Build Your Resilient Gut
MICROBIOME & BEYOND

By Kiran Krishnan
Microbiologist & Microbiome Expert

Common GI Problems & Solutions:

Root Causes & Contributing Factors to the Loss of Oral Tolerance

Video Transcript:

So, how do we lose this oral tolerance? Well, it starts with this microbiome dysbiosis, right? So I talked about how dysbiosis, and will define dysbiosis as a imbalance of beneficial supportive microbes to pathogenic or pathobionts. And many of these pathobionts, so these are opportunistic pathogens or pathogenic organisms that also have some positive functions when their numbers are maintained at the right level. When their numbers exceed a certain level of growth, they start to become more of a problem than a benefit, right? And they stop communicating with your immune system, they stop supporting and tutoring the immune system. They start up regulating inflammatory pathways instead of tolerance pathways, right?

So dysbiosis is at the core of this, and low diversity is another feature of dysbiosis, which then compromises the tutoring of the immune system. And this is all within the gulf, the gut-associated lymphoid tissue, that mucosal lymphoid connection where you've got 70, 80% of all your immune tissue being in your gut, and all of that immune tissue is associated with a very dense microbiome. So that's where a lot of this decision and training and all that happens. Beneficial microbes, because they increase oral tolerance, they can do so by upregulating those T-reg cells. So remember, the T-reg cells are so important in order to suppress unfavorable immune responses and teach

your immune system not to respond to something in a particular way. So the upregulation of T-reg cells is critically important to continuously maintain and develop oral tolerance, and you need a beneficial microbiome to do that.

The other part of it is secretory IgA production. We talked about secretory IgA in a couple modules ago, and how that is, of course, the highest concentration of antibodies being released in your body. Secretory IgA not only defends the body against a potential invasions, or infectious microbes, or toxins and so on. The other thing it does is it provides oral tolerance, because when secretory IgA binds to an antigen, it does not activate the rest of the immune system. It shows the immune system actually that, "Hey, I bound to this. This is not a problem. Don't have to activate the inflammatory immune response." This is as opposed to IgE, for example. Most of you have heard of the antibody called IgE. IgE is a hypersensitivity antibody. When something is bound by IgE, it elicits a cascade of immune responses that leads to more inflammation.

So what you really need to have good oral tolerance is an upregulation of T-reg, and an upregulation in the production and the diversity of your secretory IgA. Those are the two very, very important things to achieve and/or maintain oral tolerance. And both of those are very much dependent on the microbiome, having a diverse healthy microbiome with lots of keystone species, and lots of beneficial commensal organisms. That's how you upregulate secretory IgA production and diversify the secretory IgA so it can bind to lots of things, and that's how you upregulate T-regs as well. So dysbiosis in the gut disrupts this balance and leads to more inflammatory responses.

Now, what's interesting is when you have low levels of secretory IgA, right? This is the first line of defense, this is the thing that provides oral tolerance, one of the ways in which your body makes up for that is by upregulating IgE, because you need some sort of antibody in your secretory fluids, in your saliva, your tears, your mucosal lining, and so on. If you don't have enough IgA, your immune system tends to upregulate IgE. The problem with IgE is when it binds something, as I just mentioned, it upregulates an entire immune cascade that leads to mast cell activation, histamine release, and so on. So you don't want elevated IgE, what you do want is more IgA,

and you want an upregulation of regulatory T cells. So that is the basis of oral tolerance, and that is driven by a healthy, diverse gut microbiome. So dysbiosis leads to that dysfunction.

Leaky gut and intestinal permeability can be a real big issue for oral tolerance, in part because, of course, leaky gut leads to systemic inflammation, because of the presence of LPS in circulation in the basolateral layer, in the mucosal layer and so on. And so the presence of LPS upregulates an inflammatory response by activating dendritic cells and macrophages, especially dendritic cells.

And so leaky gut becomes a big issue because leaky gut stimulates inflammation. And then the increased permeability just means not only are the endotoxins leaking through and ending up in circulation and creating lots of inflammation throughout the body, but also because the barrier is compromised, things like undigested food components, bacterial toxins, bacteria themselves, viruses and other things can also enter the bloodstream when there shouldn't be present in the bloodstream, that causes an overt immunological response in individuals as well.

So this all sets the stage for a pro-inflammatory system that then becomes susceptible to the loss of oral tolerance, because inflammation is a self-feeding problem where the more inflammation you have, the more inflammation you'll get, because inflammation damages tissues and causes dysbiosis, which then leads to more inflammation. So leaky gut, intestinal permeability, is a big part of it. And like I mentioned, LPS is a key component. LPs on the gram-negative bacteria is a really big problem, not only in the gut, but also in circulation when it crosses across the gut barrier. And LPS binds to something called Toll like receptor 4 on these dendritic cells, and that triggers this pro-inflammatory cascade of cytokines, wherever the LPS is present, whether in circulation, in the brain, in the joints, wherever it may be, right? And it reduces the immune system's ability to achieve tolerance to harmless antigens. This all perpetuates hypersensitivity.

So, when we talk about tolerance, we have to also talk about this issue of mast cell activation. So mast cells are an important part of the defense within your immunological system, but you really don't want mast cells to be actively involved in most immune defenses, because mast cells create a big issue of releasing histamine. And they degranulate, if you will. So they have these little granules of histamine within the mast cell itself, and when they bind an antibody, it activates them to degranulate, which means the granules full of histamine inside the cell open up and they release histamine everywhere in the system, or at least in the local area.

