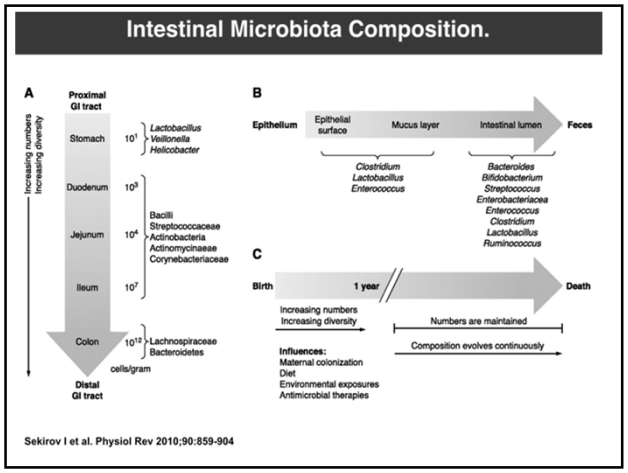
The Microbiome & the Effect on Health

Dr. Wendy Abraham
Naturopathic Physician

- Microbial genes outnumber our genes 100-150:1
- No 2 people share the same microbial make-up
  - genes encode proteins
    - proteins control metabolism



Goals and Intentions

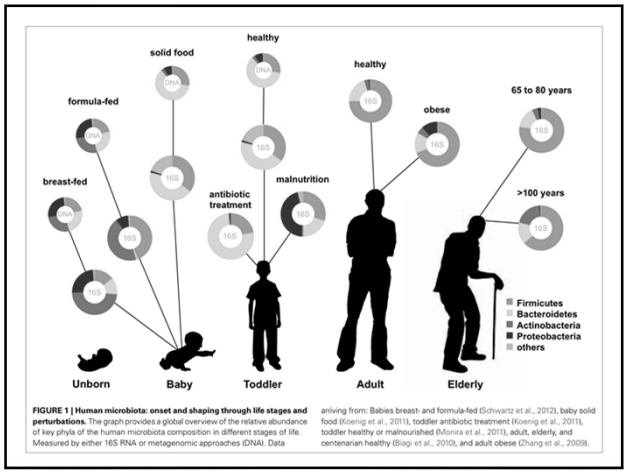


FIGURE 1 | Human microbiota: onset and shaping through life stages and perturbations. The graph provides a global overview of the relative abundance of key phyla of the human microbiota composition in different stages of life. Measured by either 16S RNA or metagenomic approaches (DNA). Data arriving from: Babies breast- and formula-fed (Schwartz et al., 2012), baby solid food (Koenig et al., 2011), toddler antibiotic treatment (Koenig et al., 2011), toddler healthy or malnourished (Monira et al., 2011), adult, elderly, and centenarian healthy (Biagi et al., 2010), and adult obese (Zhang et al., 2009).

Healthy Poop

- Optimal pH - 6.1-7.9
  - Increase in pH - may be caused by
    - High protein and/or low fiber diet
    - Dysbiosis
    - Hypochlorhydria
    - Increased bile flow rate
    - Associated with increased risk for colorectal cancer
  - Greater acidity (lower pH) inhibits the growth of potentially pathogenic pH-sensitive organisms (Prohaszka *et al.,* 1990). Lowering of pH may also help the dissociation of alkaline compounds with toxic or carcinogenic potential therefore inhibiting their absorption.

Fiber

Environ Microbiol Rep. 2013 Oct;5(5):765-75. doi: 10.1111/1758-2229.12079. Epub 2013 Jul 19.

Strict vegetarian diet improves the risk factors associated with metabolic diseases by modulating gut microbiota and reducing intestinal inflammation.

Kim MS1, Hwang SS, Park EJ, Bae JW.

