Healthy Gut

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Outline

- What is our Gut Microbiome?
- What influence does microbiome have on health?
- What influences growth of healthy microbiome?
- What influence does gut microbiome have on cancer and cancer treatment?

Gut Microbiome

- Our microbiome is the collection of trillions of bacteria species that live symbiotically in the human gut. The number of bacteria cells outnumber our cells by factor of 10.
- Imbalance of the gut bacteria is linked to conditions like IBS, inflammatory bowel disease, obesity, diabetes, and maybe many more
- Initial gut colonization in infants may be instrumental in shaping adult gut environment but that doesn’t mean we can’t change the microbiome at any time.

Symbiotic means all benefit!

- Bacteria are able to perform many functions humans can't or have limited ability like:
  - Produce vitamins
  - Synthesize amino acids
  - Transform bile
- Intestinal cells interact with bacteria to influence host's immune system. Bacteria bind and signal immune system
- Metabolize non-digestible carbohydrates
  - Polysaccharides, resistant starches, cellulose, pectins, gums
  - Provides recovery of energy and nutrients for bacterial growth
- Produce antimicrobial compounds and compete with pathogens
- Gut-brain communication influences gut function in response to stress

Nutrient contribution

- Gut microbes are able to synthesis
  - Vitamin B12, thiamine, folate, riboflavin, and vitamin K
  - Possibly 20% of circulating amino acids lysine, leucine and threonine in adult humans are synthesized by gut microbes
  - In addition microbes are involved in urea nitrogen salvaging

Functions of Microbiota

- Ferment indigestible carbohydrates into byproducts including Short-chain fatty acids (butyrate, acetate, propionate)
  - Butyrate is energy source for human colonocytes, can induce apoptosis (cell death) for colon cancer cells and activate intestinal gluconeogenesis, maintain oxygen balance and prevent dysbiosis
  - Propionate transfers to liver to regulate gluconeogenesis and satiety.
  - Acetate may also regulate appetite and influence cholesterol and lipid regulation; used by skeletal and cardiac muscle.
- More SCFAs =less obesity and less insulin resistance.

Microbiota and Health

- What the microbiota are fermenting makes a difference.
  - Fermenting meat and dairy produces Trimethylamine which is oxidized by liver and associated with increased risk of atherosclerosis
  - Fermenting dietary fiber produces Indolepropionic acid and butyrate- has potent radical scavenging activity which seems to reduce the risk of incidence of type 2 diabetes.
  - Butyrate has anti-inflammatory effects, maintains gut barrier, reduces oxidative stress in gut
  - High fat diet contribute more lipopolysaccharides to traverse gut and increase inflammation

Microbiota influences on health

- The gut talks to the brain and back. Stress has been shown to influence integrity of the gut, alter peristalsis, secretions, and mucin production.
- Probiotic consumption also has been reported to reduce self-reported feelings of sadness and aggressive thoughts
- Stress induce gut changes in permeability and the mucosal lining of gut increasing inflammation and damage to gut

Gut Microbiota and Health

- Irritable Bowel Syndrome
  - Characterized by abdominal discomfort, pain, change in bowel habits.
  - Influenced by many factors in the gut including inflammation, genetics, hypersensitivity, infection, and microbiota
  - Alteration in the composition of gut may facilitate adherence of pathogens and development of IBS symptoms.
  - Recent study looking at microbiome of patients starting vedolizumab found a more diverse microbial composition at baseline predicted week 14 clinical remission. Butyrate producing bacteria at baseline specifically where higher in those achieving remission

Low FODMAP Diet

- In case of people with IBS, diet restriction of specific carbohydrate sources may alleviate symptoms. It is believed that malabsorption of simple sugars in people contribute to excessive fermentation by colon. The SCFA produced overstimulate free-fatty-acid receptors resulting in change in motility and sensitivity of colon
- This diet restricts oligosaccharides, disaccharides, monosaccharides and polyols
- Diet restricts gluten, lactose and specific fruits and vegetables
- Specific lists of foods to eat and not eat are readily available

