Michael Roesslein:

And we are now recording. So, welcome. We are here with microbiologist Kiran Krishnan, Kiran, thank you. Apologize for the challenges, looks like Bill Gates is interfering. I don't know if they own Zoom. Somebody probably owns Zoom. I'm sure it's not an autonomous company.

Kiran Krishnan:

Mm-mm (negative).

Michael Roesslein:

We are going to talk about the hottest topic in health today, which is immunity and how that ties into the gut, the microbiome, everything going on in there and how that relates to our overall immunity, immune resilience, susceptibility to infection, severity of infections. What we are not going to do, is we are not going to tell you how to prevent COVID-19 or cure COVID-19, or anything specific to treating COVID-19. So, I'm just throwing that out there right now, so this doesn't get shut off before we get talking and I think that covers all the bases. We're not treating, we're not curing, we're not diagnosing, we're not preventing.

We are sharing information that might be relevant, especially now and ... I see the chat box moving kind of, but it seems frozen. So, let me know, just pop it up again, test. Okay, cool. No. Test. Now, I'm seeing ... I think everything's okay. Hello from Ohio. All right. I think we're okay and they'll let me know if we're not. So, I guess where we should probably start and also I would add that there is a Q&A box, which the chat tends to move really fast, you can enter questions in the chat and I'm pretty good at it, but this looks like it's going to move fast. And so, sometimes questions get lost in the chat. So, there is a Q&A button as well, which are specific for questions and that might be a little bit easier with questions. We're going to try to do some questions at the end.

I also have some in my email box that I'm going to try to decipher. Some of them are very long emails with a question tied in somewhere and then a couple from the Facebook post. So, I will carry on going and then I will try to manage the chat box and the questions from the other things and see how well we can do. So, without any more being in the way, if you would like to just give us the overview of, we all hear, "Oh, immunity starts in the gut or a certain percentage of immune function is in the gut." That's great and all, but can you give us a little bit more information in detail along those lines?

Kiran Krishnan:

Yeah. In fact, this topic is so important I prepared PowerPoint slides today.

Michael Roesslein:

Perfect.

Kiran Krishnan:

So, I'll be sharing some PowerPoint slides, but I wanted to preface that by saying that I've heard a lot of good talks on the function of things like vitamin C and vitamin D and zinc and lots of herbals and all that. Those are all important and critical as well. I just haven't heard enough about the role of the microbiome, and in fact, you can not have immunity without the microbiome. And that's one of the things I want to illustrate for you today and go into some degree of detail on that. Our immune system is dependent, in large part, on our microbiome. We'll go through how the immune system is dependent on the microbiome, what role the microbiome plays and provide evidence for that. And also, provide evidence that shows that how a disrupted microbiome leads to a significant dysfunction in immune response as well.

So, as we're paying attention to self-care, and we're thinking about important things like vitamin C and zinc and trying to improve mindfulness and all that, a lot of that, the effects of a lot of that is dependent on how healthy your microbiome is. So, that's what we want to get across today. If you want, I can just jump right in Mike and can share my screen.

Michael Roesslein:

Yeah. Go for it.

Kiran Krishnan:

Okay. I'll do that.

Michael Roesslein:

And I'm going to be trying to pull some of these questions from the emails while you do that and I'll get them succinctly listed for when we're done.

Kiran Krishnan:

Okay, cool. So, I am sharing my screen. Does this look like full screen?

Michael Roesslein:

It does.

Kiran Krishnan:

Yeah. Okay.

Michael Roesslein:

I'm going to check the chat. Can everybody ... It's weird. I see the chats moving, but it moves as if somebody types something new, but then they're all still in the same order. Okay. Yes. [inaudible] looks great. I think I'm just on a little bit of delay with the chat.

Kiran Krishnan:

Cool.

Michael Roesslein:

So, it's all good.

Kiran Krishnan:

I'm going to, while I'm talking, I'll turn off my video, so I don't look like a crazy person as I'm talking and then I'll click it back on for Q&A.

Michael Roesslein:

We're all about crazy.

Kiran Krishnan:

Okay. So, this talks all about the microbiome and immune function, we'll delve a little bit deep into that. I'll give a quick overview on the immune system itself and especially immune kinetics, which is really important in pathogen defense. And then we'll illustrate how the microbiome plays a role in each of those aspects. Right? So, to begin with, I do want to remind people of this, that I always talk about that, we are really a holobiome, which is a superorganism. So, we are essentially made up of thousands of different organisms that live together in this human shell. And as a super organism, in order to perpetuate the health and wellness of the whole, each member of the superorganism has to really communicate with the others and they all play a different job. And this couldn't be more true when it comes to immune response and I think you'll see why.

So, remember this holobiome, we are a walking, talking rainforest, and every member of this rainforest plays a critical role in maintaining homeostasis. So, a quick review of the immune system, it begins to develop, even in the embryo itself, you see early immune cells starting to develop there. Most of the immune cells come from hematopoietic stem cells and those are continuously generated throughout one's life. The stem cells differentiate into major classes within the immune system. Things like granulocytes, monocytes, lymphocytes, we'll talk about each of these a little bit more. The only major system in the body designed to protect us is the immune system, that's its entire goal, is protecting the collective. And then, of course, the ecosystem in which the immune system functions also plays a major role in the immune system's capability of protecting us.

Immune system has a lot of capability, but no real information. It's an army with no general. So, it requires training. It requires information from places like the microbiome. We'll illustrate that as well. It takes at least six months for the immune system to start to work on its own, when you're first born, within the first six months or so the baby, for example, is highly dependent on mom's immunity, mom's immunoglobulins, and so on, but then you start to develop your own immune system. And as you start to develop your own immune system, there is this intimate crosstalk between the immune system and the microbiota that then exists in your system. And then you create this long-term symbiotic relationship between the microbiota and the immune system that's developing. Stem cells continue to be produced and differentiate throughout one's lifetime, there is no significant measurable limit to the amount of immune response you can have, as long as all the systems are working. So, that's an important thing to note.

The two main parts of the immune system that we really want to focus on is the innate immune system and then the adaptive immune system. And I'll be talking about the kinetics between the two, because that's really important when we talk about pathogen control, right? So, innate is our first line of cellular defense. Some of the players within the innate immune system are antigen presenting cells, so cells like macrophages and dendritic cells, they basically find antigens and then they present the problem to the next set of cells that will take over the immune response. So, they will phagocytize, meaning they'll eat stuff, and then they will look for specific antigens within pathogens, within damaged cells, within viruses, bacteria, and so on, they'll then present those cells to the rest of the immune system for learning and response.