"Low-grade inflammation of the intestine results in metabolic dysfunction, in which dysbiosis of the gut microbiota is intimately involved. Dietary fibre induces prebiotic effects that may restore imbalances in the gut microbiota; however, no clinical trials have been reported in patients with metabolic diseases. Here, six obese subjects with type 2 diabetes and/or hypertension were assigned to a strict vegetarian diet (SVD) for 1 month, and blood biomarkers of glucose and lipid metabolisms, faecal microbiota using 454-pyrosequencing of 16S ribosomal RNA genes, faecal lipocalin-2 and short-chain fatty acids were monitored. An SVD reduced body weight and the concentrations of triglycerides, total cholesterol, low-density lipoprotein cholesterol and haemoglobin A1c, and improved fasting glucose and postprandial glucose levels. An SVD reduced the Firmicutes-to-Bacteroidetes ratio in the gut microbiota, but did not alter enterotypes. An SVD led to a decrease in the pathobionts such as the Enterobacteriaceae and an increase in commensal microbes such as Bacteroides fragilis and Clostridium species belonging to clusters XIVa and IV, resulting in reduced intestinal lipocalin-2 and short-chain fatty acids levels. This study underscores the benefits of dietary fibre for improving the risk factors of metabolic diseases and shows that increased fibre intake reduces gut inflammation by changing the gut microbiota."

Short Chain Fatty Acids

- major metabolic fuel for colonocytes with butyrate being their preferred substrate (Roediger 1982)
- colonocyte capacity to oxidize butyrate is modulated by the microflora (Cherbuy *et al.,* 1995).
  - generated in colon by bacterial fermentation of dietary fiber, protect against colorectal cancer and inflammatory bowel disease
- promote colonocyte proliferation
  - help reverse colon muscle atrophy associated with low-fiber diets
  - presence of butyrate at physiological concentrations enhances growth of normal cells and inhibits that of malignant ones
    - promotion of DNA repair and differentiation of tumor cells as well as inducing apoptosis of malignant cells(Smith *et al.,* 1998)

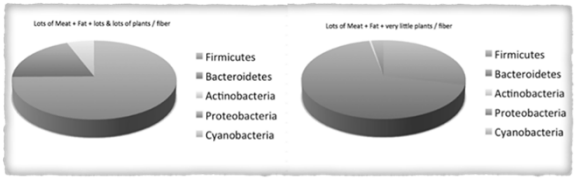
- Jeff Leach of the American Gut Project
  - no fiber for 10 days
    - the abundance of Firmicutes - specifically butyrate-producing Clostridia - was driven by the consumption and fermentation of plant fiber
    - the consumption of plant fiber led to the exact same microbiota shift as smoking cessation.

Scand J Gastroenterol. 1994 Oct;29(10):916-22.

Effect of fiber source on short-chain fatty acid production and on the growth and toxin production by Clostridium difficile.

May T1, Mackie RI, Fahey GC Jr, Cremin JC, Garleb KA.

Fermentable fibers support the growth of indigenous intestinal bacteria, particularly acidogenic bacteria, and yield large amounts of short-chain fatty acids with decreased gut pH. These factors contribute to the prevention of growth and toxin elaboration by C. difficile.



Factors affecting good bacteria

- Antibiotics - therapeutic and low dose in food supply
- Stress
- Drugs
- Nutritional Deficiencies
- Refined Sugar
- Birth
- "sterile environments" - impoverished microbial community/ influence

GI Conditions Associated with Dysbiosis

- IBS
- IBD
  - Crohn's
  - Celiac
- SIBO
- Colon Cancer

Dysbiosis

- Imbalance of gut bugs - the good, the bad and/or the ugly

Symptoms associated with dysbiosis

Fatigue, altered immune system, upsets your hormonal balance.
Forgetfulness, foggy headedness
Anxiety, depression or mood swings
Gas, Bloating, Upset stomach
Irritable Bowel Syndrome

Dysbiosis can affect almost every aspect of health.

