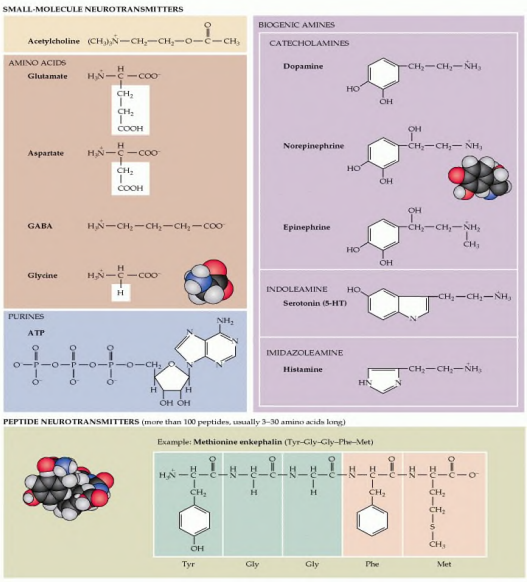
Small molecules



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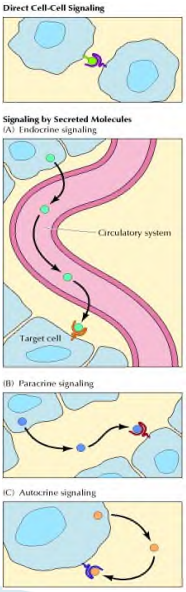
SIGNALING



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Small-molecule mediated microbe-host and microbe-microbe interactions

- The microbiota produce a range of small molecules from various classes with distinct targets.
- Four examples
  1. the nonribosomal peptide tilivalline, whose host target is unknown;
  2. the ribosomally synthesized and post-translationally modified peptide microcin E492 (MccE492), a narrow spectrum antibacterial;
  3. lipid A, the glycolipid core of lipopolysaccharide, which targets TLR4 in host immune cells; and
  4. indole propionic acid, a reductive metabolite of tryptophan that enters host circulation but whose biological activity is poorly understood. These metabolites are each produced by different species of the microbiota

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SIGNALING

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3042312/
- **Small molecules** are produced in the intestine by both host and microbial cells. Microbial molecules can exert direct effects on host cells and vice-versa. Additionally, the molecules can play an important role in interactions between different microbial components in the intestinal ecosystem; they can be used for cooperation, maintenance of community stability or recovery after an insult, and competition. The molecules can also be absorbed into the intestinal epithelium. This is true for newly synthesized microbial molecules or recycled host molecules, which can be excreted in the intestinal lumen and reabsorbed. Such molecules can reach the bloodstream and exert effects on remote organs such as the brain, lungs, and pancreas, as well as other intestinal sites. They can also affect energy balance and impact obesity and other diseases of the organs mentioned above (autism, depression, allergy, diabetes, inflammatory bowel disease, and so on). Once harvested and studied, these compounds can be used for a multitude of purposes; they can serve several therapeutic roles as antibiotics, anti-cancer therapies, anti-inflammatories, antidepressants, and probiotics, amongst others.

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It's a small-molecule world

- "Since its discovery, DNA has been considered the foundation of life. Its capacity to store information coupled with its remarkable stability make it the prime candidate for the molecule from which life, as we know it, originated. This concept is imprinted in the "central dogma", which states that DNA holds all genetic information, which is passed on to RNA as a messenger molecule and then translated into proteins, which constitute the machinery and structures that carry out the molecular processes essential for life (Figure 2). Although generally accepted, this viewpoint has been challenged. In 1986, Walter Gilbert suggested that RNA preceded DNA as a self-replicating primitive form of life, giving this molecule a main role in the formation of life [64]. Indeed, RNA molecules with enzymatic functions still exist [65]."

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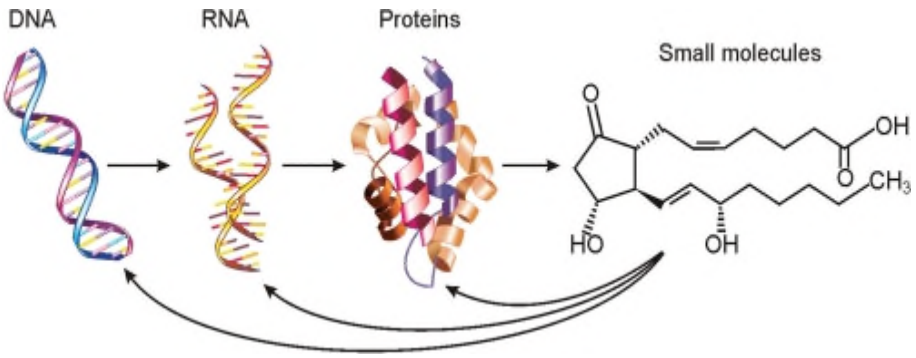
SMALL MOLECULES



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SMALL MOLECULES

- Figure 2.
- **Small molecules as important messengers of biological information and function**
- "DNA encodes the genetic information that is passed on to RNA, which acts as the messenger for the synthesis of proteins. **Protein** enzymatic function can then give rise to a plethora of **structurally diverse small molecules.** In many cases, these molecules are the primary effectors of biological functions, acting at the DNA, RNA, and protein levels."

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SMALL MOLECULES

- "Although both DNA and RNA have central functions in the maintenance and decoding of genetic information, the real effectors of these functions are proteins. In the case of **structural proteins, they represent the end of the road for a given biological property or function.** However, for the majority of proteins, **CATALYTIC ACTIVITY** is the main function, thus extending their biological properties to the products of the reactions catalyzed: a plethora of structurally diverse small molecules. It is, therefore, these **SMALL MOLECULES** that **constitute the *raison d'être* of biological function in most cases.** Without identifying and studying these molecules, we will not fully understand the functions of metabolic pathways and the interconnections between them. Nor will we be able to fully comprehend the complexities of any biological system. We now have the tools to delve into the unexplored sources of many intriguing molecules in our own bodies. This should be done not only with an intellectual view toward understanding the molecular intricacies of life in more detail but also with a practical view of benefiting from what these molecules may have to offer."

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GUT–BRAIN AXIS (GBA)

- Complex BIDIRECTIONAL communicative and regulatory system involving the brain and central nervous system and the enteric environment of the gut.
- "The enteric nervous system doesn't seem capable of thought as we know it, but it communicates back and forth with our big brain — with profound results. For decades, researchers and doctors thought that anxiety and depression contributed to these problems. But our studies and others show that it may also be the other way around,"
  - Jay Pasricha, M.D., director, Johns Hopkins Center for Neurogastroenterology,
- Irritation in the gastrointestinal system may be sending signals to the central nervous system (CNS) that trigger mood changes.