These antigen presenting cells are produced in the thymus and other lymphoid centers, but then are recruited to the gut mucosa and other mucosal tissue, typically by commensal bacteria. We'll give some examples of that as well. Now, the microbiome helps these cells by expressing things like toll-like receptors, which then help these cells identify commensal bacteria from pathogens that are coming in, both bacteria and viruses. So, this communication using toll-like receptors is a big part of expressing the presence of the commensal bacteria and their ability to help your immune system distinguish between friend and foe. Again, we'll elaborate on that a little bit more. This part I'll just give you very general overview. The microbiome even goes as far as producing energy for these circulating dendritic cells and macrophages. So, remember these are really important first line defense cells, their process that they use for defense requires a lot of energy, the production and the assimilation of energy for these cells comes from compounds that are produced in the microbiome like butyrate, for example.

Then you have neutrophils, which are key part of the first line of defense. These are killer cells that directly target harmful organisms and can eliminate these harmful organisms. They're very important to maintaining a infectious free environment like in cold and flu season, when you're exposed to lots of viruses all the time. They are dependent on the microbiota for stimulation and expression and even for equipping them with the tools that they use to kill invading pathogens, things like nitric oxide, super oxides, and so on. A lot of those tools actually come from the microbiome. Other parts of the innate immune system, natural killer cells, which are highly important in viral infections, in particular, these cells can identify infected cells of ours and eliminate it. And dysfunctions in natural killer cells, in individuals, these people would face chronic consistent infections, and there are genetic defects in natural killer cells.

And these individuals end up seeing chronic, non-stop infections because we're continuously exposed to all types of viruses and bacteria and your natural killer cells in your innate immune system do a lot of the brunt work of the initial control. The microbiome stimulates a production of natural killer cells, and the microbiome also affects the potency of the cells as well. So, providing the cells their tools to be able to perform those elimination functions. Mast cells, many people know about mast cells, they're highly important regulatory cells, especially in the lamina propria, that's the place right below the intestinal epithelium. They control blood flow and coagulation in the lamina propria. And in fact, some of the issues that are going on right now with this particular pandemic and seeing the hypercoagulation may be effected by mast cells themselves. They control smooth muscle cell peristalsis, they're an important part of that peristaltic movement in the gut.

They fight against gut permeability, so they play an important role there. They control electrolyte exchange and a poor microbiota with low diversity leads to actually fewer mast cells in the lamina propria in the gut, and ends up with more mast cells in circulation, which is one of the modes of increasing allergies, because most people know about mast cells with regards to their effect on increasing allergenic response, the IgE type of response. But mast cells in the lamina propria are really important for all of the things we just talked about. About blood flow, smooth muscle contraction, fighting against permeability and so on, electrolyte exchange. But there's a correlation between having low diversity in the microbiota and the presence of these mast cells in the circulatory system, instead of the lamina propria. Intestinal epithelial cells actually act as a bonafide part of the immune system.

These barrier cells contain lots of immune function. They release key antimicrobials to protect the barrier, and they do a lot of that antimicrobial secretion based on stimulation from the microbiota. They release chemokines and cytokines to recruit immune cells to locations where there are active infections going on. So, they're really important in that signaling cascade to alert the immune system. The microbiota stimulates intestinal epithelial cells to release antimicrobials and chemical messengers. So, a lot of the action that the microbiome wants the immune system to take, is done through the intestinal epithelium, which is the first line of communication with the microbiome and the immune system, right? Because remember the microbiome sits in the mucosa, which is right above the intestinal epithelium, so a lot of the signals that come from the microbiome get filtered through the intestinal epithelium and then those signals get propagated to the rest of the immune system.

So, that relationship is really, really important. Then looking at the adaptive immune system, which is the second line of defense and more of the longer-term protection, one of the key players, of course, in adaptive immune response is the antibody secreting cells, the B-cells. So, these are a gut associated B-cells, primarily are the secretors of IgA. This is the antibody that's made in the highest concentration, it's found in a lot of your secretory fluids in your tear ducts, so in tears and saliva, in your mucosa and so on. We make about seven grams of IgA a day. It's a very important first line defense from an immunoglobulin standpoint and it is produced by B-cells and B-cells that mature in the Peyer's patches in the gut ilium, they originate there and then they also mature and propagate there in the B-cells, in the Peyer's patches as well. The amount of B-cells and Peyer's patches, and their potency, is directly controlled by commensal bacteria.

So, the proliferation, the number of B-cells and the number of Peyer's patches, and the size of the Peyer's patches are controlled by the diversity within the microbiome. The more diverse your microbiome is, you have a higher proliferation of B-cells, you have higher surface area of Peyer's patches. So, you've got better overall immune response because the Peyer's patches are not only the proliferation site for B-cells, they are also for T-cells. IgA, unlike IgM, has a lower memory and is less specific to certain antigens. It is more of a broader binding antibody and it typically recognizes the current crop of commensals. And so, it helps distinguish between the current crop of commensals and invading organisms. A lot of the commensals, as they filter into the mucosa, get covered with IgA.

And because they're covered with IgA, then the immune system negates a response to them. That's one of the ways that the immune system distinguishes between commensal, that's been there and is there all the time versus a new bacteria that's coming in. A new bacteria that's coming in, may not be bound by IgA because the antibody doesn't have confirmational structure to bind that new pathogen. So, then when the immune system sees an unbound pathogen or microbe coming in, that signals to the immune system that this may be a new invading species and not part of the commensal microbiota. So, that helps upregulate some of the immune response in itself. So, that relationship of IgA helping recognize commensal bacteria is a really interesting angle in terms of the function of IgA.

Now, IgA also plays a big role in neutralizing things that we commonly see, bacteria and viruses that we commonly come across so that they don't actually elicit much of an immune response, IgA takes care of them pretty quickly. Low microbiota diversity, and low microbiota exposure and then, of course, low antigenic species in our environment leads to lower levels of IgA. The production of IgA is dependent on microbial exposure, and that's an important part to keep in mind, especially right now, and we'll talk about some of that as well later on. And one thing that's really interesting that I was able to find in the literature is that when you have lower levels of IgA production, which is again driven by lower levels of exposure to bacteria, lower diversity in the gut, you actually end up having a compensatory effect where your body produces more IgE instead, right? Because your body's going, "Hey, we need a certain amount of antibody titer in circulation in our secretory fluids, because we need to keep defenses up. We have low IgA, so we're going to produce more IgE instead."