- Local (GI) and Systemic Inflammatory Conditions

Conditions not commonly associated with imbalance of Microbiome

- Obesity
- Metabolic Syndrome
- Anxiety
- Depression
- Autism/ ASD
- Inflammation
- Allergies
- Cancer

- Chronic dysbiosis can lower the levels of beneficial short chain fatty acids and alter bacterial metabolic activity, thereby increasing the risk of carcinogenesis, hormonal imbalance and GI inflammation.

Mental Health & Microbiome

- Psychobiotics - a live organism (ex -probiotic) that when ingested in adequate amounts has a positive health promoting benefit for those suffering with mental health issues
  - depression, anxiety, OCD, trichotilomania, eating disorders

Gut-Brain Axis

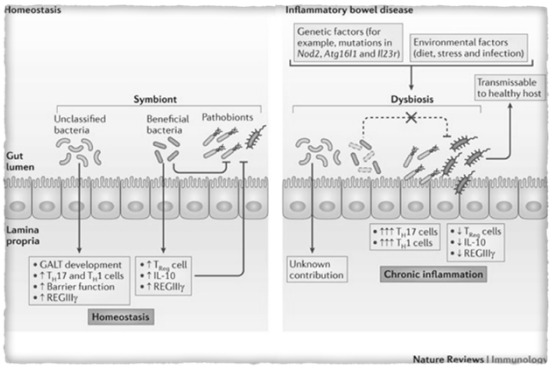
- the development of the brain is dependent on a healthy & functioning microbiota
- communication between gut and brain is via Vagus nerve
- Gut microbes are able to send signals to the brain

Microbiota & pathogenesis of IBD

- A shift from a healthy symbiotic gut to a dysbiotic environment is involved in changing the host tolerance response from a normal healthy response to one that is activated and possibly pathogenic immune response.
- Promotion of Th17 differentiation occurs - causing Dendritic Cells to produce IL-6 and TGF-B - happens as a result of epithelial cells that are infected with bacteria during apoptosis.

Second Brain?

- more nerves in GI track than in spinal cord
- gut produces the same neurotransmitters found in our brains
- 95% of serotonin is located in the gut
  - serotonin regulates mood, sleep/wake cycle and pain



Microbiome & IBD

Specific changes of gut commensal microbiota and TLRs during indomethacin-induced acute intestinal inflammation in rats.
Terán-Ventura E, Aguilera M, Vergara P, Martínez V. J Crohns Colitis. 2014 Sep 1;8(9):1043-54. doi: 10.1016/j.crohns.2014.02.001. Epub 2014 Feb 22.

Conclusion: Gut inflammation implies qualitative changes in GCM, with simultaneous alterations in host-bacterial interactions. These observations further support a potential role for gut microbiota in the pathophysiology of intestinal inflammation.

Characteristics of fecal and mucosa-associated microbiota in chinese patients with inflammatory bowel disease.
Chen L, Wang W, Zhou R, Ng SC, Li J, Huang M, Zhou F, Wang X, Shen B, Kamm M, Wu K, Xia B. Medicine (Baltimore). 2014 Aug;93(8):e51. doi: 10.1097/MD.0000000000000051.

The intestinal microbiota plays an important role in the pathogenesis of inflammatory bowel disease (IBD), and geographical and genetic backgrounds impact the composition of the intestinal microbiota. However, there is a lack of evidence regarding the overall changes and characteristics of fecal-associated microbiota (FAM) and mucosa-associated microbiota (MAM) in Chinese patients with IBD. We recruited 26 patients with Crohn's disease (CD), 46 patients with ulcerative colitis (UC), and 21 healthy individuals; we collected matched fresh fecal and mucosal samples from the same subjects. The microbial communities were studied by 454 pyrosequencing. Community-wide changes in FAM and MAM were observed in patients with IBD. The proportion of several butyrate-producing bacteria, such as of the genera Roseburia, Coprococcus, and Ruminococcus were significantly reduced, whereas the pathogens Escherichia-Shigella and Enterococcus were prevalent in patients with IBD. FAM and MAM were similar between CD and UC. FAM differed from MAM in healthy individuals and patients with UC. **In conclusion, the compositions of FAM and MAM were altered in patients with IBD. The reduction of butyrate-producing bacteria and the increase in opportunistic pathogens might be associated with the pathogenesis of IBD.**