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- *For Pert the body's "information system" has two major elements-the chemical substances known as neuropeptides and the receptors into which they fit. Neuropeptides are produced by nerve cells in the brain, and when they lock into their receptors, which are attached to other cells in the body, they make something happen (or prevent it from happening).*
- *Pert outlines a new view of the body's internal conversation, a conversation that appears to be remarkably flexible, varied, and subtle. For example, certain immune cells carry all the receptors identified so far, which means, presumably, that they can be affected by a wide range of "messages."*

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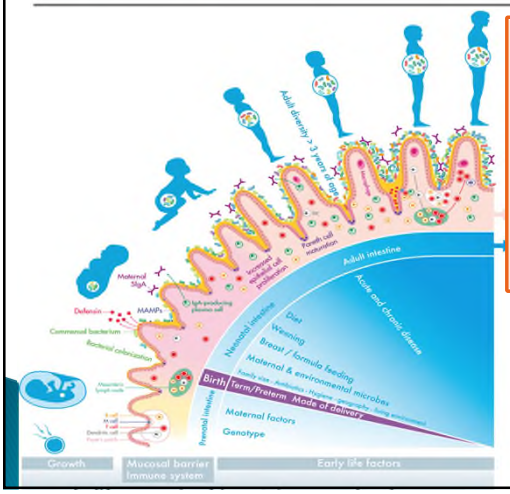
Shaping the Human Metabolome

The first thousand days – intestinal microbiology of early life: establishing a symbiosis

Harm Wopereis[1,2], Raish Oozeer[1], Karen Knipping[1], Clara Belzer[2] & Jan Knol[1,2]

[1]Nutricia Research, Utrecht, The Netherlands; [2]Laboratory of Microbiology, Wageningen University, Wageningen, The Netherlands



The development of the intestinal microbiota in the first years of life is a dynamic process significantly influenced by early-life nutrition. Pioneer bacteria colonizing the infant intestinal tract and the gradual diversification to a stable climax ecosystem plays a crucial role in establishing host-microbe interactions essential for optimal symbiosis.

- Early nutrition
- Breast feeding
- Vaginal delivery
- Eating dirt

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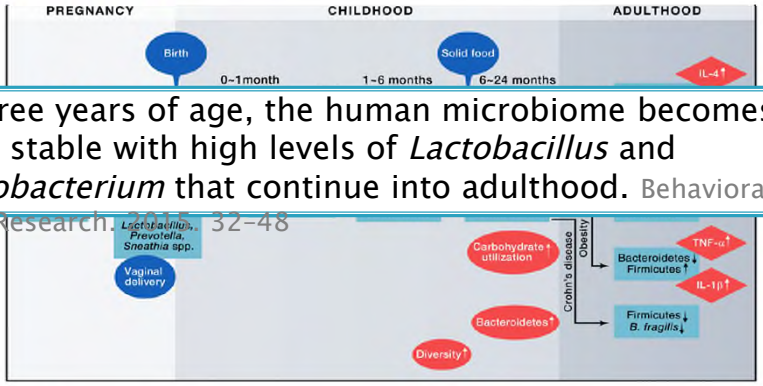
The Impact of the Gut Microbiota on Human Health: An Integrative View

Jose C. Clemente,[1] Luke K. Ursell,[1] Laura Wegener Parfrey,[1] and Rob Knight[1,2,*]
[1]Department of Chemistry & Biochemistry, University of Colorado at Boulder, Boulder, CO 80309, USA
[2]Howard Hughes Medical Institute, Boulder, CO 80309, USA
*Correspondence: rob.knight@colorado.edu
DOI 10.1016/j.cell.2012.01.035



By three years of age, the human microbiome becomes more stable with high levels of *Lactobacillus* and *Bifidobacterium* that continue into adulthood. Behavioral Brain Research, 2015, 32-48

Figure 1. Development of the Microbiota
The gastrointestinal tract of the fetus is sterile until birth, after which the newborn is initially colonized. Depending on delivery mode, the initial communities tend toward a skin-like (caesarean section) or a vaginal-like (vaginal delivery) configuration. During the first weeks of life, there is a reduced activity of TLRs, potentially allowing the necessary formation of a stable bacterial community in the gut. As the infant grows, and with the introduction of solid foods, the microbiota diversity increases, and the community converges toward an adult-like state. At the same time, the immune system "learns" to differentiate between commensal and pathogenic bacteria. By adulthood, a relatively stable community composition (but varying between different individuals) is achieved, dominated mostly by Bacteroidetes and Firmicutes. Different diseases are characterized by significant changes in the microbiota and associated changes in the production of cytokines.

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Pediatr Allergy Immunol 2008: 19: 682–687
DOI: 10.1111/j.1399-3038.2008.00731.x

PEDIATRIC ALLERGY AND IMMUNOLOGY

Review Article

Is caesarean delivery associated with sensitization to food allergens and IgE-mediated food allergy: A systematic review

Review study about n=15,000 children
Age: 2-10

This systematic review found evidence that children delivered by caesarean section have an increased rate of sensitization to food allergens compared with those delivered by vaginal birth. In addition, there is evidence from one study that symptoms of food allergy occur more commonly among children who are born by caesarean section

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GI Microbial Colonization & Development

- GI colonization begins in utero
  - Once thought to be a sterile interaction, placental and amniotic microbes may be the first influence on the fetus The Placenta Harbors a Unique Microbiome. Science Translational Medicine 21 May 2014: Vol. 6, Issue 237, pp. 237ra65, Clin Infect Dis. 1997 Jun; 24(6):1228-32.
  - Birthing methods, breast milk/formula and interaction with environment will have greatest impact on microbial diversity and numbers
- GI health has an intimate relationship with proper immune responses; up-regulation and down-regulation
  - i.e: GI health related to autoimmunity and immunodeficiency

Bifidobacterium and Lactobacillus DNA in the human placenta.Satokari R, Grönroos T, Laitinen K, Salminen S, Isolauri ELett Appl Microbiol. 2009 Jan; 48(1):8-12.
Regulation of T cell responses in the developing human fetus. Michaëlsson J, Mold JE, McCune JM, Nixon DF J Immunol. 2006 May 15; 176(10):5741-8.
T cell subclasses in fetal human ileum.Spencer J, Dillon SB, Isaacson PG, MacDonald TT Clin Exp Immunol. 1986 Sep; 65(3):553-8.

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Meet the Other Players

- There are also resident viruses, which consist mostly of bacteriophages. This is called your **virome**. Bacteriophages are viruses that infect bacteria in a highly specific manner. These bacteriophages play a role in the development of the microbiome as well as pressure bias towards one group of bacteria or another

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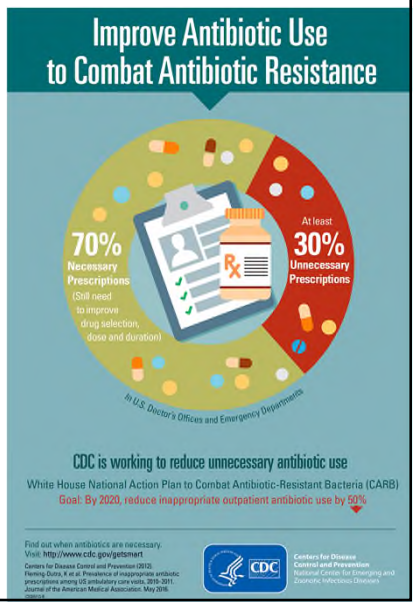
Antibiotics and the Microbiome

Even just a single dose of antibiotics can disrupt the microbiome and may take up to a year to recover. Sustained use of antibiotics may lead to permanent changes and a negative dysbiosis within the human GI microbiome



Dethlefsen L, Relman DA. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proc Natl Acad Sci USA*. 2011;108(1):4554–4561.
Relman DA. The human microbiome: ecosystem resilience and health. Nutr Rev. 2012;70(Suppl. 1):2–9.

