Kiran Krishnan:

I love Disney.

Michael Roesslein:

And we are live and recording, and everybody is trickling in. We're at, what day is this? Tuesday, Tuesday evening. I'm only one hour different from you now being in Utah, so it is five o'clock here, six o'clock there. Be curious to see what o'clock it is with some of our dedicated people who show up from Europe and Australia and New Zealand. And right, if you can see and hear us, everyone, please let me know in the chat. Just drop something in the chat that says, "Yes. See, see you hear you." And let us know where you are checking in from. We are going to give everybody a couple minutes to come in, and then we'll get started. I am here with Kiran. It's been a little while. Welcome back.

Kiran Krishnan:

Thank you. Thank you. It's good to be back.

Michael Roesslein:

Yeah, this will be fun. And for those who have been around a long time, he is no stranger to you. Anybody who is new to our community here, Kiran is the Chief Science Officer at Microbiome Labs. We've been doing microbiome and gut healing related webinars with Kiran for, I don't know, it seems about 20 years now. I think it's been six or seven years at this point, but today we are going to talk about the gut microbiome and immune connection, and connections, I guess I should say, as there's much linking there. So this is going to be a really solid presentation, I'm excited for everybody to see. It's 2:00 AM. 2:00 AM in Israel.

Kiran Krishnan:

We've got to give a shout out to Carmela.

Michael Roesslein:

Yeah.

Kiran Krishnan:

Thanks for being here at 2:00 AM. That's awesome. Hopefully you can sleep in tomorrow once you absorb all of this knowledge.

Michael Roesslein:

All right. One person's saying the last reminder email, that comes from Zoom, so that's not from me, but the last reminder email did not connect you to the webcast. I had to use the link that was sent out yesterday. Somebody shoot me messages if anybody else had any issues with any of the things. Zoom likes to just randomly change how they do things all the time to keep us on our toes. So hopefully everybody got the right link. There's over 160 people live in here right now, so I'm pretty sure links are working, but feel free to let us know if you had any tech issues.

And I think we are good to go. We both are team blurry back ground today. So you guys can enjoy that. Kiran's got a messy office, and I'm staying with family in Southern Utah for a few weeks. We left Northern California about two weeks ago, and we're going to be moving overseas soon and came here

to see some family for the holidays before we left. Very pretty red rock mountains everywhere, spent some time hiking out in nature in the desert, probably good for my microbiome, and it's nice, and it's warmer here than it was. And Kiran just got back yesterday from a trip to Florida. I saw your Disney World pictures.

Kiran Krishnan:

Yeah, yeah, that was awesome. It was great. The kids were super excited. We had to cancel two Disney trips because of the whole pandemic, and that was probably the thing that hit them the most. So being able to go back and do that whole thing was really quite nice. And that Star Wars area, man, if anyone's a Star Wars fan, you've got to make it.

Michael Roesslein:

There's like a little kid in me that's excited and wants to see that.

Kiran Krishnan:

It's crazy. That Rise of the Resistance ride, which is about a 15 to 20 minute experience, is unbelievable. You're in the movie, you're in the middle of the action. It's incredible. So yeah, they know what they're doing over there.

Michael Roesslein:

Very cool. All right. Last announcement I have is if you want everyone to see your chat comments, you need to switch the little two thing in the chat to everyone from host and panelists, otherwise only Kiran and I will see your comments. And also if you have questions, we're going to try to do some Q and A at the end. This is a loaded presentation, so we'll see how much time we have at the end. But if there's questions, I would ask that you try to use the Q and A button versus the chat. The chat can get kind of crazy and move fast, and I'm pretty good at navigating it, but things can get lost in there, where the Q and A keeps them all in one place. So on that note, I think the floor is yours, and you can begin your gut microbiome immune training here anytime you'd like.

Kiran Krishnan:

Okay, awesome. So I did cut this down to about 20 slides, and the reason for that is I wanted to make sure that we covered the most important themes. When it comes to the immune system and the microbiome and all that, there's so many rabbit holes you can go down, many of which are fantastic for researchers and big nerds like myself, but it doesn't necessarily impact how you function on a day to day basis, right? So what I wanted to do is really give you what is the most important message you need to understand the connections, the influence the microbiome has on the immune system, what you can do to modulate all of that. That's really the key here, right? That's where the rubber hits the road for most people, because at the end of the day, what you want to do is start making sure your immune system is working in its optimal way starting tomorrow, right?

So that's really the practical information and what people don't really understand well, including doctors, this has been a talk that I've given at numerous medical conferences through 2020 and even 2021, training people on understanding how the microbiome influences the immune system, and arguably is one of the most influential things on the immune system in general. So you'll start to see that I think from the talk itself, so I'll go ahead and turn off my video for a moment so that I'm not distracted by my own little bubble over here.

And then let me jump in and start with first, a quick review on this whole concept that we are a super organism, right? So we are a holobiome. We're no longer a collection of organ systems connected by tissues and veins and arteries and all that. What we are, better representation of, is a walking, talking rainforest. We are a super organism made up of thousands of little ecosystems that have to work together in order to perpetuate the health of the whole, and this couldn't be more exemplified in the immune response, and that's beauty of how the immune system works and how it works with the microbiome to really function in a proper way. I think you guys will start seeing that, and it's really quite fascinating and exciting.

Now this whole concept of a holobiome is driven by a process called symbiogenesis. Symbiogenesis is the result of this permanent coexistence of different biomes, which are different organisms, to form this holobiome or this whole microbiota, if you will. So when you force the existence of multiple organisms into one space, eventually what tends to happen is they tend to work symbiotically because it becomes clear, from a biological standpoint, that working together perpetuates the health of the whole community versus working against one another, right? So that's kind of how the human system is constructed.

Now for us to dive into this whole function of the immune system, I want to give you a quick background on immune kinetics. What happens when you get sick? What happens when you encounter a virus or a bacteria, something that looks to make you sick? How does the immune system function? And then once we know that we can pepper in how the microbiome affects the immune response. So, important thing to keep note, is that there's two key phases to the immune response. One is the innate immune response, and then there's this intermediary late innate immune response, and then we go into the adaptive response, right? And you guys have been hearing some of these words throughout the last 24 months because of COVID and all the issues there, and so the immune system is in the spotlight right now.

But the innate immune response typically happens within hours of a new pathogen entering into the system or an old pathogen or anything, the innate immune response still functions. And then within about a day or so, or upwards of 8 to 12 hours or up to 24 hours, the intermediate responders and macrophages and dendritic cells come in, and then they start the antigen presenting process which then eventually activates the adaptive immune response which can take a few days to respond to, right? So eventually when you have the adaptive immune response, you've got B-cells that become activated to whatever the target organism is. Those B-cells will produce antibodies against that organism, and then you'll even activate certain types of T-cells, like cytotoxic T-cells, which are killer cells, which have affinity towards that particular organism, and we'll go and find and kill that organism.

We see now through this pandemic virus of when you're exposed to the virus, you get both B-cell and T-cell immunity against the virus itself. So this represents a robust, long-term immunity. Protective immunity's when you have B-cell and T-cell activation. The innate immune system is supposed to contain things as much as it can and start the process of controlling and containing a infection, but really what you want to get to is this movement towards the adaptive immune response, because if you stay in the innate immune response for a while, it becomes more damaging than it becomes helpful because one of the key aspects of the function of the innate immune system is inflammation. Inflammation is critical to the function of the innate immune system, which means that as the innate immune system is responding to the presence of an infectious agent, you are getting a lot of inflammation being released, right? And I'll talk about who releases it, why it's released and so on, but just keep that in mind, that the innate immune response is supported by inflammatory responses.

And then as you are moving into the adaptive response, you actually need the very critical anti-inflammatory step in that process which then moves you into the adaptive response. Now, all the

symptomatic aspects of illness are occurring because of the innate immune response, right? The innate immune response is what gives you the fever, the chills, the body aches, or the headaches, all of the things that come along with being ill. All of that is driven by the innate immune response. Within a couple of days, you should to the adaptive immune response where most of those symptoms are abated. Now that depends on the pathogen as well because some pathogens can continue to spread throughout the body and replicate, so you're continuing to elicit innate immune responses in different parts of the body while other parts that were earlier infected are already moving towards adaptive, so your body's tackling both at the same time. So in some cases like the flu, you might be symptomatic for four or five days straight, even though in day two or three, the adaptive immune responses already started to kick in, right?