Probiotics & Allergies

- The double-blind placebo controlled study - The College of Medicine at Swansea University -Professor Stephen J Allen MD
- The study was conducted on 454 mothers-infant pairs, who took a daily dose of probiotic providing 10 billion of a specific strain from 36 weeks of pregnancy and during the first six months of life.
- The babies were assessed at 2 years of age and it was found that those taking the probiotic significantly reduced their chance of becoming allergic to common allergens such as pollen, cat dander, house dust mite, cow's milk and egg by half (50%).
- Moreover, the risk of the children developing atopic eczema was reduced by 60%
- Lecture by Nigel Plummer

Heart Disease

- link between atherosclerosis and meat/cheese consumption
  - Specific gut bugs (found primarily in guts of long term meat eaters)
    - produced Trimethylamine - gets converted in liver to Trimethylamine N-oxide (TMAO)
      - TMAO encourages atherosclerosis, interferes with liver enzymes that synthesize bile acids (therfore decrease ability to remove excess cholesterol)
      - TMAO synthesis requires microbes that digest carnitine

Microbiota & Activation of Cytokines

- Intestinal microbiota play a key role in the activation of cytokines through the up-regulation of TLR signaling (and subsequently NFκB signaling)
- Pro-inflammatory cytokines cause the rapid discharge of mucin stores in goblet cells leading to ↑cavitation
- Depletion of mucin stores in goblet cells leads to subsequent effects on the mucus layer in the intestine
- Reduced attachment sites affect microbial ecology and available nutrients for commensal bacteria -- allows aerotolerant species to proliferate

Antibiotics, Disappearing Microbes and Links to Breast and Prostate Cancer

"Some of the beneficial bacterial may never recover. These extinctions may lead to increased susceptibility to infections and disease. "

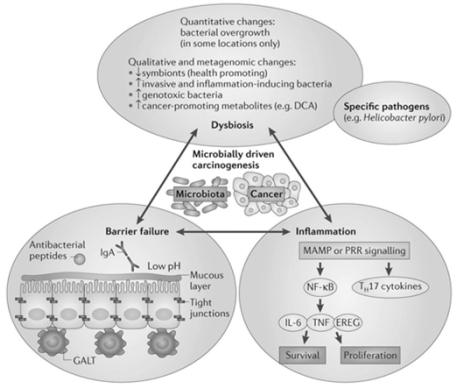
We observed a dose-dependent increase in breast cancer risk in association with the antibiotic exposure up to 15 years in the past. "However, the lack of temporal trends and the absence of class-specific effects suggest a non-causal relationship."

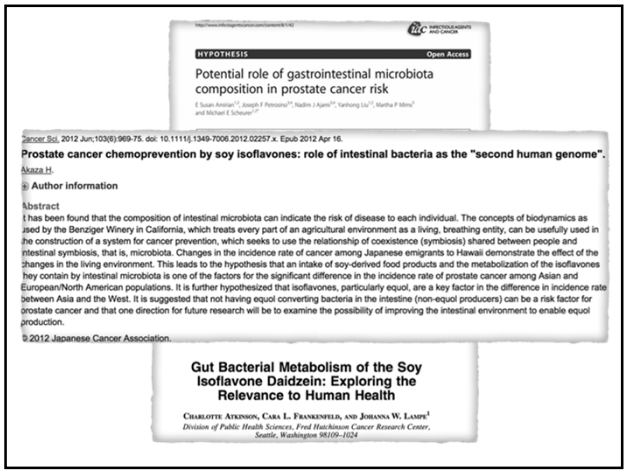
Number of antibiotic prescriptions for 1–15 years in the past was significantly associated with an increased risk of prostate cancer.