Histamine, of course, becomes a very inflammatory, very allergenic type of response. I think most people have experienced what a big histamine release feels like. And so mast cells tend to be activated when it binds IgE. So it goes back to this issue of having too much IgE and not enough IgA. And you don't have enough IgA because you don't have a functioning diverse healthy gut microbiome.

T-reg cells are also really good at suppressing the activation of mast cells. So T-reg cells can contribute to stopping mast cell activation, but again, T-reg cells are dependent on a healthy microbiome to be upregulated. So, if you have low secretory IgA, low functioning of T-reg cells, you have much higher risk of mast cell activation. And of course, this is mast cell becoming reactive to everything in the system, which means that a lot of times the food you eat, the antigens you're exposed to, the environmental components and all that, those are all a big trigger for mast cells to get activated. And you want to control the mast cells by the T-reg cells and IgA. So that's a really important thing.

So a lot of people experience this mast cell activation syndrome, histamine intolerance. It's really at the end of the day a factor of having too much mast cell activation, too much release of histamine, and sometimes that's coupled with not enough enzyme to break down histamine, which is a diamine oxidase enzyme that your body produces, so that when histamine is released, it can do its job, but then your body breaks it down relatively quickly so it doesn't build up in the system. People who end up with mast cell activation and histamine intolerance typically have low secretory IgA, low T-reg, so

you've got too much IgE, too much mast cell activation, it's releasing histamine all the time, and you're not breaking down the histamine on top of that. So that becomes a big issue with the histamine intolerance as well.

Let's continue talking about how we lose oral tolerance. Well, poor food breakdown. So insufficient stomach acid, digestive enzymes and all that lead to certain structures of undigested food that can be antigenic. Remember I talked about the proteins, this is one of the reasons why I mentioned the proteins earlier. You want these very complicated folded proteins to be unfolded, become a string of pearls, and get chopped up to the individual pearls. What you don't want is a big protein to be unfolded, become a string of pearls, and gets incompletely chopped up into strands of 10, 11, 12 amino acids, because that then becomes antigenic, it can trigger immune responses in the gut, in the gut lining. If it makes its way through the lining of the gut, it can do so in circulation as well.

So, this is another example of where something upstream, in this case the stomach or even the small intestine, part of the small intestine, where enzymes, digestive enzymes are released. If they're not functioning properly, you can get partially digested food moving into the rest of the small bowel and then eventually into the large bowel that can trigger immunological responses.

So again, that theme of things downstream being dependent on the proper function of things upstream is critically important. So this is why you can't just, if you have say a large bowel issue, you can't think of that large bowel issue as an issue of isolation. It's not just a problem in the large bowel, there's likely upstream drivers as well. So when you think about gut health, you have to think about the entire structure. This is why this course is designed this way to provide you that learning from the top all the way down to the bottom, so that you start to understand how each thing is supposed to function, what it's supposed to be doing, and what can happen if it doesn't function properly. And this is a really important build for you to really understand what gut health really looks like and what it takes to achieve serious gut health.

So when you have undigested food, you have an increased antigen load. We're taking a food chicken breast that is not antigenic, and then chopping it up into little peptides that are antigenic. So that's one of the things that can happen with impartial or incomplete digestion.

Stress, trauma, nervous system dysregulation. We've talked about how stress increases fight or flight response, which then increases inflammation. Anytime you have things that increase inflammation, you have a risk of developing oral intolerance, because inflammation negates proper immunological response. So vagus nerve dysfunction reduces digestive efficiency, your gut becomes static, it doesn't move as well. So things can putrefied, digestion becomes incomplete, HCL secretion becomes compromised. We talked about how stress is one of the key things that reduces HCL production. So now you can't digest food as well, and you get more and more undigested food moving into the distal part of the small bowel and into the large bowel, which can be immunogenic. And all of this can contribute to mast cell activation, histamine release, and more and more irritation on the lining of the gut.

Toxin exposure is another driver. So things like PFAS plastics. So heavy metals, pesticides, mycotoxins. One of the reasons why all these things can lead to oral tolerance issues is because they're all also inflammatory. They create inflammation, and anything that creates inflammation can risk the immune system going haywire. So toxins are a big part of it, and they also disrupt the microbiome and damage the gut barrier. So there are double and triple whammy in terms of how they can create and create oral intolerance and disrupt oral tolerance.

Now, chronic infections or persistent infections like Epstein-Barr virus, Lyme bacteria disease, so Lyme disease, Candida overgrowth, all can cause immune chaos as well. Again, all because they are all inflammatory. They elicit immune responses, your immune system goes haywire, especially with difficult things like Epstein-Barr and Lyme disease, where it's hard for the immune system to find the culprit. They know the spirochetes are there, they know the Epstein-Barr is there, but they can't find it

because these organisms have found very effective ways of hiding from the immune system.

So, these types of pathogens are latent, meaning they can stay with you forever, and then have these small triggers of the immune system without actually being cleared. So they act like constant drivers of immune inflammation and intolerance. So they can be a big, big problem. And of course, these can increase mast cell activation as well, and thereby histamine production and more reactive symptomology in a lot of people.