Gut Microbiota and Health

- “Leaky gut”- this terminology is controversial as some don’t believe this is true diagnosis.
  - Leaky gut refers to reduction in the tight junctions between cells of the GI tract which allow microbes and foreign material through causing inflammatory reactions
  - Factors that can influence junctions is H.Pylori, gluten for those with celiac sensitivity, alcohol, stress, age, inflammatory bowel disease, chrohn’s

Gut Microbiota and Health

- Foods that are problematic
  - Artificial sweeteners; processed foods due to additives, sugar, dyes, salt; gluten if a person is sensitive, red meat;
- Foods to help
  - Bone broth for glutamine and collagen, fermented foods, Foods high in fiber to stimulate biodiversity; omega-3 foods, Turmeric, mushrooms, green tea
  - Potentially lactobacillus plantorum and bifidobacterium both found in VSL#3 probiotic;
- What about Lectins? –Not true; there is some research on limiting lectins and adding probiotics in management of autoimmune disease but remember foods high in lectins like beans, whole grains have been shown to be beneficial in wide range of diseases

Microbiota and Health

- Obesity and Diabetes
  - There seems to be a relationship between altered microbiota in obese versus normal weight mice.
    - Studies in mice show microbiota preference for firmicutes versus bacteriodetes
    - Firmicutes being very efficient at extracting energy from diet
    - This ratio can be altered on fat restricted or carbohydrate restricted diet or intermittent fasting.
    - Studies have found during times of fasting increase in bacteriodetes and less firmicutes
  - Production of SCFA from microbiota related to signaling along the gut for satiety and regulation of food intake
  - Gut composition of study patient with diabetes showed some dysbiosis and decrease in short-chain fatty acid production.
  - Low microbiota diversity correlates with weight gain

Gut-Brain Axis

- Many pathways for communication between gut microbiota and the brain by alterations in cytokines, hormones, SCFA, or neurotransmitter
- SCFA can cross brain barrier and affect microglia and brain development. Mice that are germ free show impaired memory, hyperlocomotion, and anxiety.
- Our microbiome, carb. Fermentation may be linked to brain health

Microbiome and Cancer

Colorectal cancer:

- Studies link dysbiosis from infections, antibiotic use to increase risk Colon Ca
- several by-products of the gut microbiota directly target intestinal epithelial cells (IECs) and either mediate oncogenic effects (as reported for hydrogen sulfide and the *Bacteroides fragilis* toxin) or suppress tumorigenesis (as demonstrated for short-chain fatty acids)

Microbiome and Cancer

- Other cancers: alterations of gut microbiota influence incidence of cancers including breast, liver due to inflammatory and metabolic means.
- Potentially related to systemic distribution of bacteria and by-products that compromise integrity of gut barrier.