So this is the importance of the kinetics of the immune response. You've got these innate immune actors called the basophils, eosinophils, neutrophils, natural killer cells, mast cells. Then you've got these bridging cells called macrophages and dendritic cells which are antigen presenting cells, and that's an important aspect because what the key thing is that these cells do is they come along to the site of infection, they engulf cellular debris, including hopefully the virus or the bacteria that's causing the infection, and then they present components of that virus or bacteria to the adaptive immune system, to the B-cells, which then will allow the B-cells to produce antibodies against those specific structures, right?

So these are the guys that are going along and saying, "Hey, here's, what's infecting us. Here's what part of it looks like." The B-cells go, "Okay, I'm going to produce some antibodies against that." And the B-cells will produce IgM antibodies first which are little less specific, very neutralizing, very big antibodies. It can produce that within the first couple weeks of the infection, so it'll start producing IgM antibodies to whatever's being presented to it, and then eventually it'll produce IgG antibodies, which become the long-term immunity. So then the second time you see that organism, the macrophage and dendritic cells can quickly go to that organism, present it to the already existing B-cell that produces a specific antibody, that way you can deal with the invading organism without really activating a prolonged function of the innate immune system.

That's why you can get exposed to something, get very sick, and then build immunity against it, and the second time you see it, you don't have any symptoms at all. And the reason you don't have any symptoms is because the body skips most of the innate immune response, goes right to activating the B-cell that's specific for that organism, that's producing antibodies for that organism. Same thing happens to memory T-cells. You can go towards activating the memory T-cells that are sitting around waiting for your next encounter with that organism, right? So hopefully that made sense. That's the kinetics of the immune function. Now, when we look at the kinetics of the immune function, and we don't have to necessarily deal with what's here on the left hand side, we have these steps, right? We have the early innate response. That's the first responders to the presence of a pathogen. We have the late innate response where you've got more activation of things like natural killer cells and basophils and eosinophils, and there's a lot of inflammation happening at that stage.

Then you've got the early adaptive response where the antigen presenting cells are starting to activate the T-cells and B-cells, and there we need a very important anti-inflammatory step because we need to start bringing down the inflammation because the inflammation, even though it may be controlling or containing the infection to a certain degree, the inflammation is also damaging your own cells in a very significant way, right? I've given the analogy before, the innate immune system is like using a blow torch to kill mosquitoes, right? You're going to kill the mosquito, but you're also going to burn the wall behind you a little bit. But if you use that blow torch for long enough, you're going to burn the entire house down, right?

So that's the problem with the innate immune system. If you get stuck in the innate immune response, and you don't move towards the adaptive response, then you have this risk of going into the cytokine storm where the innate immune response takes over for long period of time, and it's the immune system that's doing the damage to the tissue like the lungs, for example, and putting people into respiratory distress and respiratory failure. And that's because the immune system is failing to move and shuttle the response into the late innate and then the anti-inflammatory, early adaptive stage of the response as well. And then from the activation of the adaptive immune system, you end up getting long-term adaptive immunity, which is true immunity. You have antibodies, you have memory T-cells, and so on.

So this is the critically important kinetic steps of how the immune system responds to the presence of something invading into your system, and at every single stage here you've got key signals or drivers from the microbiome to make the stage happen, right? So in fact, people who get exposed to a new virus and get stuck in this late and early innate immune response and get more inflammatory damage than the virus is doing itself and potentially risk going into things like respiratory distress are because they're not getting signals from the microbiome to move them into the early adaptive and the anti-inflammatory state, right? Their microbiome is disruptive enough that they're not getting the signal to push the immune system into the next stages, right? All aspects of our immune response are governed by signals from the microbiome, and even the detection of an invading pathogen is governed by the presence of the microbiome, and I'll show you that in the second.

But all of this is happening in an area called the mucosa, right? So when we talk about the immune response, we have to talk about the immunobiology of the mucosa. So inside your body, virtually every surface in your body is covered by something called the mucosa, right? The mucosa represents about 400 square feet of surface area inside the body. Translate that to the system we use, it's about 4,000, sorry, 400 square meters. It's about 4,000 square feet of surface area inside your body in the mucosa, right? So every square inch of the inside of your body is covered with the mucosa. Compare that to skin, which is only about two square meters in surface area, and we always thought of the skin is the largest surface area, largest barrier in the system. That's not true, the mucosal surface on the inside is much larger than that.

So every surface of the body, it's the largest part of the immune system. Most of that surface area is found in the gut, in the digestive tract, and we know that it lines every entry point into the body. The mucosal lines, your respiratory tract, your digestive tract, your reproductive tract, even through your skin, if things penetrate through your skin, it enters into the mucosa first, right? So the mucosa is this kind of mucus structure where the microbes all live, right? So most of the microbes that live in your body live in the mucosa, and most things that enter the body will enter through the mucosa first. So the microbes in your system get first look at everything that's coming in. We know that it's also the largest immune sampling site in the body because it covers every aspect of the inside of your body, so everything that your body encounters will go through the mucosal system and then the mucosa is covered in microbes like I said, which is so interesting, right?

Imagine the largest part of your immune tissue, where your immune system has to monitor and survey this area is already covered in microbes. It's already covered in viruses and bacteria and protozoa and so on, right? All of that surface area is already covered in microbes, that's the same surface area that new invading microbes are going to come into that your immune system is supposed to monitor. So it creates a significant issue. We think about our mucosa, right? Let's say this represents our mucosa. It is covered shoulder to shoulder with microbes already, over 40 trillion microbes sitting there in your mucosa, right? 40 trillion microbial cells. Compare that to about 200 million immune cells that are surveying and

monitoring the system. That's a 200,000 to 1 ratio where we have 200,000 times more microbial cells than immune cells in the region that has to monitored by the immune system, right?

So then it becomes a huge question as to how can the immune cells monitor this kind of surface area with that kind of microbial density looking for viruses and bacteria that may infect the host? All the while that system is covered by viruses and bacteria already, right? So that is the mind boggling part of how all of this works. And I like to give an analogy, imagine you are at a large music festival in a stadium, right? And that's an enclosed stadium, and in there, there are 200,000 people in that stadium, right? And among those 200,000 people, there may be one or two people that intend harm on the rest of the crowd, right? So you've got 199,998 perfectly fine, safe, commensal individuals, you've got two individuals in that crowd of 200,000 that could be potentially harmful. Now those two individuals look exactly like the other 199,998 individuals, and you are the loan security guard in that sea of 200,000 people, right?

How would you ever monitor that space, right? How would you ever pick out one, two, maybe three individuals in that sea of people that could potentially cause harm to the rest of the individuals? It would be virtually impossible for you to do that. The only way it could work is if the other 199,998 people were on your side, they all were wired in with walkie talkies to you, and were acting like your neighborhood watch. They were monitoring their neighbors, they were monitoring the people around them. If they saw anything suspicious, they would immediately radio into you and tell you exactly what's going on and where it was happening, right? That's the only way.

And that's exactly how the microbiome works with the immune system. Because the microbes, your commensal microbes in the microbiome, completely outnumber your immune cells and cover every square inch of your mucosal surface, which is where invading pathogens come in, it's the microbes that detect a change in the microbiota first. It's the microbes that detect the presence of an invading pathogenic organism first, and then it becomes the role of the microbes to alert your immune system to the-

-microbes to alert your immune system to the presence of an infectious agent, right? Your microbiome is acting as the eyes and ears of your immune system, alerting and monitoring, and then recruiting your immune system to the site of action. Right? And all of that happens through this process of crosstalk. I promise I'm not going to go through this crazy busy slide, but just pointing out that here's the mucosa up here, right? And these are the, for example, the intestinal epithelium, or this could be the endothelium or any sort of cell layer.