Breast Cancer and the great Soy Debate

- Conversion of isoflavones (dadzein) requires microbiota
- Breast milk containing isoflavones help a child acquire bacteria capable of isoflavone metabolism beginning in infancy
- Infants exposed to isoflavones early in life become more competent to hydrolyze glycosides allowing uptake of isoflavones to produce equol later in life


The Human Mammary Gland as a Target for Isoflavones: How Does the Relation Vary in Individuals with Different Ethnicity?




HYPOTHESIS Open Access

Potential role of gastrointestinal microbiota composition in prostate cancer risk

Cancer Sci. 2012 Jun;103(6):969-75. doi: 10.1111/j.1349-7006.2012.02257.x. Epub 2012 Apr 16.

Prostate cancer chemoprevention by soy isoflavones: role of intestinal bacteria as the "second human genome".

Akaza H.

Author information

Abstract

It has been found that the composition of intestinal microbiota can indicate the risk of disease to each individual. The concepts of biodynamics as used by the Benziger Winery in California, which treats every part of an agricultural environment as a living, breathing entity, can be usefully used in the construction of a system for cancer prevention, which seeks to use the relationship of coexistence (symbiosis) shared between people and intestinal symbiosis, that is, microbiota. Changes in the incidence rate of cancer among Japanese emigrants to Hawaii demonstrate the effect of the changes in the living environment. This leads to the hypothesis that an intake of soy-derived food products and the metabolization of the isoflavones they contain by intestinal microbiota is one of the factors for the significant difference in the incidence rate of prostate cancer among Asian and European/North American populations. It is further hypothesized that isoflavones, particularly equol, are a key factor in the difference in incidence rate between Asia and the West. It is suggested that not having equol converting bacteria in the intestine (non-equol producers) can be a risk factor for prostate cancer and that one direction for future research will be to examine the possibility of improving the intestinal environment to enable equol production.

© 2012 Japanese Cancer Association.

Gut Bacterial Metabolism of the Soy Isoflavone Daidzein: Exploring the Relevance to Human Health

Charlotte Atkinson, Cara L. Frankenfeld, and Johanna W. Lampe

Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington 98109–1024

Autism & the Microbiome

- some studies show that children with Autism lack one of the healthy fermenters - *Prevotella*
- interestingly - the Prevotella org were decreased in the subjects (study mentioned earlier) in the vegetarian subject during the animal consumption arm of the study

"The road to optimal health is paved with good INTESTINES" Dr. Deb Marcus, N.D.

- combination of genetic susceptibility, micro biome and exogenous factors (perfect storm)
  - genetic SNP - defective sulfating (can not adequately detoxify APAP)
  - leads to intestinal dysbiosis (overgrowth of Clostridia)
    - over-production of dopamine (or SNP that doesn't metabolize it) and reduced concentrations of NE - leads to reduced exploratory behavior and other learning issues
  - as the toxic levels of APAP build - excessive production of metabolite N-acetyl-p-benzoquinone imine is produced - causing a lot of other problems
  - adapted from lecture from Dr. Shaw of Great Plains Laboratory.

Principles of Holobiont Theory

- All animals and plants establish symbiotic relationships with microorganisms.
- Different host species contain different symbiont populations and individuals of the same species can also contain different symbiont populations.
- The association between a host organism and its microbial community affect both the host and its microbiota.
- The genetic information encoded by microorganisms can change under environmental demands more rapidly, and by more processes, than the genetic information encoded by the host organism.
- ... the genome of the host can act in consortium with the genomes of the associated symbiotic microorganisms to create a hologenome. This hologenome...can change more rapidly than the host genome alone, thereby conferring greater adaptive potential to the combined holobiont evolution.
- Each of these points taken together led Rosenberg et al. to propose that
- * the holobiont with its hologenome should be considered as the unit of natural selection in evolution*

(condensed from Rosenberg *et al*., 2007)