Guest: Kiran Krishnan:

So this structure here is what I call the ground zero of most health disorders. This structure occurs both in the small and large intestine and it occurs similarly in other parts of the body as well like the brain and the lungs and so on. Of course, without an intestinal epithelium, it's a different type of lining cell. But what's really important to note here is how this is structured. There's a couple of really deliberate things in how biology has designed this structure that we have to pay very close attention to because it's very unique in our own physiology.

So when you look at the intestines and you eat something, it goes into this tube that's open at both ends, right? So your mouth is one opening, the anus is the other opening. So even though something is entering into your digestive tract, it doesn't actually mean it's in your body because your digestive tract is a tube that's open on both ends.

So things aren't actually technically inside your body until they make it past the lining of the intestines and they make it into circulation. Okay? So to give you an idea of how that is structured, when you look at the tube of the intestines, my skin here on my palm would be the lining of the intestines, the hole, and the tube part of it is called the lumen, the luminal side, if you will.

So when you eat and swallow something, it's in the lumen, it's not actually in the body until it goes through the layers of the intestines and then into circulation. It goes past the lining of the gut. So up here, this top part here... Can you see my pointer when I point at things?

Host: Michael Roesslein:

Yes.

Guest: Kiran Krishnan:

Okay. So up here is what we would call the luminal side. So this is a tube part. The next layer from the tube is this mucosa layer, and this is called a mucin one layer. It's not a super solid thick layer, it's more like a loose jello-ish layer, but it's much looser than jello. Jello tends to have a more firm structure. This is where the vast majority of microbes in your gut microbiome live. They live in this top mucin one layer. So things have to go past that layer first. Then here's this other layer called the mucin two layer. This is an inner mucosal layer that's actually thicker and more solid than the top layer, the mucin one layer.

That sits directly on top of the intestinal epithelial cells, which are the gut lining cells. And those cells, the distinct structure there is that it's only a one layer thick. This is the final barrier between something being outside of the body, which is up here in the luminal side and something being truly inside the body, which means it's gone past this barrier and into circulation.

So down here where you see these immune cells depicted, that's called the basal lateral circulation. Things are now in circulation when they come down here. Now ,when things come down here, 80, 85% of everything that comes down here goes to the liver first. So that goes through what we call portal circulation. And then about 15% go into the general circulation.

But the vast majority of things end up going to the liver. First is the liver has to deal with all of the things coming in, whether it's a toxin that it's trying to neutralize and get rid of or it's a metabolite that it's metabolizing for us. So the liver is critically important in all of this here, but the two structures that are extremely unique in our biology that it's just you cannot ignore it because it's so different and so unique is one is this mucin two structure.

And what makes it so unique is that as it is depicted here, there are virtually no microbes in the mucin two layer. Everywhere in your body you have microbes. Places that we used to think were sterile like your brain or your urine, I always heard that when I was in high school for some reason. Oh, urine is

sterile. Your eyeballs, your cerebral spinal fluid, all of these internal regions in your body that we assumed there were no microbes because it'd be dangerous to have microbes in these areas because it'd be infectious and so on, all of these regions are full of microbes.

You're hard pressed to find any part of the body that doesn't have microbes, including in your blood. For every milliliter, you've got about a thousand microbial cells in your blood and you've got 5,500 milliliters. So think about the number of microbes you have circulating around in your blood. 15, 20 years ago, if a doctor found microbes in your blood, they would freak out because they think you're going undergoing septicemia or bacteremia, right?

So we now know that microbes are everywhere except this layer here. This mucin two layer is virtually devoid of microbes. And what's so unique about it is that the layer right above it, the mucin layer above it has the largest concentration of microbes in the body. So there's a very deliberate reason why there is this distinct separation where the largest concentration of microbes in the body is sitting on top of one of the only sterile components of the body.

And in a healthy situation, microbes do not penetrate from the mucin one layer into the mucin two layer even though they're fractions of a millimeter apart. So that's so interesting. There's a very deliberate reason for that. And if we ignore this, if we ignore this physiology, we're missing out on a lot of different healing opportunities looking at root cause medicine. So that's really unique physiology number one.

Really unique physiology, number two is this barrier layer. This barrier layer, which is the final barrier from something entering into the body like the skin as a barrier is actually deliberately designed to be a very robust barrier because there's many different cell layers, including the very top cell layers that are all dead cells. And the reason those dead cells are important because they're not reactive to things like live cells would be, they can just act as a physical barrier against things entering through.

And then when you go through, you look at all the squamous layers and all these cells piled up on one another to make a brick wall. So your skin acts like a very strong physical barrier given that the intestinal epithelium has higher surface area than your skin and gets almost more exposure to things than your skin does, and is the final barrier between something entering directly into your bloodstream, and the fact that it's only one cell layer thick is really, really surprising.