And underneath the cell layer is where all your immune cells are. And above it is where the microbes and all the microbiome is. And the microbes in the microbiome produce all of these compounds that bind to receptors on the cell layer. The binding of those receptors send signals down to your immune system. Your immune system can create compounds that bind to other receptors on the underside of the cell layer, which then create and release more compounds on the other side, where the microbes are facing.

So there's this really complex crosstalk between the microbiome and the immune system that is very well orchestrated by a balanced, healthy microbiome. If there's a disruption in the balanced, healthy microbiome, this crosstalk falls apart. And invading organisms have a much better chance of coming in, setting up shop, starting to infect your own cells before any aspect of the microbiome signals the immune system at all. And I'll give a little bit more detail on that, right? So that's one thing that's really important to understand is that the microbiome of the eyes years of your immune system.

The microbiome not only are acting as the eyes and ears of the immune system. It's also the job of the microbiome to train and mature your immune cells, right? So you've got your bone marrow, for

example, and your thymus that produces all these immune cells, all these white blood cells and your T cells and your macro phages and their dendritic cells and so on. But all of your immune cells are produced in naive form. Meaning they don't have information. They don't know what to attack. They don't know how to attack. They don't know how to conduct any of those immunological functions. They are producing what we call primary lymphoid organs, like the thymus and the bone marrow.

After they're producing the primary lymphoid organs, they all move to secondary lymphoid organs and tissues like the Waldeyer's rings, which are in your upper respiratory tract in your neck and so on, your bronchus associated lymphoid tissue, your spleen, your lamina propia, your Peyer's patches in your gut. All of these areas of the secondary lymphoid tissues where your immune cells go to mature and get trained.

And in all of those lymphoid tissues, your microbiome exists as a trainer of these immunological cells. Right? So your immune system not only requires a microbiome to act as the eyes and ears, the microbiome's also the trainer of the immune system. It basically starts to train the immune system to understand what pathogens look like, what microbes look like, what viruses look like, how to attack, what to attack and when to attack as well. All of those things are being conducted by the microbiome to train the immune system.

So you could start to see already, if you have a dysfunctional microbiome, not only is your immune system blind to a certain degree, not being able to see early enough the presence of a invading virus or a bacteria, your immune system is also largely naive. Right? It's not properly trained to deal with the things coming in.

So in order to have a trained, well-functioning immune system that can see early detection of the presence of pathogens, you need a healthy microbiome. Let me give you some specific examples of how the commensal microbiota are required to fight viral infections, for example. I pick viral infections because that's kind of the hot topic these days, right? So let me give you some examples.

During norovirus infection. I think everyone's familiar with noroviruses, and our kids all get norovirus from time to time. Lactobacilli and other commensal organisms start to trigger the release of interferon beta and interferon gamma the moment they detect the presence of norovirus. Right? Which in turn then alerts the innate immune system to the presence of the virus. So that is the signal or the flare that the microbiome sends out that's saying, "Hey, there is an infectious virus at this site, get yourselves over to this region." Right?

And then nutrients, like vitamin A, helps provide the substrate for the commensal bacteria to make these interferon. So that's how some of these micronutrients can help the immune system. But you need the microbiome there to convert the vitamin A into interferons to signal the immune system to the site of infection.

Another very common virus, rotavirus infection. We know that bacterial flagellin, for example, in the gut... Right? The presence of bacterial flagellin in the gut from commensal bacteria will activate the expression of something called pattern recognition receptors, that triggers the expression of toll-like receptor five. Those details aren't important. But what's important to note is it releases this interleukin 22 and interleukin 18. Interleukin 22 helps repair the damaged epithelium. And interleukin 18 helps induce apoptosis in infected epithelial cells.

So remember, rotavirus infects the gut, right? Many kids and even adults and all that get rotavirus infections quite readily. It's a viral infection in the gut. You get bad diarrhea, sometimes vomiting, nausea, and all that as well because the virus is infecting the intestinal epithelium. So you've got the single layer of epithelial cells. Some of them are now getting infected by the virus. But the bacterial flagellin in that region starts activating these toll-like receptors and pattern recognition receptors, which

then helps send apoptotic signals to epithelial cells to kill themselves when they're infected with the virus. Because remember the way viruses work, is they infect a cell, and they take over all of the cellular machinery so that the cell becomes a virus-producing factory. Right? So in order to stop your own cell from producing more virus, which will then come out and infect more cells, you need the release of this interleukin 18, which tells that infected cell, "Hey, you're infected, shut down and die." Right?

And then once that cell is shut down and dead, you now have a gap in your intestinal epithelium. You need the expression of interleukin 22, to tell your tissue to repair that with a new cell that's not infected. Those signals come from bacterial flagellin. Right? So think about that community structure in the intestinal lining. Right? You've got this bacteria, your commensal bacteria, sitting there. The moment a rotavirus infection comes in and starts damaging your cells and creating viral factories out of your intestinal epithelial cells, your commensal bacterias jump in, start sending out these signals to help those cells go through apoptosis so they stop producing virus. And then once those cells are dead and there's a gap there, it creates another signal to help fill that gap with a new healthy cell. Right? That's an amazing system that we've outsourced to the microbes living in our gut.

Other lines of evidence, bifidobacterium breve, and in combination with galacto- and fructooligosaccharides, which is part of why we really love prebiotics as a really critical part of supporting the immune system have been shown to prevent rotavirus infection by increasing interferon gamma, IL-4, TNF-alpha and toll-like receptor two. All of it which increases mucosal defenses against the virus infecting the epithelial cells themselves.

We also know that commensal bacteria produce things like short-chain fatty acids, like biurate, for example, which are required to increase and maintain mucus production. So maintain that thick mucus barrier. So it's harder for the virus to get through the mucus and get to the intestinal epithelial cells, which creates that strong barrier. In addition, commensals also increase the synthesis of antiviral compounds like reactive oxygen species and defensins, which then prevents local virus infections.

So the commensal bacteria can actually stimulate your intestinal epithelial cells to release defensins and reactive oxygen species to prevent viral infections. So the moment your commensal bacteria sees rotavirus coming in, it starts stimulating your intestinal epithelium to go, "Hey, protect yourselves. Produce antiviral compounds. Produce reactive oxygen species. Let's produce more thick layers of mucus to increase the barrier." So it creates all of these defense mechanisms to protect the host against the invading virus.

During the influenza infection, for example, commensal bacteria triggered the release of something called inflammasomes. And this occurs locally in the lungs, which is a potent defense against influenza replication. These inflammasomes actually prevent the virus from being able to replicate itself in the cells. Right? They induced dendritic cells to also migrate to the local lymph nodes. So the lymph nodes that support the lungs, for example, to stimulate influenza-specific T cells. Remember, dendritic cells are antigen-presenting cells. They're the ones that go back and reactivate the T cells or the memory B cells that you have. And so the presence of the inflammasome recruits the dendritic cells to the site of action. It ingests some of the influenza virus. It takes it to the local lymph nodes where it activates the appropriate T cell and the B cell to help respond against a presence of influenza. Right?

So we all have been exposed to influenza in the past. Most of us get exposed to it almost every winter. There's no doubt you get exposed to influenza throughout the winter season, but not everybody gets sick. And a lot of that reason is because you don't become symptomatic because your commensal bacteria are protecting your lungs. They are activating your dendritic cells to go and react quickly so that your innate immune system doesn't have to be activated. And the influenza virus doesn't have time to damage any of your lung cells to create symptomology as well.

Other examples, the gut microbiota also regulates a respiratory mucosal immune system during influenza in infection, stimulating the release of more IGA secretions, activating cytotoxic T cells through Th1 activation. So the gut microbiota can do that from the gut to protect the lungs itself.

We also know that when the influenza virus is present in the lungs, gut commensal bacteria increase the presence of innate immune cells in the lungs by causing release of cytokines like IL-33, IL-1 alpha and beta and so on. So think about that. When there's virus in the lungs, your gut commensal bacteria somehow know that there's virus in the lungs and increases the presence of your innate immune cells by increasing the release of these cytokines that recruit your innate immune cells to the lungs itself. This causes more natural killer cells, dendritic cells, macrophages, all to end up in the lungs. There is a communication between the microbes in the lungs that detect the presence of the virus in the lungs first, and then they send a signal to the microbes in the gut. And then the microbes in the gut increase the recruitment of interleukins and all that to the lungs.