And the problem with IgE is that when it encounters things, it facilitates an inflammatory, allergic type of response. So, this may be one of the mechanisms by which allergenicity increases over time because of the reduced production of IgA, which stems from lower microbial diversity and lower microbial exposure. T-cells, T-cells are really important orchestrators of our immune system. They're, of course, part of the adaptive immune response as well, CD4 T-cells are the T-cells that can differentiate into Th1, Th2, Th17. Th, by the way, stands for T helper cells. So, these T helper cells facilitate specific types of immune responses, Th1 response, Th2, 17 and then of course, Treg as well. Having a balance between these four subtypes is absolutely critical to help.

You can have disease states that are driven by an imbalance in any one of these types of T-cell responses, right? So, that is the critical aspect here. It's not like one of them is really bad, the other one is good. They're all really important. The important aspect here is balance, having a balance of all of them, right? So, Th one, for example, is one of the primary drivers of immune response and protects against intracellular, microbial infections and viral infections as well. So, Th1 typically comes to the rescue early on, when your body is being invaded by a new virus or bacteria. Th2 tends to protect against things like parasites and helps drive some of the adaptive immune response as well. Th17 is a pro-inflammatory responder, also one of the early responders, works in the heat of the battle, early on in an infection, but then should be dampened over time because you don't want a continuous inflammatory response.

And, of course, Treg does a lot of that dampening. So, uncontrolled Th expression can cause disease, like I mentioned, too much Th1 or Th17 is linked to autoimmune disease. Too much Th2 is linked to allergic and

sensitivity reactions. And Treg, the regulatory component is the one that keeps the balance and tolerance between all of these T-cell functions, right? And when Treg expression is low, it leads to autoimmune conditions, severe allergies, and it leads to things like cytokine storms, and so on. Treg in the immune kinetic response is really important, and I'll touch on where that happens in the immune kinetic response.

Now, a weak microbiome leads to Th1, Th2 imbalance and typically leans towards more of a Th2 response. And so, a weak microbiome actually provides lower rate of response to pathogens, but a higher allergenic and sensitivity type of reaction, right? So, that's where the T-cell function teeters a lot. And the microbiota is responsible for stimulation and the maturation of Treg cells, which is again, the regulatory component that is critically important to finding balance between each of these T-cell type of responses. And when the microbiota is weak, we see an increased colitis risk, for example, because we're not getting a dampening of the inflammatory response in the colon. We're not getting tolerance.

We find low levels of colonic Tregs, and so T-cells in the colon actually end up attacking the tissues and commensal bacteria, when T reg is not functioning. That is a pathophysiological finding in colitis, is lower Treg expression in different sites within the colon. And that Treg expression is required for reducing the autoimmune type of response to colonic cells.

So, looking at the immune kinetics, we always start off with the innate immune response, and here are some of the key players within the innate immune response, basophils, eosinophils, neutrophils. We talked about natural killer cells and mast cells. So, these are, again, nonspecific reactors, right? They know to find their way to a site of action, but they will start just destroying everything in that region, right? They are the equivalent of using a blowtorch to kill a bunch of mosquitoes that entered your house. They're going to get the mosquitoes, but they will also do some collateral damage to the walls and things like that. So, although you need this innate immune response, that's a first, very quick response, that happens within minutes to hours, with invading pathogen. You cannot have a sustained innate immune response because that will then lead to significant tissue damage.

The innate immune reactors, that bridge the gap between innate and adaptive response are the macrophages and dendritic cells. And in particular, the dendritic cells are really, really important because these guys show up in this early phase immune response, they look for the specific antigen that's causing the problem. They'll start digesting and killing the source of the antigen, but then they also present the antigen then to T-cells and B-cells, which will start mounting an adaptive immune response, right? And this adaptive immune response is not the inflammatory part. This part of the immune response is the inflammatory part, this is the part that you feel when you sick. If you've picked up a new virus and you got a fever or you started getting an itchy throat, you started getting shortness of breath, you started getting GI effects, loose stool, and so on.

All of those are driven by this innate part of the immune response, right? But this innate part of the immune response should be shuttling towards adaptive immune response, typically within a day or two. So, then you'll have a period of time where you have both, you have an innate response going on still, because of higher viral load and titers. And these cells continuously being activated and trying to control the amount of viral load. And it's taking time for the adaptive immune response to gear up and to start producing the neutralizing antibodies that are going to eventually neutralize all of the incoming pathogen, right?

So, you'll have a period of time where you feel nothing. Where the innate immune system is starting to take over. Then the inflammatory response will kick in as you're getting towards the late part of the innate immune response, when the macrophages and dendritic cells are doing their job you'll feel a lot of the inflammation. Now, the severity of the response and the infection will dictate what the symptoms feel like. In many cases, the pathogen can be completely taken care of with very minimal inflammatory ...

The pathogen can be completely taken care of with very minimal inflammatory response that's not even realized because the immune system is really functioning in tip-top shape. And then you shuttle very quickly to adaptive immune response. You start getting antibodies neutralizing the pathogen without really ever feeling

much in terms of the inflammatory response at all. One of the key things that has to occur during this transition, this late innate to the early adaptive is there has to be an anti-inflammatory response that kicks in to start to dampen this initial inflammatory reaction for two main reasons. Number one, because remember this inflammatory reaction also damages your own cells. So your body has to have a way of starting to tone down that inflammatory response, so you don't end up with a net of your own cells getting damaged through the process.

Then the other reason for that is because eventually if you keep having inflammatory damage, you'll keep damaging your own tissues and releasing peptides of your own tissues. And then the dendritic cells and macrophages can accidentally swallow those peptides of our own tissue and present them to T cells and B cells, as antigen and the T cells and B cells need to mount immune responses to. That self antigen presentation occurs in areas where there's lots and lots of inflammatory damage and your own tissues getting damaged and releasing peptides and antigens, or what may be perceived as antigens.

That will elicit an auto immune response. So that's a bystander effect, your own tissue becomes a bystander in the battle because your own tissue gets damaged. And then antigen presenting cells accidentally present your own tissues, your own peptides as antigens that the B cells and T cells have to react to.

So that's another really important reason why we have to dampen down the inflammatory response to move to a healthy, adaptive response. So keep in mind that there is an inflammatory response here, which is needed, but as it shuttles through to the adaptive response, the anti-inflammation process is really important to make sure the immune system is functioning properly. So looking a little bit more detail in the early part of the innate immune response, imagine a virus enters your system, and then the virus starts entering cells like epithelial cells, for example, in the airway. This is a very early part of the illness. This is what's happening in the first couple of hours. As the cells get damaged, the epithelial cells can start releasing some inflammatory cytokines. These inflammatory cytokines will then start recruiting localized macrophages to show up and start swallowing up the cells.

