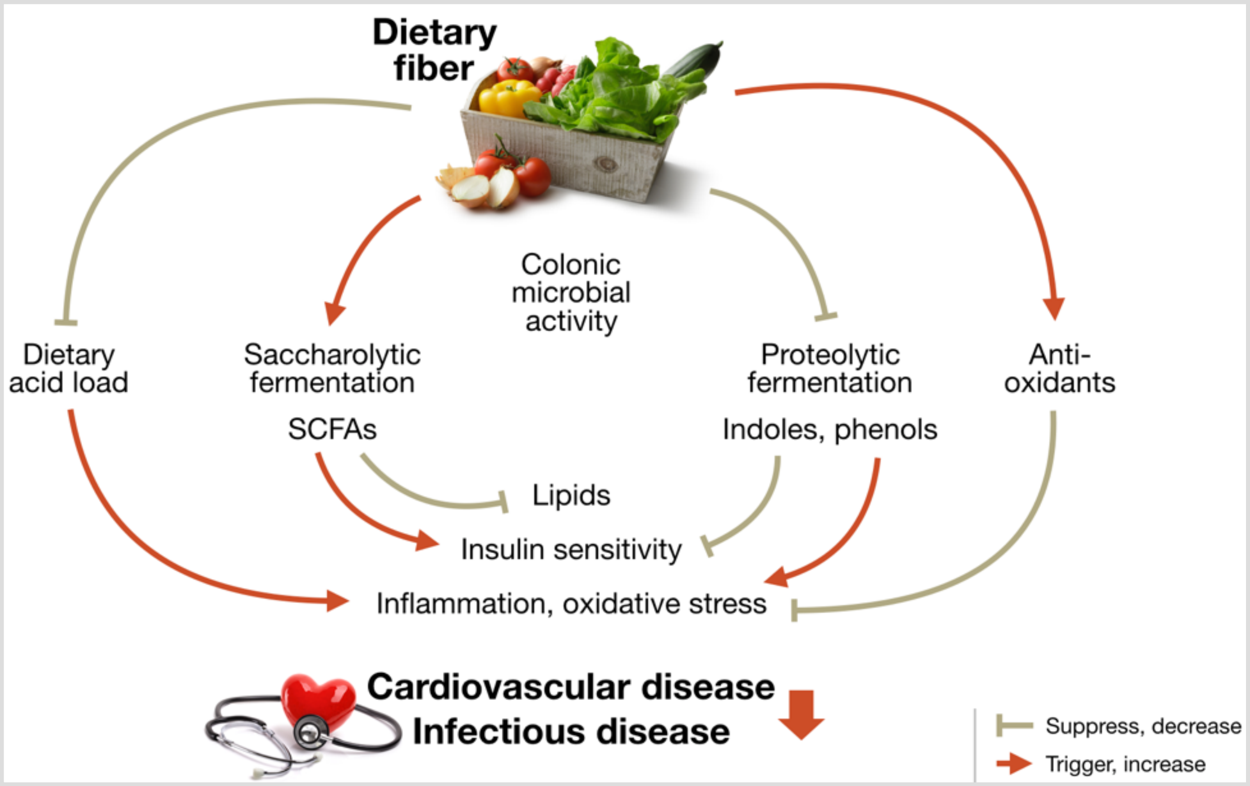
Microbiome & Intestinal Barrier - Part Two

In adults, there are several factors that are known to influence the gut microbiota, and I've just listed some of those, and probably the most prominent ones on the slide. Certainly diet, the amount, type, and balance of proteins, fats and especially carbohydrates and fiber, fermentable carbohydrates that we eat, have a huge influence and can actually change our gut microbiota composition within a matter of days. Medications, particularly antibiotics and NSAIDS, can strongly impact the gut flora of course. Chronic stress, chronic infections, especially gut infections and physical inactivity, are all known to adversely affect the gut microbiota.

The gut microbiota has three primary functions: metabolic, structural, and protective. The metabolic activity of the gut is so diverse and important that some people have referred to it as an organ within an organ. Bacteria in the gut break down dietary compounds that might otherwise cause cancer; synthesize vitamins like biotin, folate, and vitamin K; convert non-digestible carbohydrates to short-chain fatty acids like butyrate, which play an important role; provide energy and benefit cells lining the gut; and help with the absorption of minerals like calcium, iron, and magnesium. Microbes also determine how we process and store the food we eat. We know that certain patterns of gut microbes increase energy storage and lead to obesity, whereas other patterns have the opposite effect and tend to lead to a lean phenotype.