This is called the gut immune microbiome access. Right? Where there's a communication between the microbes in the lungs that see the infection first to the microbes in the gut, that then the gut microbes recruit the cells to make their way to the lungs.

Now, when influenza's not in the lungs, the actual opposite occurs, where the gut commensals send stimulating release of in the anti-inflammatory interleukin 10. And why that's important is because the lungs are constantly exposed to all kinds of irritants from the outside world. Right? Things, particulates, that you're breathing in, allergens and all that, that you're breathing into your lungs all the time. If your lungs were always activating the immune response by breathing in things, you'll always be undergoing respiratory distress or asthma-like symptoms or chronic obstructive lung disease. Those are the things that occur when your lungs are overreactive to all of the particulate matters that you breathe in.

So it becomes really important to control the immune response in the lungs, by stimulating the release of anti-inflammatory compounds when there's no infection. Right? And this is how people with disrupted microbiomes can actually have high prevalence rate or risk for asthma and hyperactive airway disease. Because they don't have that anti-inflammatory release. And everything that they breathe in, irritates the lungs and creates a hyperactive airway. This balancing act is that gut-lung access. Like I talked about where microbes from the lungs communicate with microbes from the gut, that then communicate with the immune system.

Staph aureus, for example, on airway surfaces will recruit monocytes and mature into macrophage through activation of toll-like receptors during lung activation. So this is one of the commensal bacteria that can actually help deal with acute infections because of its presence. And also respiratory commensal bacteria, like corynebacteria will modulate toll-like receptors during RSV infection by enhancing the production of other protective cytokines like TNF-alpha, interleukin 6, interferon gamma, and so on. These are all inflammatory cytokines, but they're required to recruit the innate immune cells and T cells to the site of action. Right? And this is triggered by your commensal corynebacterium.

Butyrate from commensal bacteria lower the inflammatory damage. So remember that really important anti-inflammatory step I talked about as we're moving into the adaptive immune response? That's triggered by certain microbes producing signals to release interleukin 10, which is the anti-inflammatory interleukin. And then also creating and releasing short-chain fatty acids, like butyrate, which becomes really important on activating something called G protein-couple receptors on cell surfaces, to stimulate interleukin 22, which creates repair mechanisms. Right?

So here's why this is so important. And hopefully I can explain it in a way that makes sense. When your innate immune system responds to the presence of a pathogen... Remember, I gave you the analogy that it's like a blow torch response to dealing with mosquitoes. Right? You're going to kill the

mosquitoes where you're also burning and damaging the wall behind it. So when the innate system responds, it's nonspecific. Meaning it's not responding to just one particular virus or one particular bacteria, it's responding to a region where there's a problem. And so it just comes in carpet bombs at region, which means that your own cells are also going to get damaged in the process.

Right. Now, one of the really important aspects of immune clearing, is that your own cells have to be repaired, and all of your own cellular debris have to be cleaned up. And there are cells that do that. There are cells that clean up all of that damage, but they have to be activated by activating G protein-couple receptors by stimulating interleukin 22. And all of those signals come from your microbiome.

Now, what happens if you don't fix the damage? Well, if you don't fix the damage, then all of your own cellular debris can get caught up and accidentally presented to the adaptive immune system as part of the problem. Right? Your macrophage or your dendritic cell may accidentally your own tissue proteins or your own tissue structures and present it to your T cells and B cells as the problematic or invading species. And then now you start developing autoimmune conditions. Right? That's how an infection can lead to autoimmunity.

That's what we're seeing in this pandemic virus is as well. People with long haul syndrome are seeing an autoimmune induction of their neurological system, their muscular system, and so on because there was so much inflammatory damage. And those individuals did not have a good, effective, clear repair and antiinflammatory mechanism. And so their macrophages and dendritic cells accidentally presented their own neurological tissue samples to the B cells and T cells. And then they started developing antibodies and memory T cells against their own tissue. Right? That's called a bystander effect. Where your own tissue becomes an accidental bystander in the war, in the damage, and then accidentally becomes a target.

So in order for that to not occur, you need a healthy microbiome producing the anti-inflammatory signaling, producing the butyrate to activate the G protein-couple receptors on cell surfaces and stimulating interleukin 22 to repair the damage that's going on. That has to be happening as the infection is coming under control and as the immune system is progressing along towards the adaptive. Right?

We cannot overstate the importance of a healthy microbiome in that whole kinetic aspect of how the immune system functions. If you don't have a healthy microbiome, you have a huge risk of going down the road of a cytokine storm and going down the road of auto activation, and then ending up with an autoimmune type of condition as a result of that infection.

We also to know that lactobacillus crispatus, for example, in a healthy vaginal canal, when it's dominant, can actually decrease HIV infection. And this is a big study in South African women by directly inhibiting viral function. So that studies showed that in that women that had high levels of this really beneficial vaginal bacteria, actually had lowered risk of picking up HIV infection, even when they were having sex with an infected partner. Because the microbe in their vaginal mucosa protected them against the viral effect. Right?

So we know that the microbes play a significant role in affecting the immune system's capability in recognizing, in detecting, in responding to infectious agents like viruses, bacteria, and so on. Right? And then also, the role of the microbiome in shuttling the immune system through the kinetics of the immune response. Including the repair, the anti-inflammatory part of the immune response that's absolutely critical to having a healthy response and a healthy immunity against whatever the target agent is.

But then there are also commensal organisms that have a direct effect on viral pathogens. Even without the immune system. And those are, of course, my favorite, spores. Take bacillus subtilis, for example. It

produces a surfactin that can inhibit the transmissible gastroenteritis virus from entering the intestinal epithelium itself. So this study showed that B subtilis and its surfactin... So it produces a surfactin as a post biotic, prevents the invasion from a specific type of coronavirus. Of course, full disclosure, it's not the coronavirus we're dealing with right now. This is a different type of coronavirus. So I don't want to give any sort of false information. This is other types of coronaviruses that have been shown to infect the GI tract, known as transmissible gastroenteritis virus. The surfactin from the bacteria in the gut actually prevents the infection from the virus itself.

B subtilis also produces powerful antiviral compounds. In this study, they called the compound of P18, which completely neutralizes influenza virus in vitro. Other studies have demonstrated that this strain is also effective in vivo antiviral effects as well. So this is completely outside of the immune system. The commensal bacteria themselves are directly going after viruses and stopping them.

As another example of B subtilis, bacillus subtilis, produces antimicrobial lipoproteins that contains surfactins. And then another compound called fengycin, which has been shown to have strong antiviral effects, which effectively inactivates viruses like PRV, porcine parvovirus, PPV, NDV, which is a Newcastle disease virus, and other infectious bursal diseases as well. And again, very broad spectrum activity against a whole bunch of infectious viruses, produced by this commensal bacteria.

And just think about the evolutionary significance of this. Right? We didn't have antibiotics and antivirals and all that for most of human existence, but we did have these kinds of microbes as commensal microbes. So we developed this symbiogenesis. We go back to that term from that first slide. Symbiogenesis, where we become their home. And because we are their home, it incentivizes them to protect their home against the microbes that we can't see ourselves. Right? So these commensal bacteria have developed capabilities of protecting the host against invading viruses and all that, that would normally kill an individual. But these microbes, commensal microbes, are protecting the host.

And then antiviral levans from bacillus species that are isolated from honey, have been shown to inhibit a whole host of viruses like adenovirus, including respiratory RNA viruses, like H5N1, and enteric adenovirus type 40. And this is found in the environment in honey itself. And maybe part of the reason why honey is so good for you when you're sick. Right? Mixing in some honey and in hot water can be very soothing and supportive to your immune system. And maybe from some of these levans and other compounds that microbes produce.