The next thing that shows up and it starts controlling the release of more virus because now it's eating up virus infected cells before the cells can burst open and release more virus. So this becomes a kinetic game of how quickly can the macrophages eat up a lot of the virus infected cells so that you don't get a huge load of new virus circulating around in your system there and then infecting more and more cells. So that's the first part that again, happens within hours. Now, five, six, seven hours later, you've got dendritic cells that are now turned on and they really start the more robust part of the immune response. Dendritic cells are the ones that are going to facilitate the antigen presenting to T cells and then of course, B cells ultimately through T helper cells, and eventually you'll start getting antibody production and starting to get clearance of the virus.

Now, this is the early stages of innate immune response. This is a later stage of innate immune response. And then of course, when you get down here to B cell activation, you're going into the adaptive immune response as well. So remember early innate response, then the late part of the innate response, especially when dendritic cells start getting involved that's when you start to see a lot of the inflammatory response going on as well, which is important for that part of recruiting immune cells, proliferating T cells and B cells so they can do their work. A lot of the inflammatory cytokines do that proliferation signaling, recruiting more innate cells to control larger and larger chunks of infection. And all of the signaling that's important for the immune system comes through these inflammatory mediators. But then the next part is you do have to move to the early adaptive, and then you have to turn on the anti-inflammation pathways so that this inflammatory processes don't do a net degree of damage to the tissues themselves.

And then eventually you get long-term adaptive response, which are B cells that then mature into plasma cells. These plasma cells now produce antibodies that are highly specific to that particular pathogen. And then eventually that provides true long-term immunity. That's how you have long-term immunity where next time you encounter this pathogen, you won't even feel it or realize it because what happens the next time you

encounter it is a pathogen enters back again, the macrophages will still do their job, but dendritic cells will be able to kick in with their now equipped pattern recognition receptors. So one of the things I forgot to mention is every time a dendritic cell sees a new antigen or a pathogen, it develops a new set of pathogen recognition receptors. So it houses within itself, all of these different types of pattern recognition receptors. So it can very quickly recognize a whole of different pathogens.

So now you have dendritic cells circulating around that has receptor recognition of this previously seen infectious virus. And then this dendritic cell can get turned on faster and start presenting the antigens to your B cells, your T helper cells, and then eventually your B cells faster. So then the plasma cells that make the antibodies against this specific antigen start to activate much faster. This can now happen within a matter of a day or two versus earlier on the first time you encountered this particular pathogen to get to the plasma cell level, might've been six, seven, eight days.

Now, it can happen because these plasma cells already exists within one day and you won't even notice that you've ever been infected. Now, all of these processes, all of this kinetic, this early innate response, late innate response, the inflammatory signaling that's so critical to facilitate the immune response, the shuttling to an early adaptive response, the anti-inflammatory response as you start getting adaptive immune system going the long-term adaptive response, and finally the long-term true immunity. All of these things are dependent on the microbiome. And that's what I want to illustrate for you in the next upcoming slides.

Now, to really understand immune response and what's happening, we have to talk about the mucosa because the mucosa is the largest surface area in the body. It's about 400 square meters. If you were able to fold out all of your mucosal surface in the body, compare that to the skin, which is two square meters in the body, you've got almost 200 times the size of the dermal layer in mucosal layers inside the body. It covers every orifice in your system. So any way that a pathogen can enter your system, it has to enter through a mucosal layer.

PART 1 OF 3 ENDS [00:25:04]

Michael Roesslein:

Hold on, I got to interject. You said 400 square meters.

Kiran Krishnan:

Yeah.

Michael Roesslein:

Okay. For Americans, that is 4,305 square feet.

Kiran Krishnan:

Isn't that [inaudible]?

Michael Roesslein:

So for people who have homes or apartments, which would probably be everyone on here and can translate that into size of home or apartment flooring, that's 4,300 square feet. I just typed that into a calculator for mind-blowing [inaudible], because America doesn't understand square meters. All right, go ahead. That's all.

Kiran Krishnan:

No, it's important. I'm glad you mentioned that because when you think about it, like a 4,300 square foot house is a massive house.

Michael Roesslein:

That's a big house.

Kiran Krishnan:

Right, it's a big house. Most people are living in 1,000 square foot apartments. And so your mucosal system is that big. It's a mansion, if you will, it's an immune mansion in your body and it's massive. It covers every office. And it's the largest portion of the immune system. Most of it is found in the gut. So most of that mucosa is found in the gut. Now, it's... Let me make sure the slide's going to advance. And it lines every entry way into the body, the respiratory tract and digestive track, the reproductive track, through the skin, even if something penetrates through your skin, it will encounter a mucosal system once it gets past the top layers of the skin.

So every pathogen that enters your body basically enters into the mucosal system. Now, and that's really important to understand, and you'll know why in a second, but also keep in mind that the mucosal system then because it is the entryway into the body becomes a largest site of immune sampling in the body. Everything that possibly requires an immune response has to go through this important mucosal layers that are illustrated here. And your immune system has to sample what that thing is and decide whether or not it has to mount an immune response to it. That's the largest site of immune sampling. So the function of the mucosal immune system's absolutely critical to the function of your entire immune response. And the crazy thing about the mucosa is that the mucosa is covered in microbes. Every part of the mucosa in every part of your body, that 4,000 or so square feet of mucosa in your body is all covered with microbes, is covered every square meter of it.

So you've got this huge population density problem. So when you think about the job of the immune system, this is where you have to really appreciate the crosstalk and the connectivity between the microbiome and the immune system because imagine the mucosa is a primary site of sampling. Every pathogen has to enter the mucosa and the mucosa is completely loaded with microbes, with bacteria, viruses, fungi, and so on. So every one of these square millimeters is actually covered with microbes. You have about 40 trillion or more microbial cells sitting in your mucosa. All of these commensal viruses, bacteria, and all that are sitting in the mucosa, 40 trillion or so of them sitting in that mucosal structure. You've got only about 200 million immune cells to survey and monitor this entire region that is covered with microbes already. So you've got about 200,000 times more microbial cells than immune cells available to the entire system.

