The Microbiome & the Effect on Health

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Goals and Intentions

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

Intestinal Microbiota Composition.

Figure 1: Changes in microbiota occur and shape through life stages and include birth, formula and solid feeding, treatment, and aging. The gut microbiota develops after birth and is influenced by the environment. A healthy gut microbiota is essential for overall health. (Adapted from various sources.)
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.

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)

Fiber

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

“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 microflora 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 pathobacteria 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 underscored 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.”

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

May TL, Mackin RI, Fahey GC Jr, Cronin 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

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

GI Conditions Associated with Dysbiosis

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

Conditions not commonly associated with imbalance of Microbiome

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

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
- 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.
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 & 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 TLs during interleukin-12 induced acute intestinal inflammation. In mice.

Conclusions: 1) Deficiency in particulate materials in the environment is involved in changing the host tolerance from a normal healthy response to one that is activated and possibly pathogenic immune response. 2) Specific changes of gut commensal microbiota and TLs during interleukin-12 induced acute intestinal inflammation. In mice.


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

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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 (therefore 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 microbial 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 (daidzein) 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
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

- 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"

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