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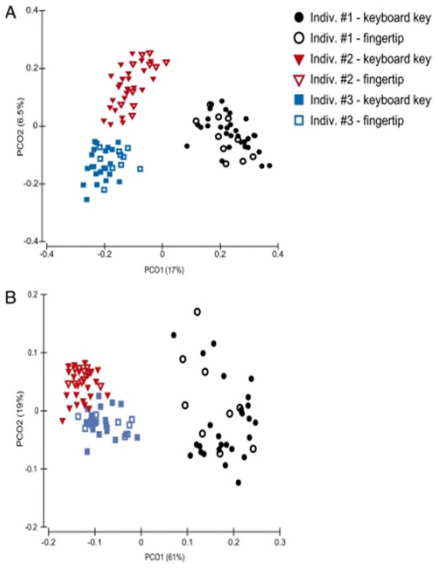
The Microbiome

- You are unique but it may not be your DNA that makes you stand out…
  - 99.99% of your genome is identical to your neighbor yet you may only share 10% similarity in your microbiome makeup
  - Up to 90% accuracy scientists can match you to the mouse/keyboard you use at work *Proc Natl Acad Sci U S A. 2010 Apr 6; 107(14): 6477–6481*.



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You are Outnumbered

In terms of our human cells- microbes outnumber us 10:1

We have about 20,000 genes- microbes have about 2-20 million genes

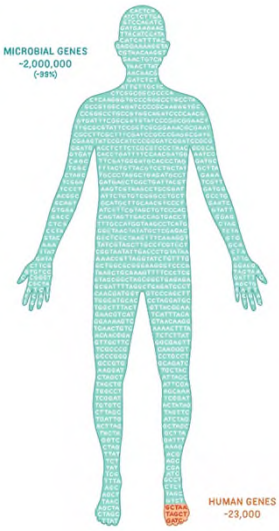

Image source: Gaby D'Allesandro/ American Museum of Nat

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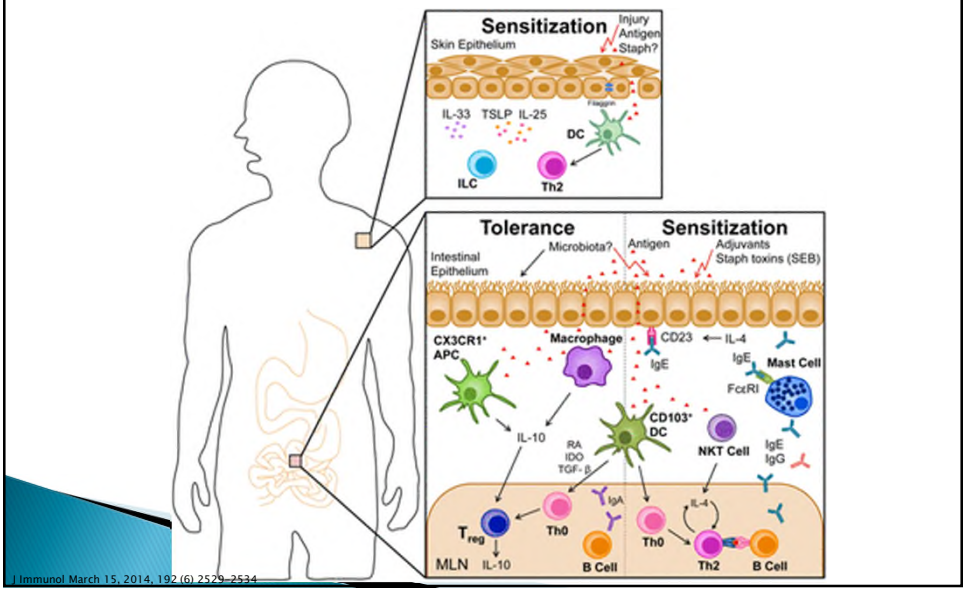
Allergies and Asthma

- Regulation of a proper, or improper immune response
  - "HYGEINE HYPOTHESIS"- the lack of exposure to different infectious agents early on in life as well as symbiotic organisms does not properly balance the immune response and thus leading to a potential up-regulation in Th2
- Antibiotics, diet, stress, and lifestyle can all alter the microbiome leading to altered mucosal immunity

Allergy Asthma Clin Immunol. 2015;

28

Sensitization and Tolerance



J Immunol March 15, 2014, 192 (6) 2529-2534

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Additional Diseases/Symptoms

- Low immune status (sIgA)
- Insomnia
- Increased risk of mood disorders- anxiety, depression, PTSD
- Cognitive decline
- Inflammatory bowel disease
- Poly-neuropathy
- Cancer

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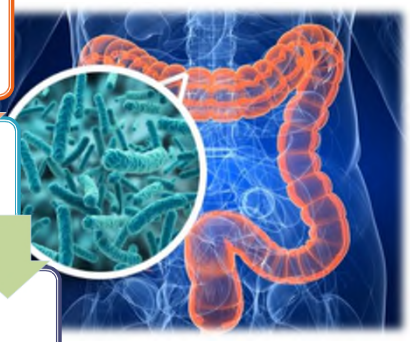
Gastrointestinal: Definitions

Microbiota– collection or community of microbes

Microbiome– microbiota plus their genetic material

Metabolome– microbiome plus it's collective metabolites



http://learn.genetics.utah.edu/content/

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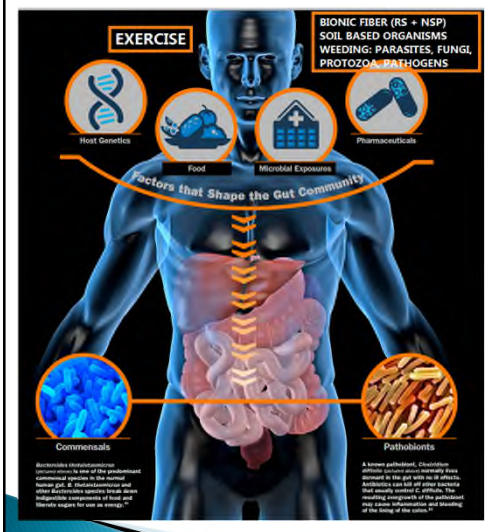
Gastrointestinal: Definitions



- Dysbiosis- microbial imbalance on or inside the body
  - This could be a pathological imbalance or a beneficial imbalance
  - In the context of health care this term normally indicates some negative impact on the human
- SIBO- Small Intestinal Bacterial Overgrowth- increased numbers and/ or abnormal type of bacteria in small intestines