That's a mind-boggling task for the immune system. So think about it, the immune system's job is to monitor the mucosal surfaces, what things are entering. And it's supposed to figure out what his friend and what is foe and what to attack and what not to attack, all the while the area that it's monitoring is already covered in bacteria and viruses and fungi to the order of 200,000 times higher than there are immune cells to monitor that area. So the only possible way that your immune system can even function is if there is some sort of neighborhood watch going on. Because you could have little microbes pop in or viruses pop in in this sea of microbes and your immune system would have no idea they are even there because you only have 200 million immune cells monitoring the entire ecosystem of over 40 trillion microbial cells.

The only possible way your immune system can even start to function is if you have a neighborhood watch system where your microbes that inhabit the mucosa are signaling to your immune system what is happening in that ecosystem? That part is that thing called the microbiome immune crosstalk. Your immune system cannot function without the microbiome immune crosstalk. I want people to understand that whole problem really well because that will then help you illustrate how important of a role the microbiome plays in your

immune function. Just understanding this part alone is enough to understand the scale in which your microbiome has to help the immune system function.

We keep talking about immune stimulants and immune support. We keep thinking about compounds that help your immune system function. We're not talking enough about the role that the microbiome plays in even allowing your immune system to exist and conduct basic functions in the sea of microbes that exist inside your body. So this microbiome immune crosstalk is at the core of how the immune system functions. The immune system actually would not exist if it wasn't for the microbiome. That's important and I'm not going to go through this whole schematic that is somebody who [crosstalk].

Michael Roesslein:

Yeah. I just got a headache and a flashback to my master's program.

Kiran Krishnan:

Right. But-

Michael Roesslein:

Which one was the one in the joker hat?

Kiran Krishnan:

Oh, is that funny?

Michael Roesslein:

Yeah. I see that in the bottom left, that was the boss.

Kiran Krishnan:

I was trying to figure out what is this picture from? And where I found it, didn't really illustrate what this picture is from or this seems like a crazy crowd.

Michael Roesslein:

I would say [inaudible] they have coats on and way too much clothes. So-

Kiran Krishnan:

Right. And it looks like a much older population in general when you look at it. So it's interesting. [crosstalk].

Michael Roesslein:

Yeah. I mean, maybe it was a bunch of people trying to look like the microbiome.

Kiran Krishnan:

Right. Exactly. So I'm not going to talk through this schematic, but this is one of many, many you can find that really show a complicated relationship between the microbiome and the immune system. What I will do is go through very specific examples of viral infections, for example, and how certain parts of the microbiome play a role in signaling to the immune system. So that's how I'll go through it for you so you have a sense of how the microbiome really orchestrates an immune response. So and before we can even touch on that, we have to talk about the role of the microbiome in the development of secondary lymphoid organs that manage all of

your immune tissue. So your lymphoid organs are section to primary and secondary lymphoid organs and tissues.

The primary lymphoid organs are the ones that we develop ourselves. We code for, we have the genetic components to develop them and that's the thymus and the bone marrow. Outside of the thymus and the bone marrow, all of the other immune organs, all of the other immune tissue, the lymph nodes, the tonsils, the adenoids, the bronchus-associated lymphoid tissue, all of the lymph nodes all over your body, your spleen, your lamina propria in the gut, your Peyer's patches, your mesenteric lymph nodes, your genital lymph tissue. All of those tissues are all matured and develop by the microbiome by signals from the microbiome.

Studies show in gnobiotic mice or mice that are treated with heavy levels of antibiotics is you get disrupted development of all of these secondary lymphoid tissues. So you might develop the thymus and the bone marrow, but you will not develop appropriately the secondary lymphoid tissues. And this is seen in microbiome disrupted conditions and models. Now, of course, this is not something you can study very well in humans, but they've done extensive pathophysiology and mechanistic studies of this in various types of animal models. So right off the bat, just the presence of the vast majority of your lymphoid tissues and organs, their maturation and their function is dependent on having diverse microbiome over a period of time throughout the development stage.

But let's go through some examples of how commensal microbiota are required in fighting a viral infection, for example. So we'll talk about a norovirus infection, for example, lactobacilli, some of the commensal lactobacilli and other commensal bacteria trigger the release of things like interferon beta, and interferon gamma, which then alerts the innate immune system to the presence of the virus.

Remember in that sea microbes, you might have a norovirus show up, but your immune system would never know it's there because it's sitting in a sea of 200,000 times more microbial cells than immune cells that can actually monitor all of this space. So the only way the immune system would even know that that virus has shown up is the commensal microbes detect the presence of the virus, and then start releasing these cytokines that then trigger the innate immune system to move to that location. And then certain nutrients like vitamin A, for example, provides a substrate for these commensal bacteria to make the interferons. But that's where the nutrient comes into help facilitate some of this response. But if you don't have adequate commensal bacteria, you're not getting that response anyway.

Another example in rotavirus infection, for example, a bacterial flagellin from commensal bacteria can activate the expression of pattern recognition receptors. So those are those receptors that dendritic cells and all hold in them to recognize patterns on pathogens that your body's tends just to see over and over again. And this triggers the expression of something called Toll-like receptor-5, which then stimulates the release of interleukin-22 and interleukin-18 because remember a rotavirus is a gut infection.

So one of the things that occurs is the intestinal epithelium gets infected and damaged by the virus. And then the flagellin from bacteria will stimulate more pattern recognition receptors so that your immune system can start to recognize commensals in that area and not the presence of the virus and start dampening immune response so that your body can start to heal. And that is done by the release of interleukin-22, which helps repair the damaged epithelial cells and interleukin-18, which induces apoptosis in the infected epithelial cells so they can die off and a new epithelial cell can be put in its place. So this is an example kind of the late phase, innate moving into the adaptive response when you want to start dampening the inflammatory response in the body.

The intestinal microbiota plays a role in that as well. In the case of rotavirus infection, additionally, things like bifidobacteria breve, for example, and the presence of oligosaccharides like galactooligosaccharides and fructooligosaccharides have been shown to prevent these infections by increasing the expression of interferon gamma IL-14 [inaudible] Toll-like receptor-2, which then increases mucosal immune defenses. So this would be an early part of the innate immune response, which starts recruiting immune cells to the site of infection

when the rotavirus shows up. So now you've got these bacteria and these gut associated oligosaccharides, these beneficial oligosaccharides that conduct the facilitating of the cytokines that bring immune defense cells to that part of the mucosa to neutralize the virus.

And then once the virus has been neutralized, the flagellin from other bacteria start dampening the inflammatory response and allow for the repair so that the intestinal epithelium doesn't get overtly damaged during the process. Commensal bacteria also produce things like short-chain fatty acids, which is required to increase and maintain the mucus production, which is again, the barrier system that prevents all of these microbes from entering into our cellular system and into our blood system, which then creates a stronger barrier against pathogen.

