**The Metabolic Role and Therapeutic Potential of the Microbiome**Louise Olofson  
This scientific review covers everything on the microbiome and your overall health, from effects to mechanisms.   
  
Both researchers either receive funding from pharma or are shareholders. The review is funded by public money and non-profit money. **Introduction**  
Gut microbiota are a critical part of human physiology. It can be seen as a quasi-endocrine organ as it takes nutrients from our diet and produces metabolites that interact with the intestines, liver, fat cells, and the nervous system.

**Gut Microbiota**  
  
Vaginally born babies obtain microorganisms from their mother's vagina and gut, as opposed to babies born via C-section are colonized by organisms from skin and the environment. Some microbes are considered early colonizers of the body vs others being late colonizers; for example, bifidobacterium is the most abundant bacteria when a baby and lives off human milk oligosaccharides.  
  
These early microbes create the environment for more anaerobic microbes that arrive as the baby moves to solid food, leading to increased diversity in the first 5 years of life. However, the evolution of the diversity is still not complete to adult levels.   
  
Cessation of breastfeeding is necessary to achieve that maturation to adult composition, and switching from animal to plant based diet leads to significant changes in gut microbiota. Mild changes lead to mild changes in microbiota, so it tracks with the level of change. Physical activity, immune system, infection, and antibiotics affect the composition of the microbiome.   
  
People can have the exact same diet, yet the metabolites that are produced by their microbiome can be quite different, due to the composition of their microbiome.   
  
Fine tuning the gut microbiome can lead to changes in the immune system, as well as protect from infection by taking up nutrients, leaving little for infectious bacteria to feed on. The microbiome can also synthesize vitamins.   
   
**Alterations in Gut Microbiota Composition and Metabolic Disorders**  
  
Obese individuals have a reduced diversity of their microbiome, and leaner individuals have higher amounts of Christensenella, a bacteria that is associated with good health. Lack of richness of the microbiome was linked to obesity, insulin resistance, and dyslipidemia.   
  
There is a consistent link of depleted butyrate producing bacteria and type 3 diabetes.   
  
**Causal Role of Microbiota and Metabolic Disease**Germ free mice have been used to study causality. When fed a high complex carbohydrate diet, germ free mice have reduced weight and body fat compared to conventional mice. However, when introduced to colonies of bacteria, their weight increases (likely from greater bioavailability of the nutrients from the biota helping break down the nutrients). Gut microbiota metabolize otherwise indigestible complex carbs to short chain fatty acids.   
  
 **Microbially Produced Metabolites**  
  
Microbes in the colon digest complex carbohydrates to short chain fatty acids like acetate, propionate, and butyrate. Butyrate, especially, promotes better epithelial cell function by promoting more tight junction. It also has an anti-inflammatory effect, like it suppresses LPS activated NF kappa B induction in immune cells, but it does lead to the release of prostaglandins E2 and expression of IL-10 (anti-inflammatory). It also reduces histone deacetylase, promoting histone acetylation and regulating gene expression related to immune cell proliferation, differentiation, and general inflammation. Greater systemic butyrate is associated with lower blood sugar levels. SCFA can also act as signaling molecules by binding fatty acid receptors in the intestines, adipose tissue, skeletal muscle, liver, and pancreas. Supplementing SCFA in high fat fed mice led to higher energy expenditure and reduced weight gain. Butyrate also suppressed the activity of neuropeptide Y (pro-food consumption protein). Butyrate also promotes fat oxidation and increased brown fat thermogenic capacity.   
  
SCFA are also the main energy source for colon cells lining the colon. They can switch to glucose oxidation for energy, however. Colon energy levels also modulate GLP-1 levels, with energy deprivation in the colon leading to more GLP-1, and more bacteria in the colon leading to lower GLP-1 levels, which may be a reason why people who are anorexic may have higher levels of GLP-1.   
  
In certain conditions, too much SCFA (butyrate) has been shown, in mice, to increase lipogenesis and metabolic impairment.

**Microbial Regulation of Gastrointestinal Hormones**  
  
GLP-1 is produced by the L Cells of the intestines, as well as by the brain stem. Low SCFAs and low microbes in the intestinal microbiome are linked to higher GLP-1 levels, certain microbes can also produce SCFAs that increase GLP-1 levels (SCFA type dependent?). GLP-1 acts to decrease consumption on the brain. L Cells also secrete Peptide YY and GLP-2, and gut microbiota can increase SCFAs to increase both of these hormones, as well. Peptide YY is also a hormone that reduces appetite.   
  