Microbiome and treatment

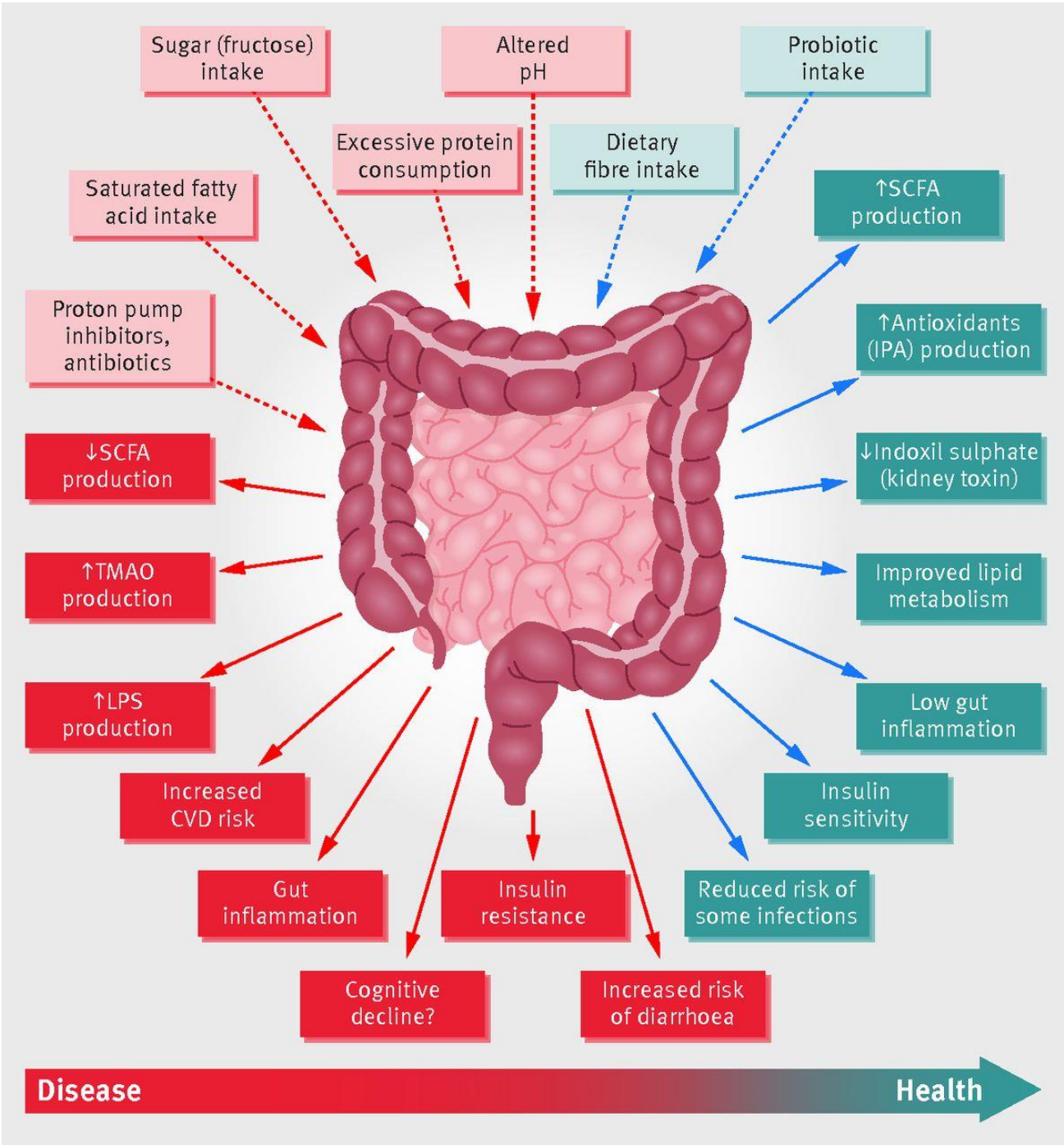
- Treatment for cancer can exert toxic effect on bacteria promoting dysbiosis for example radiation therapy, transplant, irinotecan, 5-FU can be toxic to gut microbiota. And exert unwanted side effect to intestinal tract.
- Gut microbiota may also influence efficacy of chemo; in irinotecan opportunistic gut bacteria (bad) associated enzymes are able to reactivate drug in gut contributing to diarrhea from the medication.
- Evidence that dysbiosis contributes to infections and intestional GVHD (graft versus host disease)

Microbiome and Treatment

- Treatment can promote 2 opposite types of dysbiosis: detrimental and beneficial
- Pharmacological manipulation of the gut holds great promise as adjunct to improve therapeutic effects of treatment but more research is required.
  - For example a potent inhibitor of bacteria B-glucuronidase has been shown to protect mice from intestinal effects of irinotecan

Cancer treatments

- Immunotherapy
  - We know microbiota help shape the immune system
  - People on immunotherapy for Melanoma (anti-PD-1 checkpoint blockade) with most diverse gut microbiome had better response (5 times more likely to respond) to immunotherapy
  - In this study probiotic supplementation was not associated with diversity
  - Diversity was associated with high fiber diet
  - Other studies with immunotherapy found poor effectiveness in people who recently took antibiotics.