So we know that the microbes facilitate the immune response, they're acting as the eyes and ears of the immune system. They're recruiting the immune system to the site of action. They're also helping repair the damage, reducing the inflammatory damage, protecting the body from going into the autoimmune type of response that can occur from infection. And then there are microbes like the bacillus species that are commensal, that themselves can directly inhibit viruses and other infectious bacteria. So we know all of that. And we also know that the-

Bacteria. We know all of that. We also know that the microbes provide the signals for the immune system to even respond. They control the fitness of the immune system. This is two complicated studies that I'll try to explain in the most simplest form, what this study, these two studies are showing. These studies are 10 years apart but they build on the same topic. They basically show that your dendritic cells and macrophages, which are your very, very important antigen presenting cells that move the immune response from the innate to the adaptive, your dendritic cells and macrophages cannot respond to the presence of infection without getting a type I interferon signal from the microbiome.

They started these studies on animals. And what they did is they raise mice that are called gnotobiotic mice. These are mice that have no microbiome but they have all of their immune cells. They have all of their immune tissue, all of their immune organs so they have all their dendritic cells, macrophages and

all that. They just have no microbiome. When they infect these cells with the virus, the immune cells, the dendritic cells will just stand by and watch the host cell get infected and eventually the host dies. The immune cells are there. They're not responding to the presence of an infectious agent. The moment they implant a microbiome into these organisms, the immune system starts to respond, especially the dendritic cells and macrophages. Because it's a signal from the microbiome that tells the immune system when to respond. Now, the reason for this is twofold, I think.

Number one, it allows the microbiome to control the threshold at which the immune system responds because for most exposures, you don't necessarily want the immune system to respond. Because as dangerous as it is as having a nonresponsive immune system, it's equally dangerous to have an over-responsive immune system because most of the microbes and things you're going to encounter throughout the days of your life are not necessarily going to be harmful. Your immune system has to have a certain degree of tolerance to those things. And that tolerance is dictated by the microbiome. The microbiome determines at what stage of exposure and to what you're being exposed. Is it going to release a signal to activate your immune system?

Think about that evolutionarily. We have an immune system whose sole job it is to protect us, protect us the host. But our immune system cannot activate and function until the microbiome provides it a signal because it's the microbiome that is forward facing and looking at the world around us. It's not the immune system, the immune system's tucked in behind and waiting for signals from the microbiome. It's really mind boggling. And we know anytime you disrupt the microbiome through use of antibiotics and so on, you completely disrupt the function of the immune system. These are just some articles that show that how antibiotics are found to weaken the body's ability to fight off disease. Antibiotics used during flu season, weaken the defenses against the flu in lungs. In fact, it can make the infection much worse. Antibiotics bug the immune response. There's lots of examples of how the use of antibiotics that disrupt the microbiome can lead to a disruption in the immune system. And this couldn't be more evident in immunotherapy for cancer.

There's a number of cancers like melanoma and so on that could be well treated through immunotherapy. In immunotherapy are these compounds called checkpoint inhibitors that increase your T cell's ability to detect, find and deal with the cancers. And when you take a 100 individuals who have, let's say non-small cell lung cancer or melanoma, what you find is that when you treat a 100 of them with immunotherapy, somewhere around 30% of them get amazing responses where their immune system's able to get activated, find the cancer, suppress the cancer and then also build longterm immunity against that type of cancer cell so they go into really good remission. Their reversion rates are really low. But about 60, 70% of individuals get almost no response from the immunotherapy at all. And then that was a big question in the world of cancer research is why is it that certain patients, 60, 70% of patients get no response to immunotherapy? Whereas 30% of the patients get amazing responses and their cancer is gone and hardly ever comes back with very little side effects?

And the big difference has been, what does that individual's microbiome look like? And the first clues that started to come about that the microbiome impacted the response of immunotherapy was when individuals who were about to undergo immunotherapy were given a course of antibiotics, when they were given a course of antibiotics, the immunotherapy did not work. And if they had a healthy microbiome by high diversity, high keystone species, the immunotherapy tended to work better. That is a great example of showing how if you disrupt the microbiome immune response is going to get disrupted. If you don't disrupt the microbiome, you have a healthy microbiome, immune response is going to be much more effective.

And so here is a problem that we end up in modern society. The language used by the microbiome to communicate with immune system early on, when it first detects the presence of an infectious agent are

all these types of cytokines. Interferons and cytokines, interleukins, interferons and so on. All of these messengers are inflammatory messengers. And the way your body's supposed to work when it's healthy is you're supposed to have low levels of inflammation throughout your body. And so that if all of a sudden there's an inflammation flare in some part of your body, it quickly attracts your immune system to that side of action. That's the signal that the local microbes use to recruit your immune cells to that site of action. These are the examples of the interferons and interleukins that are the inflammatory cytokines that the microbiome uses to recruit your immune cells.

The problem is in places like North America, in the Western world, at least 50% of adults have high levels of chronic illness and all of the chronic illnesses that we have, like diabetes, autoimmune disease, arthritis, cardiovascular disease and so on, are all hallmarked by having chronic inflammation, which means all of these signals are chronically elevated in these individuals. Here are individuals with predispositions like obesity, diabetes, hypertension, cardiovascular disease, renal disease, autoimmune conditions, pancreatitis, IBD, all of these conditions are hallmarked by having elevated chronic levels of all of these inflammatory markers. That creates a significant problem for how your immune system is supposed to respond.

That creates a significant issue of something called loss signaling, which I'll talk about in a second. But the biggest driver of chronic inflammation in chronic illness in the Western world is leaky gut. The moment your gut becomes leaky, you got this translocation of LPS, lipopolysaccharide into circulation and when you get the translocation of this endotoxin that's made by bacteria in your gut, when you get that translocation into circulation, it turns on all of those very same inflammatory markers systemically. It does it in local tissue but it also does it systemically and disruption so the gut microbiome can drive this kind of chronic inflammation.

It leads to this problem of loss signaling, which I want you guys to understand because it explains a lot about how certain people responded to the pandemic virus versus others. Let's use this analogy, let's imagine that the invading pathogen is a flame, it's an actual flame. And then the disruption to that ecosystem is the smoke that results from the flame burning things. The microbiome is like a smoke detector. It's going to be the first thing to detect the presence of the flame, through detection of the smoke and then like any good smoke detector, it should sound an alarm, which in the case of your biology, it's your microbiome releasing these cytokines, these interleukins, these inflammatory cytokines, like an alarm and that should hopefully recruit the immune system. In this analogy, it'd be the firefighters coming and responding to the alarm.

Now, if you have chronic low grade inflammation from conditions like obesity, diabetes, autoimmune conditions, metabolic syndrome, so on, inflammatory bowel disease, celiac disease, leaky gut, any of those things, what tends to happen is you have alarms going on all over your body all the time. That when a flame, when a chronic invading pathogen or when an invading pathogen does show up and the smoke is there and the smoke is detected by the microbiome, the microbiome sends out a signal but this signal ends up being lost because the immune system cannot tell the difference between the microbiome signal to recruit the immune system to site of action versus all of the signaling that's going on because of chronic low grade inflammation from those preexisting conditions. What tends to happen then in this case is that the invading pathogen has more time to infect more cells before the immune system ever understands that there's an invading pathogen there because the immune system is distracted by all of these other alarms throughout the body.

Now you've got a pathogen that has more time to infect more cells and increase the viral or pathogen load before the immune system finally detects it. And once the immune system finally detects it, now the viral load is much bigger. The problem is much bigger. Now the innate immune system responds with a much more aggressive response, a much bigger blow torch, which then damages more tissue and

puts the body at further risk of that cytokine storm. And on top of that, because the microbiomes dysfunctional clearly because of this chronic low grade inflammation, the leaky gut and the presence of chronic preexisting conditions, the microbiome is also not providing those repair signals and the anti-inflammatory signals so then immune response goes haywire into a possible autoimmune response and chronic inflammatory signaling, so that cytokine storm. This is where the immune system starts to fall apart and the immune response starts to fall apart.

That's why it's no surprise that people with chronic conditions that are hallmarked by chronic low grade inflammation had the worst responses to this pandemic virus. People with cardiovascular disease had 10 times the death rate than in same age individuals without cardiovascular disease. People with diabetes had seven times, chronic respiratory disease had six times the increased rate. I don't have the slides here but there are at least four published, really well done studies on the microbiome and this pandemic virus.