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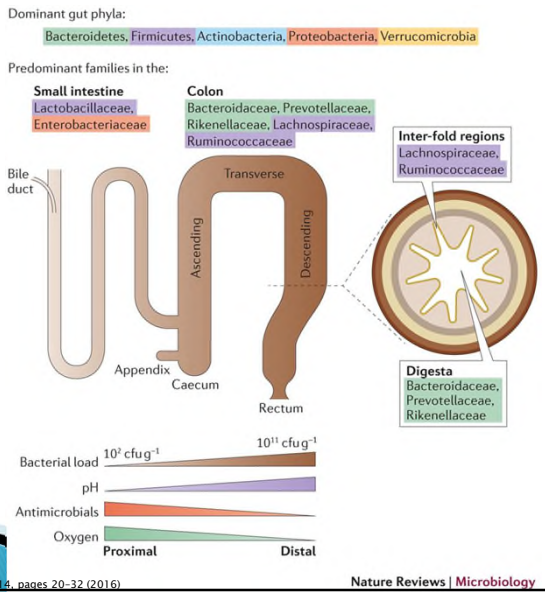
Gut Bacteria and Locations



Nature Reviews Microbiology volume 14, pages 20–32 (2016)

Nature Reviews | Microbiology

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Not One Size Fits All

There is a high amount of individuality that needs to be accounted for when interpreting the microbiome

- There is no "one size fits all" population ratio
- Definition of a healthy microbiome- ideal collection of genes and pathways (healthy metabolic functions) rather than specific populations
- Survey of 4788 samples from 242 "healthy" adults noted fecal bacteria populations were varied yet metabolic pathways conserved
  - "Microbiome fingerprint"

Defining a healthy human gut microbiome: current concepts, future directions and clinical applications. Cell Host Microbe. 2012 Nov 15;12(5):611-22

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The Human Ecosystem

Most scientists are now alluding to our resident microbes as being a SEPARATE ORGAN

- Microbes are found
  - Skin (e.g. Staphylococcus aureus)
  - Mouth (e.g. Streptococci)
  - Stomach (e.g. H. pylori)
  - Intestines(e.g. lactics, enterics, enterococci, bifidobacteria)
    - Also contains low populations of pathogenic bacteria C. difficile that remain asymptomatic until the beneficial flora is reduced
  - Urogenital (e.g. staphylococci, corynebacteria, enterics)
    - Vagina (e.g. lactobacilli)
  - Nasal cavity (e.g. staphylococci and corynebacteria)

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Microbial Shift Disease/Dysbiosis/SIBO

- A shift in microbial balance can begin to breakdown the barrier system within the GI tract (sometimes termed “leaky gut” or increase intestinal permeability)
  - This will lead to elevations of pro-inflammatory compounds often times chronic which can trigger alterations in pain thresholds, disruption of endocrine function and causal links in mood disorders
- There is bidirectional communications between the gut and the CNS

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Microbial Shift Disease/Dysbiosis/SIBO

- Vagal nerve afferent stimulation and possibly direct transport vessel to the brain *Acta. Neuropathol. 128, 805–820 (2014), Med. Hypotheses. 68, 1252–1257 (2007).*
  - Disruption of neuro-immune cross talk *Immunol. Res. 63, 38–57 (2015).*
  - "Leaky gut"- releasing compounds such as LPS endotoxins into circulation which stimulate systemic and CNS inflammation
    - Alter phase I (CYP450- enzymes) detoxification strategies of the body
  - Increased neurotoxin exposure

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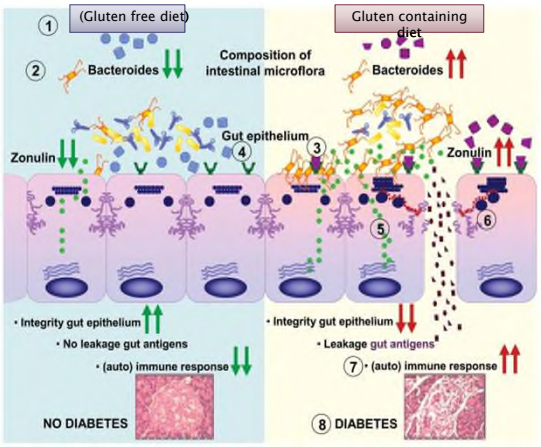
Intestinal Permeability and Diabetes



Imbalanced microflora that favors Bacteroides over *Bifidobacterium* and *Lactobacillus* activates zonulin which dissembles tight junctions

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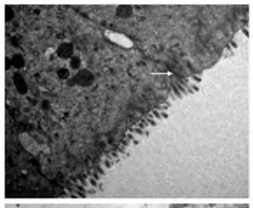
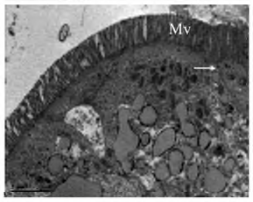
Intestinal Permeability

- Vitamin D- 2,000-10,000IU/day
- L-glutamine 2-20g per day- growth promoting amino acid; aids in repair of damaged tissue and can "fuel" entero- and colono-cytes; prevents bacterial translocation
  - Also great for burn victims, hepatobiliary dysfunction, and cancer patients
- N-acetyl glucosamine- improves intestinal barrier function Bangladesh J Pharmacol 2012; 7: 281-284
  - Essential for glycosaminoglycan synthesis→ attached mucin layer and protects against harmful bacteria





Wang, B., Wu, G., Zhou, Z. et al. Amino Acids (2015) 47: 2143. https://doi.org/10.1007/s00726-014-1773-4

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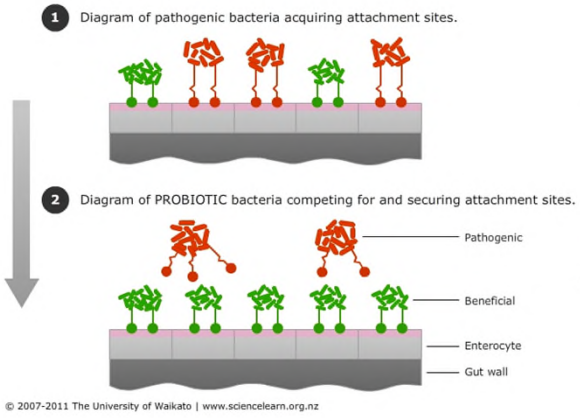
Probiotics and Pathogenic Microbes