In addition, these commensals also increase the synthesis of antiviral compounds like reactive oxygen species, defensins and so on which prevents localized viral infection. So when your commensal microbiota notices a virus, for example, entering the space, an unknown virus that it's not familiar with, it will then stimulate the production of antiviral compounds by your intestinal epithelial cells. So it'll send signals through the mucosa, to the intestinal epithelial cells to increase the secretion and production of antiviral compounds like reactive oxygen species and defensins, for example, so that you can start quenching the viral replication right there in that localized region. That signaling again comes from the microbiota. Another example is during influenza infection, commensal bacteria will trigger the release of inflammasomes. Inflammasomes become really important to controlling influenza infection that inflammasome acts as a potent defense against the influenza replication.

So this inflammasome then induce dendritic cell migration to the area and then the dendritic cells will migrate to the localized lymph nodes where it starts stimulating specific T cells and B cells that exists against the influenza virus itself. And this occurs in localized tissues like the lungs, thereby shuttling the response more to a potent, less damaging early adaptive immune response. So to go over that again, influenza enters the system, one of the responses that the commensal bacteria will have in recognizing the presence of this viral pathogen is by triggering the release of these inflammasomes. These inflammasomes then recruit dendritic cells to that area.

Dendritic cells remember are the antigen presenting cells that then trigger T cells and B cells. So dendritic cells come to the area. They start grabbing antigens from the influenza and influenza-infected cells. They will then migrate to local lymph nodes near the lung tissue, where they will stimulate an influenza specific T cell response. The T cells will then stimulate B cells, and then cytotoxic T cells will come and start attacking influenza-infected cells while the B cells produce antibodies against the virus itself. So that whole process, that whole way of diminishing the influenza response starts with the triggering of the inflammasome by commensal bacteria that recognize the presence of the virus itself.

Other ways, for example, the gut microbiota can regulate a respiratory mucosal immune response in response to influenza infection through the simulation of secretory IgA and Th1 activation, and then the activation of and priming of cytotoxic T cells. They do this again through interferon signaling and inflammasome signaling. So the microbiota is doing that in the respiratory mucosa itself, the gut microbiota. So the gut microbiota is responding to a disruption in the respiratory mucosa by the presence of a pathogen like influenza. Then the gut microbiota stimulates the secretion of more IgA into the respiratory mucosa and activates Th1 and cytotoxic T cells to go to that spot and start fighting the infection. That's the gut microbiota doing that-

And start fighting the infection. That's the gut microbiota doing that for the lungs. And that's interesting because the gut microbiota can speak to the lungs through a connection with the lung microbiota itself.

So, another example of this is when the influenza virus is present in the lungs, the gut commensal bacteria increase the presence of innate immune cells into the lungs by causing the release of these types of cytokines, interleukin 1 alpha, beta 12, interferon gamma, interleukin 33. So, that's the gut microbiota going, "hey, we

need to increase these inflammatory signals to recruit more innate immune actors into the lungs." So, this causes more natural killer cells, dendritic cells, macrophages, and all that to end up in the lungs.

But then when the virus is low and not present, the gut commensals do the exact opposite. They stimulate the release of the anti-inflammatory interleukin 10, which then dampens any sort of inflammatory response in the lungs, because we don't want to end up with a net damage to the lung tissue. Because if the influenza infection and the innate immune response to that infection is allowed to take hold and carry on for too long, it may start to control the infection itself, but it'll also do damage to the lung tissue.

So, the stopping of that overt response of the innate immune system also comes from the gut commensal bacteria. But how does the gut commensal bacteria know what's going on in the lungs? Well, this really interesting balancing act is an example of the gut-lung axis, where microbes in the lungs actually communicate with microbes in the gut to inform of the presence of pathogens. So, microbes in your lungs will see the pathogen first, and then will signal through other cytokines that will be picked up by microbes in the gut. And then the microbes in the gut, which are managing the central command center for immune response, will recruit all of the immune actors to the lungs itself.

Now, there are other commensal microbes in the lungs that play important role. For example, Staph aureus exists on the airway surfaces and it has the capability of helping recruit monocytes, which then mature into macrophages through the activation of toll-like receptor two during a lung infection. And this leads to eventually a reduction in the damage by the acute infection in itself. Because eventually, as these commensal bacteria start to notice that there are lower and lower levels of the pathogen, they will start recruiting more of the cytokines to dampen the inflammatory response once the innate actors are already there.

Respiratory commensal bacteria called "Corneum bacteria" can modulate toll-like receptor three antiviral response of things like RSV, the Syncytial virus, respiratory virus, and enhance the production of things like TNF alpha, interleukin six, interferon gamma, interferon beta, all of that through increasing T-cell proliferation. So your commensal bacteria in your lungs are creating a cytokine response that then can be picked up by local immune cells. But it's also picked up by your gut microbiota. And then the gut microbiota send more recruits to that site of action so that your body has a nice, profound impact. But then ultimately your local microbiota in the lungs and your gut microbiota will start stimulating the anti-inflammatory response. So you don't end up with that inflammatory damage in that tissue. You don't end up with that cytokine storm type of progression, even things like butyrate from commensal bacteria will lower inflammatory damage in the post early innate activation. And it does it through butyrate binding through G protein-coupled receptors, which are receptors on cell surfaces that can stimulate further expression of things like interleukin 22, which is again a dampening repair type of interleukin.

So your gut commensal bacteria plays such an important role in detecting the presence of an invading pathogen, eliciting the important innate immune response to the presence of that pathogen, and then shuttling the immune response from that innate response to adaptive in the middle of it, dampening the inflammatory damage so that your tissues themselves don't get damaged overtly and then your immune system can move to that better protective longterm memory type of immune response in the adaptive side.

Another example of this is in the vaginal canal. There studies that show that lactoBacillus crispatus, when it's the dominant bacteria in the vaginal mucosa in women, this is a study in South African women, they show that higher levels of lactoBacillus crispatus was able to decrease HIV1 infection by directly inhibiting viral function itself. And then the lactoBacilli in general, in the vaginal canal can inhibit viral replication through the lactic acid they produce and through the interleukins and cytokines that they induce, they can actually help reduce the infectivity of HIV exposure.