Sugar (fructose) intake
Altered pH
Probiotic intake
Excessive protein consumption
Dietary fibre intake
Saturated fatty acid intake
↑SCFA production
Proton pump inhibitors, antibiotics
↑Antioxidants (IPA) production
↓SCFA production
↓Indoxil sulphate (kidney toxin)
↑TMAO production
Improved lipid metabolism
↑LPS production
Low gut inflammation
Increased CVD risk
Insulin sensitivity
Gut inflammation
Insulin resistance
Reduced risk of some infections
Cognitive decline?
Increased risk of diarrhoea
Disease
Health

What Influences Gut Microbiota Growth

- External Influencers
  - Microbial load in the environment
  - Type of food eaten
  - Feeding habits
  - Temperature
- Internal Factors
  - Intestinal PH
  - Microbial interactions
  - Environment temp.
  - Peristalsis
  - Bile acids
  - Drug therapy
  - Bacterial mucosal receptors

Influencers on Microbiota

- Influence of foods we eat on microbiota
  - Artificial sweeteners-animal studies show disrupt microbiota balance and diversity; increasing pro-inflammatory genes and metabolites
  - Food additives, emulsifiers, reduces gut diversity and increase inflammation promoting proteobacteria.
  - Restrictive diets like raw food, clean eating, gluten-free; in gluten-free diet since avoid whole grains, have increased risk of heart disease; Low fiber diet reduce microbiome diversity

Influencers on Microbiota

- Resistant starches can enrich bacterial groups in people which will be variable to the starch and person.
- Fiber in diet can significantly effect GI microbiota but only last as long as food is included in the diet.
- Low fiber intake reduces SCFA leading to production of detrimential metabolites, degrades colonic barrier, microbiota encroachment, and inflammation
- High fat diets impact pentrability of mucus layer.

Foods to support diversity

- Resistant Starches
  - Grains: oats, pumpernickel, pearl barley
  - Seeds
  - Legumes, lentils, peas, corn
  - Raw potatoes, plantains
  - Green bananas
  - Potatoes and rice that are cooked and COOLED

Pass through digestion and feed good bacteria forming SCFA butyrate

- High Fiber foods
  - Peas
  - Broccoli
  - Greens
  - Brussel Sprouts
  - Raspberries
  - Pear
  - Apple
  - Strawberries
  - Raw carrot
  - Cauliflower
  - Chia seeds
  - Quinoa

Support diversity

- Eat a high fiber diet full of prebiotics and probiotic rich foods
  - dark leafy greens, onions, garlic, soybeans, artichokes, beets, sweet potato, butternut squash, apricot, cherries, kale, pineapple
  - Fermented foods as more diverse source of probiotics like kombucha which can contain up to 50 different probiotic strains versus a pill supplement that might only have 2. others are yogurt, kefir, sauerkraut, kimchi, tempeh, miso

Fermented food

- Kombucha like Synergy, Pilot Kombucha, and others-look for drinks made with fruit juices not sugar
- Yogurt drinks like Siggi's plant-based probiotic yogurt
- Kefir
- Probiotic shots: sunny culture turmeric ginger probiotic shot, Suja immunity or digestive shot also has turmeric or ginger
- Sauerkraut; fermented vegetables, miso, tempeh, kimchi

Other influencers

- Replace saturated and trans-fats with omega-3 fats from fish, flaxseeds, olives, and nuts
- Go out in the sun for short periods of time (don’t burn) to support production of vitamin D. Vitamin D supports gut diversity
- Stay hydrated!
- Changes in your diet can change microbiome within days and have lasting effect on your health

Future research directions

- Analysis of gut microbiome may predict patient likely to have immunotherapy colitis
- Probiotic mixtures ideal for best response to cancer treatments
- Using microbiome and diet algorithms to predict glycemic response to meals and better control blood sugars in Diabetics
- Fecal transplants in treatment of c. diff and obesity, alzheimer's, other diseases
- Need technology for personalized characterization of the gut to manipulate biome favorably

Thank you !