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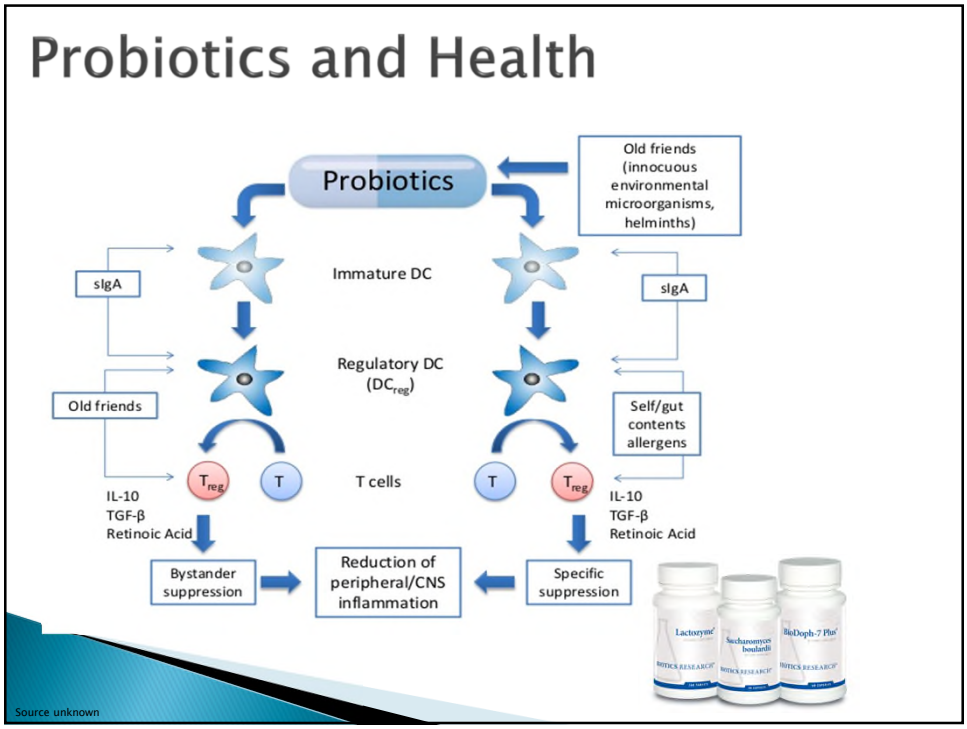
Probiotics and Health
Probiotics
Old friends (innocuous environmental microorganisms, helminths)
Immature DC
sIgA
sIgA
Regulatory DC (DC_{reg})
Old friends
Self/gut contents allergens
T_{reg}
T
T cells
T
T_{reg}
IL-10
TGF-β
Retinoic Acid
IL-10
TGF-β
Retinoic Acid
Bystander suppression
Reduction of peripheral/CNS inflammation
Specific suppression
Source unknown

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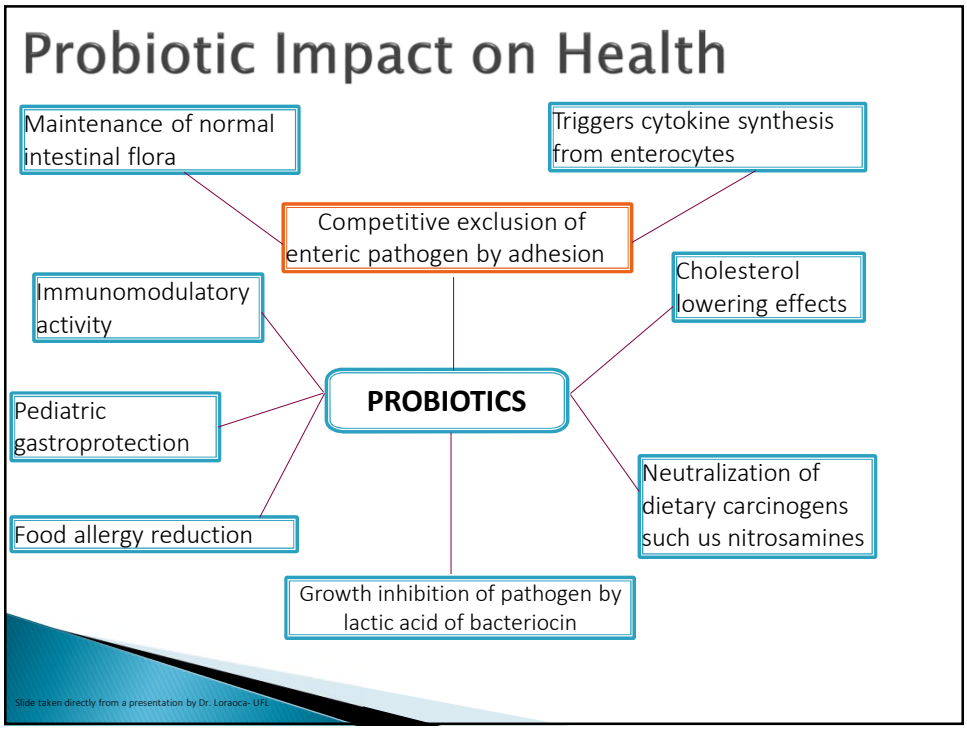
Probiotic Impact on Health
Maintenance of normal intestinal flora
Triggers cytokine synthesis from enterocytes
Competitive exclusion of enteric pathogen by adhesion
Immunomodulatory activity
Cholesterol lowering effects
PROBIOTICS
Pediatric gastroprotection
Neutralization of dietary carcinogens such us nitrosamines
Food allergy reduction
Growth inhibition of pathogen by lactic acid of bacteriocin
Slide taken directly from a presentation by Dr. Loraoca- UFL

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Probiotics and GI Inflammation

- Lactobacillus species can reduce inflammation as proved by the reduction of serum studies of nuclear factor-kappa (NF-kB).
  - Further studies have been performed in human models diagnosed with ulcerative colitis and the effects of oral supplementation of *Lactobacillus* [species] were remarkable. The anti-inflammatory effect of the oral probiotics was greater than the group who received sulfasalazine, a common anti-inflammatory for autoimmune IBD

    World Journal of Gastroenterology : WJG. 2010;16(33):4145-4151.

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Probiotics and GI Inflammation

- Reduction of inflammation → reduction of IL-6, leukocyte recruitment and myeloperoxidase activity

  World Journal of Gastroenterology : WJG. 2010;16(33):4145-4151.
  - Probiotics may also stimulate GSH production: ROS and hydroxyl radical scavenger *Mazidi et al., 2017; Asemi et al., 2013; Hegazy et al., 2010*
- *Mazidi et al.* conducted a large meta-analysis of random control trials on the effects of probiotics and their impact on C-reactive protein. This study demonstrated that probiotics do in fact significantly lower C-reactive protein.

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Probiotcs

Probiotics also lower inflammatory proteins such as IL-8 and TNF-α, effectively reducing intestinal permeability and that cascade of events described previously.

Lactobacilli strains have been noted to inhibit IL-8 production in colorectal adenocarcinoma cells (Caco-2), which were induced by TNF-α. Lactobacilli colonies that were stressed via antibiotics and sonication preserved their inhibitory actions; although heat treated Lactobacilli did not. These results further exemplify the preventative anti-inflammatory effects of lactobacillus.

Ren, Da-Yong, Chang Li, Yan-Qing Qin, Rong-Lan Yin, Shou-Wen Du, Fei Ye, Hong-Feng Liu, Mao-Peng Wang, Yang Sun, Xiao Li, Ming-Yao Tian, and Ning-Yi Jin. Lactobacilli Reduce Chemokine IL-8 Production in Response to TNF-α and Salmonella Challenge of Caco-2 Cells. *BioMed Research International*. (2013): 1-9.