Gut microbes also play a structural role. Bacteria foment carbohydrates to produce short-chain fatty acids like butyrate or propionate, short-chain fatty acids then stimulate the growth and differentiation of epithelial cells, they also inhibit cell proliferation in the colon, which can lead to cancer, and we know that an altered gut microbiome can lead to the production of endotoxins like lipopolysaccharide, which activates zonulin, which is a protein that regulates intestinal permeability via its effect on the tight junctions, and so this production of lipopolysaccharide can make the gut barrier more permeable.

Finally, the microbiome has a protective function. The gut is first and foremost a barrier designed to let certain things like nutrients in and keep other things like pathogens or toxins out. The mucosal lining is the primary interface between the external environment, which is the contents of the gut as we talked about earlier, and our immune system. The surface area of the gut is a hundred times larger than the skin, and the gut contains 70 to 80 percent of the immune cells in our body. These form a layer of tissue called the gut-associated lymphoid tissue, or GALT, and microbial composition of the gut has been shown to affect the composition and function of this gut-associated lymphoid tissue. Bacteria in the gut also help us to resist invasion by pathogenic microbes, and studies have shown, for example, that germ-free mice that have been bred to have sterile guts are highly susceptible to infection.

Let's move on to the gut barrier. As we've discussed, the gut is a hollow tube that passes from the mouth to the anus. Anything that's inside the gut is technically outside of the body, and anything that's not absorbed by the gut is eliminated as waste and won't enter the body at all. So the gut barrier essentially serves as a gatekeeper that decides what gets into the body and what stays out. This normally works well, if it didn't we'd be dead, we wouldn't be able to absorb any nutrients, and we'd just be completely overwhelmed by antigens and toxins. But when the gut barrier becomes inappropriately permeable, and I think that's a key distinction to make, because our gut is always supposed to be permeable, at least to the right substances, so when we say inappropriate permeability it means that our gut has become hyper-permeable, permeable to the wrong substances, or permeable at the wrong times, so that's inappropriate permeability, then what happens is that substances that shouldn't get in like pathogens, toxins, and large food molecules go into the bloodstream, then these particles are viewed, rightly so, as foreign invaders and the body mounts an immune response against them. We now know that this response contributes to everything from chronic inflammation to autoimmune disease to depression to skin disorders to obesity.

The pathophysiology of intestinal permeability is complex. It's quite fascinating and I'm going to cover it in a little more detail when we talk about testing and treatment of intestinal permeability later in the GI unit. Again, I don't feel like this is the place to do that since we're focusing on practical application, but there's a lot of information on my blog and elsewhere if you really want to dive in there. I do want to talk briefly about a protein called zonulin, which was discovered by Alessio Fasano, who I interviewed on the podcast if you want to listen to that. Zonulin plays a major role in increasing intestinal permeability, and zonulin levels have been shown to be high in celiac disease, type one diabetes, MS, rheumatoid arthritis, inflammatory bowel disease, and other autoimmune conditions. Researchers have found that you can induce type one diabetes actually in mice almost immediately by exposing them to zonulin. These mice develop leaky gut and then begin producing antibodies to cells that are responsible for making insulin. I'm going to again talk more about this later, but I just want to float this idea out right now. Leaky gut I think is important and is certainly a part of pathological presentation in people with gut issues, but I also think it's been a little bit over-hyped, and we always have to ask, if some problem is present, whether it is a cause or an effect, and I think in many cases leaky gut, while it can contribute to a number of different conditions, is often an effect or consequence of other more fundamental pathologies, so again we'll talk about this more later.

There are several known factors than can increase gut permeability. Diet is one, of course, we see an increase in gut permeability when people with celiac disease and even non-celiac gluten intolerance consume gluten. We find that flour, sugar, and seed oils have been shown to alter the gut microbiota in a way that leads to increased production of lipopolysaccharide, which as I mentioned earlier causes the release of zonulin, which can trigger leaky gut, things like CIBO, chronic stress, infections like h. pylori, parasites, or bacteria like clostridium difficile, excess alcohol consumption, medications, particularly acid-blocking drugs like PPI's or NSAIDs, aspirin, antibiotics, can all contribute to leaky gut via their effect on the microbiome, and then certain environmental toxins like bisphenol A, BPA, and heavy metals have been shown to contribute to leaky gut, and I'm sure there are others that haven't been studied yet that fit into that category.

Okay, that's it for now, if you want a little more background on these topics you can check out the recommended resources for this week in the supplemental materials, and I will talk to you soon.