So a lot of what I talked about is indirect effects from the microbiome, helping the immune system recognize that there's a pathogen present and then helping shuttle the immune system in various ways to get the innate immune reactors there. Once the innate immune reactors are there and starting to act shuttling it more

towards an adaptive immune response. So you have that longer term immunity. All of that is being done by signals from the microbiota, both locally in local tissues, but then also through the central command center in the gut. But then there are commensal microbes that also tend to have a direct effect on viral pathogens for example. And these are some of our favorite bacteria that we talk about all the time.

For example, Bacillus. Bacillus subtilis has been shown to produce these surfactants. And this study showed that Bacillus subtilis and the surfactant that it produced, prevents the invasion of this specific type of coronavirus in the transmission to gastroenteritis. So this is the prevention of the cell entering into the epithelial cells and causing the infection. Let me note, this is not the SARS COV-2 that we're dealing with right now. So we're not saying that this is a way of preventing SARS COV-2, but this is another Coronavirus that has been tested against the surfactant that is produced by commensal Bacillus subtilis. So this is an example of a commensal bacteria that actually directly produces antiviral compounds that can affect it.

Another example of that with Bacillus subtilis anti-influenza activity, Bacillus subtilis produces a powerful antiviral compound called P18, that completely neutralizes influenza virus in vitro. This has been studied in vitro, not in humans, but it shows that these bacteria have the capability, not only of detecting the presence of these pathogens, but some of these bacteria, like the Bacillus species can actually produce antimicrobial and antiviral compounds to actually directly target and reduce the presence and the infectivity of the pathogen itself.

Here's another interesting one with the antiviral activity of an antimicrobial lipopeptide from Bacillus. So Bacillus produces this antimicrobial local peptide, which contains both the surfactant and a fengycin. This also has a strong antiviral effect, which effectively inactivates viruses. And they looked at a number of viruses like PRV, this Porcine parvovirus, parvovirus and dogs I've seen studies on. Newcastle disease, virus, infectious bruise cell disease virus, and so on. So they looked at the capability of this combination of compounds that are produced by commensal Bacillus against viruses. And they find lots of really interesting activity. And Bacillus also produces another antiviral called [inaudible], which is actually, this was isolated from honey and it's found in honey, and it's sows that this Lavonne, this antimicrobial compound, which is produced by Bacillus subtilis inhibits various forms of adenovirus, including respiratory RNA viruses, like H5N1 and enteric Edna virus type 40, which is a DNA virus.

So this was really interesting because as you guys know well, that bacillus is a commensal bacteria. So you've got commensal bacteria that do all of this important immune signaling to alert the immune system, to the presence of pathogens, to recruit innate immune cells to the area of action, so that innate immune cells can star the immune process. And then signals from the microbiota also shuttle the immune system from that innate to the adaptive response, where you get the non-damaging longterm, robust immunity against that pathogen. And then here are other commensals, especially in the Bacillus genus, that actually directly produce antimicrobials and antivirals that help the body defend against pathogens. And then overall, and this is some of the latest studies, this study, the second one here, was published just in may of this year. This very month itself, where they're looking at the fitness of the immune system is dictated by the microbiome.

This is a study from I think, 2012. And this is more of like a follow-up study on some of the similar topics they concluded that collectively, the data indicates that commensal derived signals provide tonic immune stimulation that establishes the activation threshold of the innate immune system required for optimal antiviral immunity. This is the conclusion from the study, and that's really important because remember that the activation energy, the understanding of the basal level of microbial existence, the presence of pathogens, the ability to kind of rear up the immune response, all of that seems to be dictated by signals from commensal bacteria. This latest study here showed that type one interferon that is actually produced by the microbiota, signaling from the microbiome, was shown to be required to tone and poise dendritic cells to respond to pathogen entry.

Especially important for antiviral function, without the signal from the microbiome dendritic cells cannot Mount an immune response. So this is really important. You might have dendritic cells in your system. You might have the nutrients that the dendritic cell may require to conduct its function, but without these signals from the microbiome, in this case type one interferon, the dendritic cells cannot actually function and cannot actually go after the pathogens that are now present in the system. So the microbiome communication and signaling is absolutely critical to the activation of the immune system. And in this particular study, they went through and they did a bunch of animal model studies where they start to knock out or diminish the microbiome. And they find that the dendritic cells can not respond to the presence of pathogens. Even then, if they injected interferon, it didn't have the same response without the interferon coming naturally from the microbiota itself.

So the energetics and the ability of the immune system to function depends highly on the presence of the microbiota itself. We also know that disruptions to the microbiota, a lead like dysbiosis, leads to disruptive immune response. There's lots of studies on antibiotics weakening antiviral response in the immune system. This one shows "Antibiotics found to weaken in the body's ability to fight off disease." "Collateral damage." "Detrimental effects of antibodies on the development of protective immune memory." "Antibiotics bug the immune response." So lots and lots of studies showing when you damage the microbiome through something like antibiotics and lots of studies have been done on antibiotics. That's why I'm showing them not to pick on antibiotics. Anything that really damages the microbiota in a significant way, like glyphosate in a Roundup, things like dysbiosis driven by poor lifestyle, all of those things that lead to dysbiosis disrupt the immune response in the body and disrupts kind of normal basal immune response in a very significant way.

It cannot be seen more clearly than in the case of cancer immunotherapy. Because this is a big area of research right now, because it could save thousands and thousands of lives annually. So disruption to immune response due to dysbiosis has been shown in cancer Immunotherapy. What is cancer immunotherapy? Well, some of the most severe forms of cancer, things like lung, Non-Small Cell Lung Cancer, Melanoma that tend to have high mortality rates, can have success when being treated through immunotherapy. Immunotherapy, which is called anti PD-L1 checkpoint therapy, those therapies basically enhance the immune response against the cancer cells, that's what the immunotherapy is doing. It's basically trying to improve the T cell response against the tumor. And what they find is that if you take a hundred people who have melanoma or a hundred people who have a Non-Small Cell Lung Cancer, and you put them through immunotherapy, about 20, 25% of them will have a beautiful response to it.

Meaning, the cancer will be basically gone in about six months of therapy and rarely does it come back. There's almost no side effects and everything is hunky Dory. Everything works beautifully well, but that's only in about 20 to 25% of people. In another about 60 or so percent of people, they get no response at all. And then in a few percentage, in about five to 10% get really a toxigenic response. So then the big question in this whole immunotherapy is, "what is going on?" "What is the difference between the 2020 5% they get this beautiful response and a cancer is completely gone versus a 65, 70% that get almost no response at all." And they find that the gut microbiota plays a critical role in the antitumor immune response. And there's increasing data that shows that antibiotics treatment prior to immunotherapy changes the composition of the gut microbiota that affects the efficacy of these checkpoint inhibitors.