45

MSM– Methylsulfonylmethane

- MSM is known to reduce inflammatory pathway mediators
  - IL-6
  - TNF
  - Homocysteine
- Also effective in extra-intestinal cases
  - Osteoarthritis *Osteoarthr. Cartil. 2007, 15, C123.*
  - Allergic rhinitis *J Altern Complement Med, 8 (2002), pp. 167-173*
  - Reduction of lipid peroxidation *Lipids, 22 (1987), pp. 643-646*

Ahn, H.; Kim, J.; Lee, M.-J.; Kim, Y.J.; Cho, Y.-W.; Lee, G.-S. Methylsulfonylmethane inhibits NLRP3 inflammasome activation. Cytokine 2015, 71, 223-231. 12.
Oshima, Y.; Amiel, D.; Theodosakis, J. The effect of distilled methylsulfonylmethane (msm) on human chondrocytes in vitro. Osteoarthr. Cartil. 2007, 15, C123.
P. Usha, M. NaiduRandomised, double-blind, parallel, placebo-controlled study of oral glucosamine, methylsulfonylmethane and their combination in osteoarthritis Clin Drug Invest, 24 (2004), pp. 353-363

46

GI Environment

- Not all patients exposed to a pathogenic microbe with develop disease
  - Patients biochemical individuality and genetic uniqueness play a large role in the pathogenesis of disease
- On the other hand, some otherwise benign commensal microbes can cause dramatic responses which can result in disease

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Dysbiosis

- Dysbiosis contributes to immune, metabolic, and neurologic dysfunction and resultant clinical disorders
  - Prevention of pathogen penetration into the lamia propria is via goblet cells and their production of mucins, which forms a protective mucous layer Cell. 2014 Feb 27;156(5):1045-59
    - Microbiota also regulates general functions of the GI: mucous production via the goblet cells is regulated by the microbiota on the intestinal epithelium and thus can be disrupted by dysbiosis Ann Nutr Metab. 2013;63 Suppl 2:28-40

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Secretory IgA (sIgA)

- Est. 80% of total body sIgA is in the gastrointestinal tract
  - 1st response to enteric pathogenic microbes
- sIgA mechanism: binds to proteins (epitopes) on microbes

FEMS Immunol Med Microbiol (2001)30:31-35
Clin Microbiol Rev (2006)19:315-37
JPEN (2012)36:1005-175

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Protective Substances in the GI: Mucous and SIgA

- Bio-Ae-Mulsion Forte: 100,000-300,000IU/day in acute phase
  - Maintenance for gut health- 10,000IU/day or 1 drop of Bio-Ae-Mulsion Forte (12,500IU)
- Okra
- L-Glutamine (can go up to 1 gram per 1 kg (2.2lbs) of body weight)
- Aloe
- Zinc: 10-25mg/day *Cent Eur J Immunol. 2014; 39(2): 165–169.*
  - Zinc carosine is the ideal form for GI issues

Halpern, Georges, Zinc Carnosine Nature's Safe and Effective Remedy For Ulcers, Square One Publishers, May 1, 2005

50

Short Chain Fatty Acids (SCFA)

The Microbial Metabolites, Short-Chain Fatty Acids, Regulate Colonic T_{reg} Cell Homeostasis

Patrick M. Smith,[1] Michael R. Howitt,[1] Nicolai Panikov,[1] Monia Michaud,[1] Carey Ann Gallini,[1] Mohammad Bohlooly-Y,[1] Jonathan N. Glickman,[6,7] Wendy S. Garrett[1,2,3,4,*]

Regulatory T cells (T_{reg}) that express the transcription factor Foxp3 are critical for regulating intestinal inflammation. Candidate microbe approaches have identified bacterial species and strain-specific molecules that can affect intestinal immune responses, including species that modulate T_{reg} responses. Because neither all humans nor mice harbor the same bacterial strains, we posited that more prevalent factors exist that regulate the number and function of colonic T_{regs}. We determined that short-chain fatty acids, gut microbiota–derived bacterial fermentation products, regulate the size and function of the colonic T_{reg} pool and protect against colitis in a *Ffar2*-dependent manner in mice. Our study reveals that a class of abundant microbial metabolites underlies adaptive immune microbiota–host metabolic and immune homeostasis and health.

T_{reg} cells are critical for regulating intestinal inflammation

Bacterial fermentation products (SCFA) regulate the size and function of T_{reg} cells

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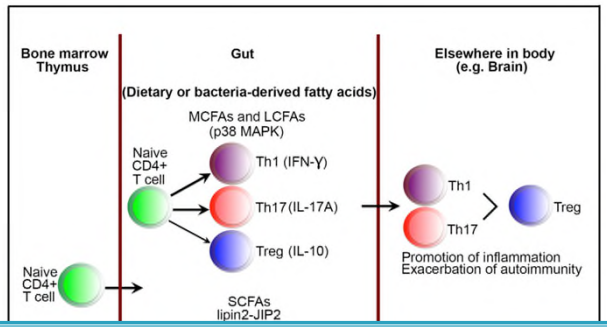
Published in final edited form as:
Immunity. 2015 October 20; 43(4): 629–631. doi:10.1016/j.immuni.2015.09.014.

Short, but Smart: SCFAs Train T Cells in the Gut to Fight Autoimmunity in the Brain

Yangzom D. Bhutia[1] and **Vadivel Ganapathy**[1,*]



The findings indicate that modification of gut microbes and their metabolism are viable targets for treatment of not only multiple sclerosis but potentially also other autoimmune diseases. The goal of such a strategy is to promote generation of SCFAs in the gut so as to drive the differentiation of naive CD4+ T cells into Treg cells and not into Th1 and Th17 cells. This can be achieved with the use of appropriate types of dietary fiber that have the ability to support the growth and proliferation of SCFA-producing gut microbes.

Cruz Ramos H, Hoffmann T, Marino M, et al. Fermentative Met… …acillus subtilis: Physiology and Regulation of Gene Expression. Journal of Bacteriology.

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SCFA and the GUT

Psyllium (Plantago ovato) (seed)
Mannitol
Kelgin (Sodium alginate)
Apple Pectin
Peppermint (Mentha piperita) (leaf)
Flax Seed (Linum usitatissimum)
Anise (Pimpinella anisum) (seed)
Bromelain (from Pineapple)
Celery (Apium graveolens) (seed)
Lactobacillus acidophilus (DDS-1)
Aloe Vera (Aloe barbadensis) (aerial part) *(extract)*
Prune (Prunus domestica) (fruit)

Butyric Acid
Calcium
Magnesium
Panthothenic Acid
Vitamin A

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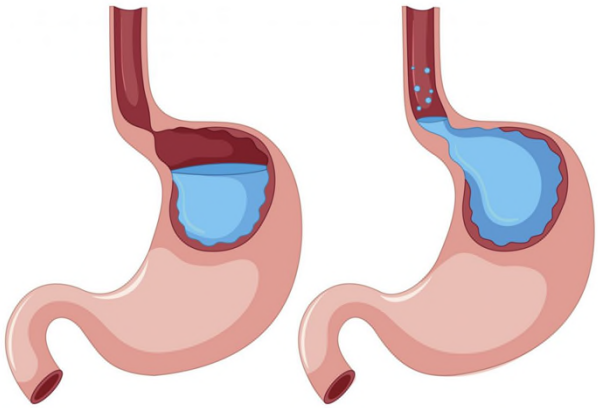

Gastroesophageal reflux (GERD)

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PPIs and GI Infections

PPIs can increase a person's risk of developing gastrointestinal infections, with the most common causative agent being *Clostridium difficile*.