As depicted here, these are cells sitting shoulder to shoulder. This is the final barrier between something entering into the body and staying outside of the body. Now, there's of course purpose for this, right? And the purpose is that we do want lots of things to move through this intestinal epithelium, nutrients, for example, right? That nutrients you digest up here and you start absorbing through here, there has to be a way for those nutrients to get through.

And so that's why this barrier is flimsy, but very dynamic, meaning some nutrients go through what we call the transcellular pathway. They can make their way through the cell themselves. There's receptors up here to pick up the nutrients, transport it through the cell and spit it out the other side into circulation. And then there's the paracellular pathway, which is in between the cells.

Now, in between the cells there are these proteins that stitch these cells together, and those are called clodin proteins. This is their tight junction. So these proteins, what they do is they relax when we want the cells to open up so that nutrients can pass through, and then they cinch up tight and close up the cells when we don't want things to pass through. So this very strict control mechanisms involved in all of that.

Now, if something happens to these proteins and they degenerate, then the cells basically stay open all the time. That's part of the physiological impact or changes that occur when you have leaky gut. The other very unique thing about this intestinal epithelium layer is it's unlike our skin. It's a multifunctional layer, so it actually acts like an immune organ and it acts as an endocrine organ, right? Within the

intestinal epithelium, every few cells are these intro endocrine cells because they can sense things that are happening up in this top luminal layer, which is where they get messages from, what's what kind of environment the host is in, and they can change the types of hormones that they produce or induce in order to adapt to that environment.

So it's a bonafide endocrine organ. Your intestinal epithelium is not acting just as a barrier, it's acting as an endocrine organ making hormones for you all the time. Then the other component of it is it's a bonafide immune organ as well because every four or five cells is a different type of immune cell.

You have L-cells and M-cells and paneth cells and so on. Think about that differently from your skin, how the outer barriers of the skin don't have any endocrine cells, don't have any immune cells. They're basically just barrier cells acting as a wall. In this case, this is much more dynamic. There's tons of immune cells in the intestinal epithelium and tons of hormone cells in the intestinal epithelium as well among other cells like goblet cells that actually reproduce the mucin layer.

So it's a very dynamic, unique barrier system. And again, all of this is so deliberate. So why are there so many immune cells in this area? Well, this is the most forward facing component of your immune system. Keep in mind, we don't have any outer immune cells. We don't have immune cells on our forehead and our outer skin to understand what the environment is like that we're in to try to protect the host.

Your immune system is one of the only systems that adapts constantly to your environment. If I were to go, I'm flying out to London tomorrow. When I get to London, what I'm exposed to in London for my immune system is going to be different than what I'm exposed to here. My immune system needs to learn what the exposures are there, what antigens I'm breathing in and so on, and then adapt to those antigens. Or I'm going to feel sick when I get there or I might be more susceptible.

I may not have tolerance of the things that are in their environment and I get hypersensitivity reactions and so on. So my immune system has to be able to understand what's out there and adapt to it quickly. The way it does that is that virtually everything you're exposed to somehow ends up in the digestive tract, right? Because the biggest exposure we get is to the things we eat and drink. So food is a huge exposure to what's happening in the environment around you. Drink is a huge exposure as well.

But keep in mind when you breed stuff in, everything goes into your upper respiratory tract. And then you've got things like the mucociliary elevator in your lungs, these tiny hairs that move all these antigens up to your throat. So you swallow them and it ends up in your gut. Your eyes, your ears, your nose, all of that, all of the stuff that goes in there, those orifices all drain into your throat and then you swallow all of that.

So your station tube is in your ears, drain into your throat. Your eyes drain into your throat. So your nose of course is connected and drains into your throat. So virtually everything you get exposed to when you go out into any sort of environment ends up in your gut and that becomes the largest sampling site there is. So what happens when these things enter in, whether it's food or antigens or toxins or viruses of bacteria from a new place, is that it goes into the gut microbiome. It goes into this luminal side, and if you have a healthy gut microbiome and one that's working for you, you will have these microbes translating these messages to your immune system.

And communicating to the immune system whether or not you should have tolerance to this thing that you're now exposed to or if it's a problem and you need to elicit an immune response. That's something called crosstalk between the microbiome and the immune cells, and the immune cells that they're talking to are the immune cells in the intestinal epithelium, the L-cells, the M-cells, the paneth cells, all of these cells that are found within the intestinal epithelium.

Now, they speak the conduit between which the microbiome and the immune system speak is this mucin two layer. And this is why the mucin two layer is sterile. There's been an agreement to the course of evolution between the immune cells here and all of the trillions of microbes that live up here that, "Hey, we're cool. We know how to work together, but we have to keep a certain distance from one another."

So this proximity to the immune cells in here is extremely important, meaning we need these microbes to be close but not too close. So that's one of the key roles that the mucin two layer plays is it provides a proximity comfort for the immune cells in the intestinal epithelium that allows those immune cells to not overreact and yet communicate with the microbes that are up in mucin one layer.