And what those studies showed was that individuals with low diversity and low protective keystone species like faecalibacteria, Bifidobacterium longum, people with those low levels of those organisms had the worst outcomes when exposed to this pandemic virus, they had the highest rate of hospitalizations and the highest death rate as well. And in fact, the presence of the microbiome became predictive of how that individual is actually going to respond to the exposure to this pandemic virus. It's really important to note how critically important the microbiome is to the overall function of the immune system. The immune system would cease to function and to a certain degree ceased to exist without a healthy microbiome.

Here's some basic conclusions, a healthy, diverse microbiome provides critical signaling and energetics and threshold activation to the immune system to elicit proper immune function. Higher pathogen load in the system, higher levels of opportunistic organisms will disrupt the immune response because opportunistic organisms or pathogens in your microbiome do not want to help the immune system protect the host. They are in fact, looking for quote unquote, the opportunity for the immune system to be suppressed so that they can elicit their own virulence factors. Having more of those pathogens or more of the opportunistics actually disrupt the communication between the microbiome and the immune system and a disrupted microbiome leads to improper and attenuated immune response against pathogens.

A disrupted microbiome is also the most prevalent source of chronic low grade inflammation through leaky gut, endotoxemia and barrier dysfunction. And so immune support ingredients, as important as they can be, vitamin C and D and zinc and so on, cannot overcome the negative effect on the immune system from a dysfunctional microbiome. You cannot take enough vitamin C, you cannot take enough vitamin D or zinc to overcome the disrupted immune response that's a result of dysbiosis from your microbiome because remember your microbiome controls your immune response. If you're looking to support and enhance your immune system's function, taking your vitamin C and zinc and D and so on is important but it's even more imp to ensure that your microbiome is in the healthy state, in a state that will support your immune response. The success of preventative measures like things like vaccines and so on will also depend on one's immune capabilities.

Because if you can't mount an effective response to the vaccine, you're not going to get the adequate protection and so even exposure to the virus like low levels exposure to any viruses will require effective immune response to provide that immunological protection. Simple measures can make a big difference. Here are the things you need to do and can do to improve your microbiome with respect to immune response.

Number one, you have to diversify your diet because a diversified diet provides diversity in the microbiome and all of the studies on this topic point to the more diverse your microbiome is, the more

effective your immune response is going to be. That diversity is critically important. Diversifying your diet creates that. Reducing stress, stress induces the overgrowth of opportunistic and pathogenic organisms. Stress also can create leaky gut, which creates chronic low grade inflammation, which creates that issue of loss signaling that I talked about. Managing stress, as you're looking at improving your immune response is going to be critically important.

Getting outdoors because getting outdoors improves the diversity of your microbiome, gets you more exposure to microbes in the outside world, trains your immune system, keeps your immune system functioning at a state of functional readiness. Using spore based probiotics, like a research probiotic like MegaSpore becomes extremely important to stop that leaky gut, reduce that chronic low grade inflammation. And then like we showed, bacillus species have all of these direct effects against pathogens to support the system. Of course, we also have published studies showing that the spores increases diversity within the microbiome, dramatically increases the production of short chain fatty acids, which you remember are really important for anti-inflammatory and repair and also facilitates the growth of keystone species like faecalibacteria and akkermansia and so on.

Focusing on leaky gut is going to be critical. You have to improve that barrier function. You have to have a good, thick, healthy mucosa. You have to have good diversity within the microbiome and bringing down inflammation in general is going to be important for your immune system to function because remember all of the signaling between your immune system and the microbiome is done through inflammatory cytokines. Having that systemic inflammation is only going to disrupt all those signals. Working on bringing down inflammation using things like prebiotics can have a major impact on that. Polyphenols and omega fatty acids also can be very powerful, supportive tools, especially when we talk about systemic inflammation that should be coming down as well. And I think that's the very end of it. We can go to questions if we have time for that.

PART 1 OF 3 ENDS [00:23:04]

Michael Roesslein:

Sorry, I was muted. I only took about five pages of typed notes this time versus the nine I took last time before you removed some of the slides. But it's about the fifth time I've been hearing a lot of this stuff from you and I'm finally starting to get it. And it makes a lot of sense that the immune responses go haywire when the microbiome isn't really there to say, "Okay, now it's time to go to this. Now it's time to switch to this. Now we can turn off." It's kind of like the driver of the car is asleep or not present in the cars, then just run all over the place. And it's starting to make a lot of sense. Some of the exact examples and details through some of those, I think there were some people that were trying to keep up and pay attention and memorize all of those different, this organism does this with this.

And I think you were just trying to get across the main gist of the idea there is that these things don't happen if these organisms aren't present and if these don't happen, here's what happens. And so you don't have to memorize everything. I let everybody know in the chat, there's no quiz at the end of this and we'll have a recording on Friday so you can catch the more geeky parts again and pause them and take notes if you want to. But I do have some questions in the Q and A. Most of them are pretty relevant to this presentation so I think we could probably get through them in about 15, 20 minutes. Would that be okay?

Kiran Krishnan:

Yeah, that'd be great.

Michael Roesslein:

All right, cool. I'll try to reign you in, if you go too far on any of them.

Kiran Krishnan:

Awesome.

Michael Roesslein:

This one I could have of answered but I wanted you to speak on biofilms. Do the bacillus species in MegaSpore break up biofilm in the gut? And my question would be is, do you even want to break up biofilms?

Kiran Krishnan:

Yeah. There are clearly PA pathogens that also utilize biofilms to protect their presence. And there are pathogens that will cooperate with one another to create biofilms that they can all live within. And so being able to target those particular biofilms will be really important. And the good thing about microbes is they know how to do that. Versus using kind of a broad spectrum biofilm disruptor, which will also disrupt all the commensal biofilms because most of your commensal organisms all also live within biofilms. We don't want to just go through and busting biofilms left and right. The good thing about the bacillus is it seems to be able to target pathogenic organism biofilms, it produces an alpha amylase enzyme that does break away at biofilms and exposes the pathogenic organism so it can do that with some specificity.

Michael Roesslein:

Makes sense. I just want to announce, I promised a special present for anybody who attended this live. We're going to be running a really big Black Friday weekend, Cyber Monday special on our shop. For people who are here on Tuesday, I just put the code that we're going to send out on Friday in the chat. It's in the chat box there.

There's a code to save 15% off our entire shop where a lot of the products Kiran has formulated that he talked about in the presentation, MegaSpore is back in stock. That's been out of stock everywhere for quite a while and it's back and we have the prebiotics and the MegaMucosa and the MegaIgG. A lot of the things that he referenced in the presentation, they're all in stock now. And the link is there, the 15% off our entire shop. That's Microbiome Labs products and everything else that you find in there. And there's free shipping on orders of 75 bucks or more. I just want to let everybody know that's in the chat. If you want to grab anything that was talked about tonight and then we'll go back to the Q and A. Check that out.

Next question is, what functional medicine testing? I could have answered this one too but I wanted to hear your rationale. Can you do for a test for leaky gut and microbiome imbalances?

Kiran Krishnan:

The best thing is using a whole genome sequencing stool test. That's the best tool we have on hand at the moment that science has for you. We have the BiomeFX tests that not only gives you all kinds of parameters, looking at your diversity, the relative abundance of pathogens and opportunistic organisms, which gives you a real strong understanding of how problematic are pathogens and opportunistic organisms in your microbiome. And it also gives you over 35 different functionalities within your

microbiome as well. Look at the BiomeFX stool test. I think Michael has all kinds of amazing information on BiomeFX and actually provides support. I think you may still be doing the consultations and so on.

Michael Roesslein:

Yeah. If they order it through our site, we have coaches that do consultations with them on their results. I'm just trying to find, we did a webinar on it and I'm trying to find the link on the fly to post in the chat. But we can go onto the next question. But we do consult with a coach and your report and everything else. It's a really cool report that seems to have evolved quite a bit too, since we kicked those off.