In a study of **1,815 people**, it was noted that those who took PPIs had a substantial increase in bacteria within the *Stretptococcus*, *Enterococcus*, *Staphylococcus*, and *Eschericha coli* families.

This study demonstrated that significant disruption in the gut microbiome are present in people who use PPIs. These changes can cause dysbiosis and can predispose users to a higher risk of developing C. difficle infections

Imhann, Floris, Marc Bonder, and Arnau Vich Villa, et al. Proton pump inhibitors affect the gut microbiome. *Gut.* (2016);65(5): 740–48.

55

Patient Case: Janise 46 yo F

- Has had GERD for at least 10 years
  - Currently on omeprazole (PPI) for the last couple year with mild improvements
  - She has tried many natural supplements with little to no success

Diagnostics

- Endoscope was clean other than the expected results for long-term GERD
- Low serum protein levels
- Positive H. pylori stool antigen

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Patient Case: Janise 46 yo F

- Treatment
  - Ingredients from GI Resolve in powders form- mixed with room temperature water- small amount about 2-3oz
    - Patient instructed to sip over 30-60min 2x per day
      - After one day patient was having noticeable improvement in symptoms
  - While remaining on the PPI we introduced 2 Hydro-Zyme with each meal
  - Bio-HPF - 2/3x per day 15min before meals- CAN take with GI Resolve if she wanted

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Patient Case: Janise 46 yo F

- Treatment cont.
  - Within a week the patient was nearly 50% improved but had a new symptom of bloating
    - Hydro-Zyme was increased to 4 per meal—bloating quickly subsided and has not returned
  - Patient is to remain on recommendations for at least a month
    - We will re-test H. pylori stool antigen, once cleared we will begin tittering off the Omeprazole

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Products for GERD

Powdered products are ideal for GERD as they can have action above the stomach, the esophagus, as they are ingested.

- L-glutamine powder
- Aloe leaf- liquid or powder
- Deglycyrrhized licorice (DGL)
- Okra

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Additional Products for GERD

- HCL Ease: for GERD- dosing in-between meals as well as during may help
- Hydro-Zyme: commonly 2-4 with each meal
  - Can dose up to "stomach tolerance"; Higher dosages look at Betaine HP
- Gastrazyme: 3-4 t.i.d.
  - Can also be used to lessen offensive odor of BM, can also add B12-2000 (hydroxocobalamin)
- Berberine HCL: 2-3 t.i.d. w/meals

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Aloe Vera Leaf

- Aloe vera, like okra, is a mucilaginous compound
- Free radical scavenger Planta Med 2002; 68(11): 957-960 and anti-spasm effects (spasmolytic)
- Used for wound healing

Fabiana Andréa Moura, Kívia Queiroz de Andrade, Juliana Célia Farias dos Santos, Orlando Roberto Pimentel Araújo, Marília Oliveira Fonseca Goulart. Antioxidant therapy for treatment of inflammatory bowel disease. Does it work? Redox Biology 6 (2015) 617–639.
Asadi-Shekaari A[1], Mozaffari S, Sanei Y, Baeeri M, Hajiaghaee R, Monsef-Esfahani HR, Abdollahi M. Benefit of Aloe vera and Matricaria recutita mixture in rat irritable bowel syndrome: Combination of antioxidant and spasmolytic effects.
Journal of the American Podiatric Medical Association [01 Feb 1994, 84(2):77-81]

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Licorice (DGL)

- Taken from a Biotics promotional piece:

"The licorice in GI-Resolve™ has been processed to remove glycyrrhizin, which has been associated with sodium and water retention."

- DGL may have a protective effect on the GI track from the carcinogenic process *Oncotarget. 2016 Nov 1; 7(44): 71960–71973.*
- Effective against H. pylori *J Res Med Sci. 2013 Jun; 18(6): 532–533.*

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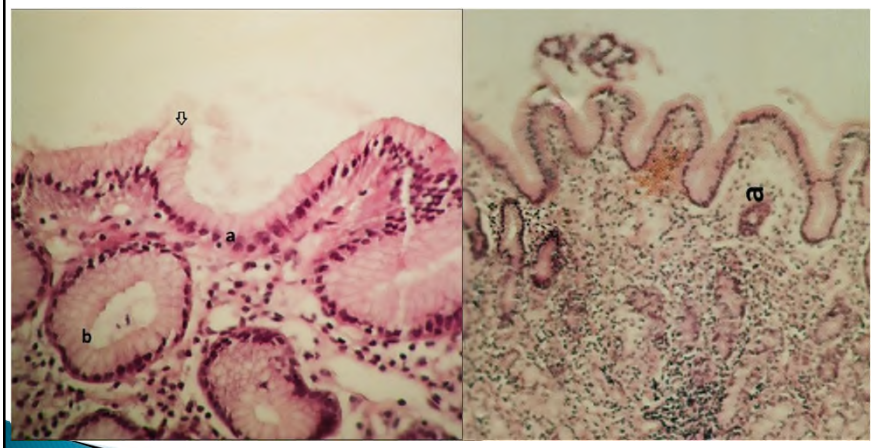
Licorice (DGL)- 250mg t.i.d. for 30 days

Before Treatment | After Treatment



J Res Med Sci. 2013 Jun; 18(6): 532–533.

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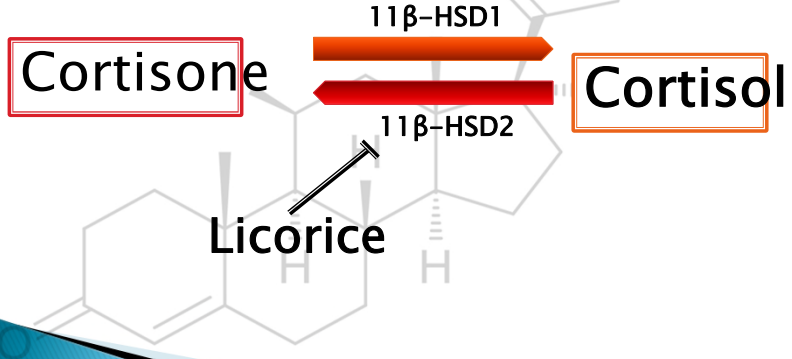
Cortisol and Cortisone

- Glycyrrhizin from licorice will preferentially inhibit 11β-HD2 thus stabilizing the free active form→ cortisol



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"Water Runs Right Through Me"

- This is a common complaint that is usually sign of a poor aldosterone response and may serve as a surrogate marker of "adrenal health"
  - Licorice root inhibits 11β hydroxysteroid dehydrogenase II which increases aldosterone thus resorbing more sodium and H_20, lessening the amount of filtrate
    - Licorice can also bind to mineral-corticoid receptors *J Clin Endocrinol Metab. 2004 Apr;89(4):1973-6.*
    - Inhibits hepatic degredation of aldosterone by blocking 5β reductase *Steroids. 1990 Feb; 55(2):52-8.*

Ther Adv Endocrinol Metab. 2012 Aug; 3(4): 125–138.