Microbes can also metabolize bile acids into secondary bile acids, which also encourages the release of GLP and Peptide YY.   
  
90% of the body's serotonin is produced in the enterochromaffin cells of the gut wall. SCFAs and this secondary bile mechanism may change serotonin levels (increasing their levels) by increasing the expression of Tryptophan Hydroxylase-1 (TPH1). Serotonin can reduce intestinal motility, and has an affect on blood sugar regulation. Inhibiting TPH1 leads to *improved* glucose tolerance.   
  
**Gut Microbiota and Metabolic Effects Beyond the Intestines**Gut bacteria can move into the blood stream and cause disease (metabolic disease, included).

**Gut Microbiota and Liver Function**  
  
There is cross talk between the gut microbiota and liver, which happens through the portal vein, biliary tract, and systemic circulation. Some examples of molecules that interact with the liver via the portal vein are SCFAs, as well as LPS. For example, imidazole propionate (secreted by the gut microbiome) impairs liver insulin signaling at IRS. Also, SCFA absorption into the liver can promote denovo lipogenesis and increase fatty liver. Liver TLRs, when bound by LPS, leads to metabolic disease (liver steatosis, reduced insulin sensitivity).

**Gut Microbiota and Adipose Tissue Function**  
  
Gut microbiota suppress the lipoprotein lipase inhibitor angiopoietin-like protein and can therefor regulate lipid uptake into the adipocytes. Reduced microbiota also promotes browning of subcutaneous fat, as well as visceral fat, associated with better glucose tolerance and insulin sensitivity. There have been conflicting results on this outcome, however. Cold exposure also changes gut microbiota composition.   
  
Rodents fed a high fat diet made up of saturated fats increased activation of the adipose tissue TLR leading to increased inflammation in adipose tissue, as well as increased insulin resistance compared to mice fed a fish oil based diet. Microbiota transplanted from mice fed a saturated fat heavy diet compared to fish oil heavy diet into germ free mice that are then fed a heavy saturated fat diet. The microbiota from the fish oil fed mice led to the mice having reduced weight gain and reduced inflammation in the adipose tissue.

**Gut Microbiota and the Gut-Brain Axis**  
  
Particular enteroendocrine cells lining the small intestine make contact with the vagus nerve by synapsing with the neurons of the vagus and relay sensory information via glutamate. These cells might be able to sense microbial metabolite production and relay that information to the brain. Vagal neurons can also bind to GLP-1 and serotonin produced in the gut. Hypothalamus inflammation can lead to leptin resistance and subsequent weight gain.   
  
Bile acids signal to the brain by acting on the TGR5 receptors in the hypothalamus, activating the sympathetic nerves, decreasing food intake and increasing energy expenditure. Bile acids can be found in the blood stream, as well as in the brain when fed a high fat meal.

**Microbiome Therapies**  
  
The composition of one's microbiota likely matters in regard to how modulating the microbiome might help someone. For example, someone with diabetes that already has high levels of butyrate producing microbes may not benefit from improving their microbiota even more - compared to someone with low microbiota diversity.   
  
Researchers were able to predict blood glucose responses to identical meals based on the composition of their microbiota. They were able to change dietary recommendations and stabilize blood sugar levels with a personalized nutrition plan.   
  
Another therapy is Fecal Matter Transplantation. It used to only be possible through colonoscopy, but now can be done through capsules. Researchers showed that insulin sensitivity was improved when replacing insulin insensitive microbiota with leaner individuals'. However, the effect is acute and dissipates over time. Many more studies need to be performed.  
  
Prebiotics are foods with substrates that are selectively utilized by the microorganisms conferring a health benefit, like fibers. Some studies show improvements in insulin sensitivity with prebiotics.   
  
Probiotics are actual live organisms and have been shown to, preiminarily, improve glucose homeostasis, but it likely depends on the delivery method since the bacteria have to survive the exposure to oxygen, stomach acid, bile acids, and enzymes, so microencapsulation is likely the best method to achieve the desired result. Second, the microorganisms may need to engraft onto the wall of the intestines, which may require co-consumption of different substrates and microorganisms that support that process - known as a synbiotic.   
  
Drugs can inhibit the growth of microorganisms in the gut, with 24% of drugs targeted toward humans leading to the inhibition of at least one strain of microorganism.