Kiran Krishnan:

Yeah. And we're constantly adding to it. You'll really get a deep dive understanding on what your microbiome looks like from all the parameters that are important for immune response, metabolic response, hormone balance, virtually everything. But on top of that, you can also have your functional medicine doc run an immune panel, which just looks at your cytokine levels. It looks at interleukins and interferons and all that and then see if you're elevated in all of those. Because if you're elevated in all of those...

See if you're elevated in all of those, right? Because if you're elevated in all of those, that means you've got some chronic inflammation going on which will disrupt your immune response.

PART 2 OF 3 ENDS [01:09:04]

Michael Roesslein:

Okay. There's the link. That is a link to a webinar we did, and a Q and A. There were so many questions from that webinar, we did a Q and A, so both of them are linked there in the chat to learn about Biome FX if you want to.

All right. I've heard and read how important to akkermansia muciniphila, I don't know if I said that right, species is to gut immune health, and I've seen a new probiotic, I believe it's called Akkermansia, I get ads for it too, product advertising itself as an effective means of restoring this species to the gut. I have looked at it, it's extremely expensive. I know that you've talked about akkermansia quite a bit and that your product, the MegaSpore and the prebiotic, I believe have both been shown to increase akkermansia, but the akkermansia is only one of several keystone species that you'd want to look at. Another question I probably could have answered, but I wouldn't answer it as well as you do. So how'd I do?

You're muted.

Kiran Krishnan:

No, you did great. And here's the other point to that. So akkermansia is critical, right? And I love, it's one of my favorite keystone organisms, it protects the body in so many ways. It is an obligate anaerobe, so it's very hard for it to be stable outside of the body. It's also very hard for it to be ingested and then engraft or colonize appropriately.

The probiotic that has the akkermansia in it, from what I've seen, they've got two studies on use of it in diabetics, but these are diabetics on Metformin as well, right? So they compared diabetics who are on Metformin and then diabetics who are on Metformin with the akkermansia probiotic, and they saw a slight improvement in glucose control. That doesn't necessarily demonstrate that the akkermansia is going in there, living, and creating all of the benefits that we hope for it to create. And also does that

akkermansia match with your system's akkermansia because your akkermansia came from your mom, it's quite unique. So for us, the most important way of increasing, not only akkermansia, but all the other keystone species, is to increase your own endogenous unique akkermansia, right? And that's through the use of polyphenols, that's the use of prebiotics, doing some fasting, adding the spores, all of that increases your akkermansia within your system.

Michael Roesslein:

Perfect. So not all akkermansia is created equally.

Kiran Krishnan:

Yeah.

Michael Roesslein:

All right. Quick question, does Vitamin D help move you more quickly to the adaptive immunity stage? I actually don't know. I know Vitamin D is all the rage for immune function, but I don't know what it actually does related to what you presented tonight.

Kiran Krishnan:

So Vitamin D will help activate macrophages, right? So macrophages are part of the antigen presenting cell class, so those are important cells to go grab whatever the infectious agent is and present it to the adaptive immune system, the T-cells and B-cells. So it could, but you could take all the Vitamin D in the world, and if you don't have the healthy microbiome, signaling the macrophages and providing the signals for the macrophages to come get recruited to the site of action and then present effectively, it's not necessarily going to help. So you really need to ensure that your microbiome is healthy in order for Vitamin D even to help with your immune response, right? So these micronutrients will have to go hand in hand with microbiome-based immune support.

And that's really the key message here, right? Because when I talk to consumers, everybody has become heightened about immune support, right? They want their immune system to function better. We realized through this pandemic crisis that so much of the population has a relatively weak immune response against a new virus, for example, and so many people died unnecessarily because of that. And I think what people do, as a knee jerk reaction, is you go to your micronutrients. You go to the Vitamin C's, you go to the zinc, you go to Vitamin D, and that's fine. But what people are forgetting is that the function of the immune system is based on your microbiome. That's the key message I want to put across.

So all the specifics and all that within the presentation, you don't necessarily need to remember and memorize, just know that when your child is sick, just know when there's a rotovirus infection going around school, right, or you're concerned about them going to school with potential exposure to things, or you are going to an office or an airplane or you're traveling. Know that it's not just enough to buy your Vitamin C and increase your zinc, and so on, you have to ensure your microbiome is there and healthy to support your immune system. And that's a diverse microbiome, high keystone species, high production of butyrate and other short chain fatty acids. Those are the key things to keep in mind.

Michael Roesslein:

Okay. Next question. My more urgent question is a transmission of H. pylori. I could answer this one, too maybe. I've been on a lot of these web webinars, I know about 80% of the answers to most of these

questions, but my urgent question, transmission of H. pylori between people if some of them are careless in hygiene and hand washing even if they prepare food? How and what do you know of this in cooked and raw food? And my answer is everyone has H. pylori, it's a commensal organism, and that just because somebody has an issue with it as an overgrowth doesn't mean someone else, if exposed to it, would also develop a problematic overgrowth. Is that correct?

Kiran Krishnan:

Yeah. That's another terrain versus germ situation, right? You can have H. pylori and be perfectly fine and never have any sort of issues or symptomatic issues with it. If your stomach acid and your gastric mucosa is healthy, you've got the right microbes in that space, it will control the H. pylori, your immune system can control the H. pylori as long as your microbiome is healthy, right? And then if you start taking things like PPIs, inhibiting stomach acid, if you start taking anti-acids a lot, you have leaky gut, you have all this inflammation, then the H. pylori is given the right terrain to start proliferating and creating problems.

Michael Roesslein:

Okay, I did pretty good on that one.

Kiran Krishnan:

Yeah.

Michael Roesslein:

From what you were saying, people that have colectomies, oh, removing colon, for severe, recurrent diverticulitis should have impaired immunity and recurrent infection, systemic inflammation? I believe that is true.

Kiran Krishnan:

Mm-hmm (affirmative).

Michael Roesslein:

Yeah.

Kiran Krishnan:

Yeah, typically that becomes a unfortunate.

Michael Roesslein:

Reoccurring side effect.

I always have high IgM to a lot of things, lab test, and the immunologist shaked her head saying, "Some people just do." Parentheses is not worried because I have IgG and IgA, so not a primary from birth problem thing. Since I have inflammatory arthritis, I want to do AIP diet. Do your microbiome labs products help calm this over immune response I seem to have? How would it relate to the high IgM? Anything that you can speak to in that in general?

Kiran Krishnan:

So having high IgM doesn't necessarily mean you have an inflammatory response, right? So what you'd want to look at is things like your Th17 or Interleukin 17 expression. Having high IgE, basophil, or a eosinophil reaction, those are the things that create that unwanted inflammatory response. IgM is a target-specific neutralizing antibody, so you've got B-cells that produce high levels of IgM. It doesn't necessarily mean it's an inflammatory response because IgM doesn't lead to inflammation, right?

So you've got good protective immunity, that's not where the problem is. The problem is if you have a lot of IgM to your own tissue, right? Which I think you mentioned osteoarthritis or rheumatoid or something like that, right?

Michael Roesslein:

Yeah.

Kiran Krishnan:

If there's an autoimmune condition there, that means that your T-regulatory cells aren't functioning, right? That's something called a FoxP3 T-reg system. That system's not functioning properly. That system requires a diverse, healthy microbiome to be up-regulated. So that's where using a probiotic, prebiotic to increase diversity will help with up-regulating the T-regulatory side of it, which helps bring down non-beneficial immune responses.

Michael Roesslein:

Makes sense. Okay. From what you were saying with the advent of antibiotic use which can cause the extinction of various species of bacteria in a person's microbiome, we should be seeing an increase in viral illness. Yes. Is this line of reasoning correct? Basically does the overuse of antibiotics set us up for pandemics like that?

Kiran Krishnan:

I think it weakens our ability to deal with the new virus, right? I mean, our immune system is quite elegant and amazing and is well designed to deal with all kinds of invading pathogens. Just because it's a new virus that our system hasn't seen doesn't necessarily mean it should kill us, but if our system is weakened by over exposure to antibiotics and then not correcting that exposure, that becomes a big problem, right? Antibiotics, I don't want to villainize them all the time because antibiotics can be very important and necessary to save your life, right, but it doesn't mean you can't recover your system from an antibiotic exposure. And in a single exposure, a single course, antibiotics won't necessarily extinguish any given specie? Right. So what antibiotics really do is it brings down everything, and then when things regrow, they regrow in different proportions.