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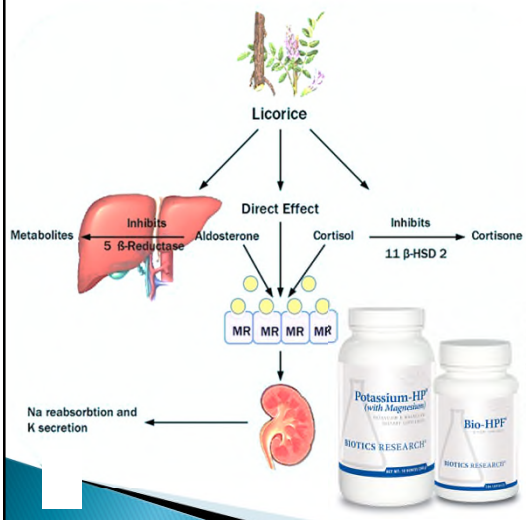
Licorice Root



Aldosterone can be increased by increasing potassium intake. Aldosterone's responsibility is fluid retention thus aiding in the balance of potassium and sodium. Thus increasing potassium will trigger aldosterone activity.

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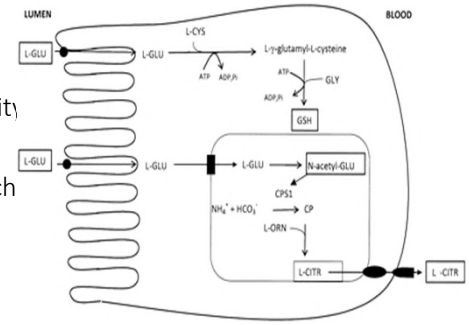
L-Glutamine

- 4,000mg per serving
  - In rat studies glutamine reduces intestinal permeability as well as prevents some invasive bacterial species such as enteropathic E. coli, after just short exposure Gut 1996;38:878-885.
  - Can be a source of fuel for coloncytes- precursor to GSH and N-acetylglutamate



The American Journal of Clinical Nutrition, Volume 90, Issue 3, 1 September 2009, Pages 814S-821S,

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Okra-*Abelmoschus esculentus*

- Mucolaginous, can be used as a coating agent and a binder (Also: ***Saccharomyces boulardii***)
- May have anti-lipidemic effects as well as anti-diabetic mechanisms *Rat study: J Pharm Bioallied Sci. 2011 Jul-Sep; 3(3): 397–402.*

MUCILAGE, OKRA. "INTERNATIONAL RESEARCH JOURNAL OF PHARMACY."
Gemede HF, Haki GD, Beyene F, Rakshit SK, Woldegiorgis AZ. Indigenous Ethiopian okra (Abelmoschus esculentus) mucilage: A novel ingredient with functional and antioxidant properties. Food Sci Nutr. 2018 Feb 2;6(3):563-571.
Ortaç D, Cemek M, Karaca T, Büyükokuroğlu ME, Özdemir ZÖ, Kocaman AT, Göneş S. In vivo anti-ulcerogenic effect of okra (Abelmoschus esculentus) on ethanol-induced acute gastric mucosal lesions. Pharm Biol. 2018 Dec;56(1):165-175.

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Acid Reflux & GERD Stats

- People with acid reflux more than twice a week, are classified as having gastroesophageal reflux disease (GERD).
- Up to 10% of adults in US have daily heartburn, and 44% have this symptom monthly.
- Approximately 25-30% of adults in the US have GERD.*
- Babies hospitalized for GERD increased 42% from 1998 to 2005.**
- Children ages 2-17 hospitalized for GERD increased 84% in the same timeframe.**

*www.Medscape.org **National Institute of Diabetes and Digestive and Kidney Diseases El-Serag HB, Sweet S, Winchester CC, Dent J Update on the epidemiology of gastroesophageal reflux disease, a systematic review. Gut.

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Low Stomach Acid (Hypochlorhydria)

- Incomplete solubilization of essential minerals
- Increased risk of bone fractures Bacterial overgrowth
- Impaired absorption of vitamin B12 Incomplete protein digestion • Chronic indigestion
- Normal pH is 1.5-3.5

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Acid Reflux Medications

Ironically, most recommendations for Acid Reflux address ways to decrease stomach acid: as1

- Antacids to neutralize acid
- Protein Pump Inhibitors to decrease production of HCl

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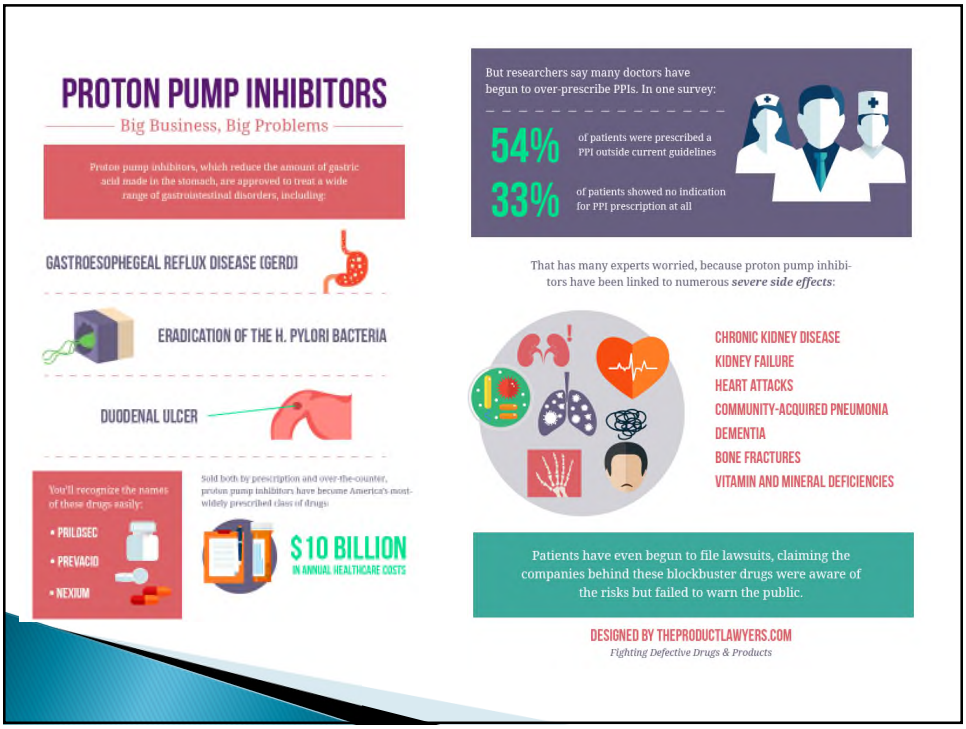

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Slide 72

as1 andjela subotic, 8/16/2020

Long-Term PPI Use

• PPIs resolve symptoms, but people become dependent on them and long-term use associated with:
- Risk of fractures
- Hypomagnesemia
- Clostridium difficile-associated diarrhea (Seto Microbiome Study showed lower microbial diversity)
- Vitamin B12 deficiency
- Acute interstitial nephritis (AIN)
- Dementia
- 7-fold increase incidence of SIBO

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