If this proximity is encroached upon, meaning if this layer gets eaten up or broken down somehow and all of the microbes in the mucin one layer move closer to the intestinal epithelium it starts to freak out the intestinal epithelium cells causing them to elicit really robust immune responses at the lining of the gut.

So this is what I call the de-militarized zone. If this zone exists, then the immune system and the microbes can talk happily. The immune system can adapt, the microbes can communicate what it needs from the immune system because the microbes do that, right? So for example, when you're eating food and food is passing through your small intestine. You release bile in order to help not only detox from any fat soluble toxins that are in the food, but also to break down and absorb fatty acids and fat soluble nutrients.

And then as the bile is circulating through, when it goes back into the liver at the very end of your small intestine, it triggers a receptor called a nuclear FX receptor, which then causes your intestinal epithelium immune cells to release antimicrobials into the mucin one layer to bring down or reduce the growth of microbes. That's one of the ways in which our body protects us naturally from SIBO from overgrowing bacteria in this small intestine. And the microbes in the small intestine love that because they don't want a whole bunch of non-native microbes coming in there and overgrowing which was what happens in SIBO.

You get all of these gram-negative non-native bacteria to that region overgrowing. So the local bacteria, the gram-positive indigenous bacteria to that region are very happy to trigger the intestinal epithelium immune cells to release antimicrobials to maintain the low levels of microbes.

That's just one example in which the intestinal epithelial cells produce things that are useful for the microbes in maintaining the ecosystem there. So there's this constant crosstalk. All of that gets dismantled the moment you start losing this demilitarized zone. So the vast majority of diseases will occur because we have somehow compromised this mucin two layer.

Think about even just really deadly conditions like colorectal cancer. 50,000 people this year will die from colorectal cancer. We know celebrities that have been diagnosed and don't make it very long, despite looking and seeming quite healthy and so on. Colorectal cancer starts because two microbes move from this mucin one layer slightly into the mucin two layer.

Bacteroides fragilis and E coli. Those two microbes move from this layer into this layer, just a millimeter or two move. They start setting up shop producing inflammatory compounds, starting the inflammatory damage that occurs to the intestinal epithelium. And in some people, that inflammatory damage will lead to the formation of tumor cells. Now, you have colorectal cancer.

So 50,000 people will die from a devastating condition because two bacteria went from here to here. That's how important the structure is. If we're not maintaining homeostasis and regenerating the structure in those who have it broken down, it becomes really hard to heal from anything.

So what within the microbiome maintains this structure? Number one, high diversity, high levels of alpha diversity. That means more viable species in the gut microbiota will maintain this structure for us. And then the presence of critical protective strains. These are called keystone species like akkermansia, like faecalibacterium prausnitzii, like bifidobacterium longum, all of these organisms have been shown to be inversely correlated with disease.

Akkermansia, for example, is inversely correlated with everything under the metabolic syndrome spectrum. That's like 40 plus conditions. If you have high akkermansia, you're protected against all of those conditions. How does akkermansia protect against all those? And we're talking about obesity, diabetes, cardiovascular disease, polycystic ovarian syndrome, dementia, all of these conditions. How does one bacteria protect against all of that? Does it have a magic compound that it produces for each of those conditions? No.

The way it protects against those conditions is because it plays a very critical role in maintaining this mucosal structure. So just from doing that, this bacteria can protect against almost 60 different chronic conditions. And the studies in akkermansia are absolutely clear. When you have high akkermansia, you have very low risk for all of these conditions.

Faecalibacterium prausnitzii is another important one to note. Faecalibacterium prausnitzii is inversely correlated with everything under the inflammatory bowel spectrum. So Crohn's, colitis, micro-colitis, colorectal cancer, and so on. All of those conditions, devastating conditions are protected against if you have high faecalibacterium prausnitzii.

So how does it do it? Does it produce some special compound against those disease? Nope. Faecalibacterium is very well known to regenerating and maintaining this structure. So that's all it does. One of the key things of how these microbes protect against the destruction of this structure is the production of short chain fatty acid. So butyrate propionate and acetate. Butyrate propionate and acetate Are very critical in maintaining the structure. Butyrate, for example, is a primary fuel for the intestinal epithelium cells. So to get them to repair and turn over when they're damaged, you need more butyrate so that you don't leave giant gaps in the intestinal epithelium.

Goblet cells that are responsible for making this mucin two and mucin one layer because you have to keep regenerating this layer. Goblet cells require butyrate in order to make the mucin one and mucin two layer. And then finally well formed type junctions. We need those proteins in between those cells to be stitched up right, be able to relax when something has to get through, but cinch up when something should not get through.

So the presence and the expression of the tight junction proteins so far we know only come from signals from the microbiome, especially from a highly diverse microbiome. So if you don't have the right microbes, you're not getting the signals to express those proteins. And anytime they get damaged, the cells remain apart and your gut remains leaky the whole time.