So it screws up the balance within the microbiome, and that's enough to cause disruption in the system. But if you bring in a different force, like improved diets, using the immunoglobulins, using prebiotics, probiotics, and so on, you can bring back the balance and shift back your microbiome. So just in general, philosophically, yes, overuse of antibiotics, both as prescriptions and in food and in our water is going to create a weakening of our immune system which can make us more susceptible, but it doesn't mean that we can't repair that either. Right? We can.

Michael Roesslein:

Gotcha. Can spore probiotics stimulate inflammation if a mold infection is present? We actually used it as part of our protocol when we knew a mold infection, mold toxicity was present. But do you want to speak on that for a second?

Kiran Krishnan:

Yeah, it can up-regulate immune response. Right? So one of the things that the spores do is it up-regulates something called toll-like receptors. In one of the examples I showed how commensal bacteria can up-regulate toll-like receptors to improve immune response against viruses and so on. So the spore probiotic will up-regulate toll-like receptors so that your immune system is more alerted to dealing with something like a present mold or mold toxin, and so on. So it facilitates your immune system to respond, and that's a really important aspect of it.

Michael Roesslein:

Are long haulers likely to have high Interleukin 22 when tested? This came in, when you were going through the interleukins and things of that nature. I don't know if that's a quick answer or not.

Kiran Krishnan:

Yeah. So long haulers actually tend to have high levels of Interleukin 6, Interleukin 1 beta, and TNF and interferon. There's a couple of studies looking at long haulers in cytokine response. Long haulers have classic autoimmune leaky gut kind of pathologies and immune responses. So things that bring down those inflammatory cytokines are being studied to see, can they help with long hauler syndrome?

Michael Roesslein:

Perfect. Trying to find, there's questions piling in faster than we're answering them, and I know we have to go in a few minutes. So a lot of questions that were answered, go back on the recording and watch the last slide with the recommendations. There's a lot of questions coming in right now that are related to what was explained on that slide. If you want to send questions afterwards, I might be able to try to get some answers for you. Can probiotics provide commensal bacteria able to increase our immunological fitness, especially if the microbiome has been damaged by antibiotic use? If so, it would be a temporary effect needing daily dosing of a probiotic, correct?

Kiran Krishnan:

Yeah, and it depends on the probiotic completely, right? So some probiotics will actually make it harder for your own microbes to regenerate, will actually compete for binding sites with your own commensal bacteria. Those can be problematic. So you want to make sure that it's a probiotic that has clinical research behind it, that talks about, that shows immunological support, right? So you want an immunogenic probiotic that can improve immune function, and not all probiotics will do that, and not all probiotics will do that in the proper way. Keep in mind that the vast majority of probiotics don't have any research behind it, right? You have no idea nor do the companies that produced them have no idea what they actually do in the system. So make sure it's a clinically researched probiotics so that you have some confidence that it's actually going to support the immune system when needed.

There's a question here that I see from somebody looking at the upper ranges of Bacillus subtilis and the GI map stool tests, asking if that's correct. There's a massive issue with that kind of stool test, right? Number one, the accuracy. It's using something called 16S sequencing, which can be very inaccurate when you're looking at species level detection, and this limits is so arbitrary. There's no microbiome

science around limits of any organism in the microbiome, whether it be Bacillus or any one of the tens of thousands of organisms that can exist, right? That's not how the microbiome is designed. That's one of the things that really drives me crazy about these stool tests that are giving people false information. It's completely nonsensical information. Any stool test that gives you a CFU count makes absolutely no sense at all, right? You can't get a colony forming unit count from an effective stool test.

So the fact that they have some upper limit for Bacillus species, which I think is at 10 to the 4, is completely nuts because there's lots of published studies that show that that's normal levels. In fact, there's no upper limit for any of these organisms, it's all based on what the total ecosystem looks like, right? It's all relative abundance of organisms, and in everyone's gut it's going to be a little bit different. And so looking at those kind of things, they're completely nonsensical, that's why they're not used in any research studies. They're very inaccurate, and it doesn't make any sense at all scientifically. And keep in mind, most of these stool tests were developed well before any studies on the microbiome were published. So they were all developed in a vacuum information, right? So it's just, unfortunately it gives you a lot of wrong information, and people are spending their money on it.

Michael Roesslein:

Go figure. I can't believe that would actually be happening in such a. All right. Let's try to just, trying to find one more that's kind of a quick answer. C. bo. We're going to have a whole nother webinar specifically on C. bo. I see several questions in here about C. bo.

Kiran Krishnan:

Yeah, come join us for that.

Michael Roesslein:

I guess just this one. You mentioned it in the last slide, but we'll repeat it. Can you reverse heavy damage to your microbiome from excessive use of antibiotics in your life? I'm over 60 years old.

Yes. That is not a death sentence by any means to your microbiome. The last slide on his presentation had a whole bunch of recommendations, but we've had people use the biome FX test and order multiple tests and over time have seen increases in diversity and lower inflammatory markers. Do you want to just kind of end on a note about how possible it is to improve that?

Kiran Krishnan:

Totally.

I mean, keep in mind you, it's very hard to eliminate microbes completely, right? So even though you feel like I've had lots of courses of antibiotics, and all my good bacteria are gone, they're not gone, they're just at such low levels where they're not functionally helping you. It's just like every disinfectant, you see how they have to say kills 99.9% of microbes, they can never say a hundred percent because you can never ensure you kill a hundred percent of microbes, right? They're just that resistant and resilient and always is one that survives. And so you have microbes in there, you have beneficial microbes in there. It's about creating the conditions and the right stimulus to allow those to grow, and it's never too late to recover, repair, and restore your microbiome.

I don't care if you're 60 or you're 80 years old, you can absolutely always improve the ecosystem within your microbiome, and you will feel that improvement in terms of your symptomology and the things that you're dealing with, right? So you can always improve your diet, improve your environment, improve some of the lifestyle choices, all the things we talked about. Using the right probiotic, prebiotic,

mucosal support, polyphenols, all of those things will drive significant changes in your microbiome, and it's never too late. So that's the important hope that people should feel you always have within you some power and capability of affecting your health in a positive way, because you can always change your microbiome.

Michael Roesslein:

Amazing. Well, we're at time, I want to be respectful of that. We had 200 people stay on plus for an hour and a half, which is amazing. I'm going to try to figure out how to save the chat or the Q and A. Actually I'm just going to copy and paste it because there's some questions in there that I know I can answer. So we'll do a follow-up email, and I'll try to answer some of these questions for you, and I'll hit Kiran on up if I need help, but I'm getting there being able to answer a lot of the questions because I've been in a lot of these webinars. So I'll do my best. We have another one coming up pretty soon. I responded to the shipping internationally question twice in the chat. I don't know if you didn't see my messages. It depends on the country. So just send us an email, let us know. Some countries, yes, some countries, no. It depends on their rules and regulations and taxes and a whole bunch of things that they're going to try to charge you for getting the product in.

So thanks for all the amazing questions. I did copy the Q and A, so I will try to get to as many of those, and we'll do a follow-up email maybe next week. We'll be seeing Kiran again soon, and we'll be doing that presentation entirely on C. Bo, which I don't think I've seen your C. Bo presentation, so I'm pretty excited about that. We've talked about it. We did a webinar on it once, like a hundred years ago, where we just talked and did like questions and talked about it. I haven't seen any C. Bo specific presentation.

Kiran Krishnan:

Awesome. Well, I'm excited to do that then.

Michael Roesslein:

Yeah, because there's a lot of misunderstandings out there on that topic.

Kiran Krishnan:

Yep.

Michael Roesslein:

It'll be great to clear it up. Thank you, everyone. Thank you, Kiran, we'll talk to you soon.

Kiran Krishnan:

Appreciate it.

Michael Roesslein:

Have a great holiday.

Kiran Krishnan:

Take care. Bye.

PART 3 OF 3 ENDS [01:29:34]