So what they've been able to show, and we actually got into this space with the idea of improving and modulating the microbiome prior to checkpoint therapy, so that we may be able to get a better response to checkpoint therapy by fixing dysbiosis. That's the work that we started doing with, with Arthur Frankel now on hold, of course, because of the COVID-19, but they've shown this paper shows the meta-analysis that the findings of a meta-analysis indicate that antibiotic use is negatively associated with outcomes and progression free outcomes in cancer patients treated with immunotherapy. So survival and progression free outcomes in immunotherapy is negatively associated with the use of antibiotics before the start of immunotherapy. So this is a beautiful mechanism to show that the immune system has an amazing capability of controlling

dysfunctions, like tumor productive progression, but when you disrupt the microbiome, it completely screws up that response of the immune system.

So that's one of the most important messages I want you guys all to understand from this particular talk, is that not only does the microbiome play a significant role in the signaling and the activation of the immune system and all that, but a disruptive microbiome is at the core of a disrupted immune response to anything. Whether it's tumor cells, viruses, bacteria, and so on. So now this next part is important because this plays a really important role, especially in the Western world, because remember the language used by the microbiome to communicate with the immune system is typically focused in these cytokines and interleukins and chemokines. So interleukin one alpha, interleukin one beta, interferon gamma, interferon beta, IL-12, TNF alpha, interleukin six. These are the signals that the microbiome is using to recruit and activate and alert the immune system to the presence of pathogens in all kinds of locations within the body. Whether it's localized in somewhere like the upper respiratory track or it's in the gut, it doesn't matter.

These are the signals that the microbiome is using in order to trigger immune response in the body. The problem here is you guys will all be familiar, if you've listened to other talks that I've done, the many talks that you hear in "Rebel Health Tribe", and so on. These are also the same players in chronic disease. Remember, 50% of Americans have at least one chronic disease. And one in four Americans have two or more chronic diseases. These are the main chronic diseases within Americans: heart disease, cancers, chronic lung disease, Alzheimer's, strokes, type 2 diabetes. Chronic inflammation is the driver of all of these chronic diseases. And these are the same players in chronic inflammation. So chronic inflammation, driven by these cytokines, chemokines, interleukins, are the root cause of the signaling that the microbiome uses for immune activation.

Now, why is this important to know? Because it leads to loss of signaling. And I'll explain that in a second. So remember when you have a gut that's leaky like this, you've got all kinds of disruptions that occur to the immune system. For one, the mucosal immune system, the largest site of sampling in your body, the area where your immune system, through the help of the microbiome, decides what type of immune response it's going to elicit to the antigen, the pathogen that it's looking at. That immune system gets completely disrupted when your gut is leaky. When you have infiltration of commensal bacteria into the inner part of the mucosa, this completely disrupts mucosal immune response. Everything gets an inflammatory response. And then, other opportunistic pathogens in the system can take advantage. For example, segmented filamentous bacteria can increase inflammatory damage of tissue and can drive autoimmune development by being allowed to migrate into this inner sanctum and even past the barrier system in leaky gut.

Things like HSV, herpes simplex virus, and cytomegalovirus, when they are allowed to proliferate because of this inflammatory situation going on because of leaky gut, they tend to infect T cells, macrophages and monocytes, right? So the infection of the T cells and macrophages and monocytes, obviously it attenuates really important players in the immune system. Epstein BARR virus, for example, when it's allowed to proliferate because of this chronic low grade inflammation, and this inflammatory picture during leaky gut, actually will infect B cells. So now you've got these B cells circulating around here in the lamina propria, in the basal lateral circulation, that are there to protect the body against future encounters with pathogens that it produces antibodies to. And then because of this chronic dysfunction through leaky gut, you get an activation of Epstein BARR virus, and then that Epstein BARR virus goes and infects the B cell that is there to protect against other pathogens.

So now the susceptibility of infection by the pathogen that is coded for by the B cell, becomes increased. Because now your B cell is compromised. Also, another really interesting thing. Remember a big driver of dysbiosis in the gut microbiome, and then a big driver of endotoxemia and leaky gut is that [inaudible] to gram negative bacteria. Gram negative bacteria are the ones that contain LPS. So you end up getting higher and higher levels of free LPS in the lumen of the gut and in the mucosa. And when you have higher levels of free LPS in the mucosa, there are a number of viral pathogens that can actually use LPS as a way of entering cells.

Because our immune cells and our epithelial cells are designed to engulf LPS when it sees it as a way of trying to protect the body from the inflammatory damage that LPS causes. Then the viruses, what they do is they attach an LPS to themselves so then they get accidentally engulfed, or in their purposes, engulfed, but then our immune system accidentally engulfs them. And then the virus can start trying to replicate in the cell that engulfed them. So they will use LPS as a carrier, into other cells within the system. And then of course, chronic inflammation can drown out the immune signals. So that's one of the things I mentioned in the last slide, the drowning out off of the immune signals. That's the part I want to emphasize in the second, because it's important that people understand this.

So remember, when you've got an info invading pathogen, it's like a flame. The presence of the flame will create a smoke. And that smoke is a disruption to the ecosystem. That disruption to the ecosystem can be picked up by the microbiome, which is like a smoke detector. So then the microbiome sees that there's an invading pathogen and it's causing disruption. It then signals to the immune system through cytokines, that's how it sounds it's alarm. That's the analogy that the smoke detector, the microbiome is causing an alarm and it does it through interleukins and cytokines like IL-1, IL-6, interferon, and so on.

Then when your immune system, the firefighters hear that alarm, they know to come to that site of action and start eliciting the immune response. This is what is supposed to happen when your body encounters a new pathogen. The problem is when you have chronic low grade inflammation, what you tend to have is an overt presence of this cytokine response all over the body. You have it either in localized tissue, you have it systemically. You have systemic IL-6, systemic TNF alpha, systemic interferon gamma, systemic interleukin-1, always being propagated. You've got high levels of this alarm signal going on all the time.

So that in this scenario, when an invading pathogen comes in and the microbiome detects the presence of that invading pathogen, the microbiome sounds the alarm because of the invading pathogen, this alarm signal gets completely lost because this signal is all over the place. The immune system is constantly reacting to signals coming from all kinds of tissues in the body, because of the chronic low grade inflammation. So the really important potent signals from the microbiome to tell the immune system that a pathogen is present, gets lost in the mileu of lots of signaling from an inflammatory standpoint.

So that is a really important part to understand. How chronic low grade inflammation attenuates immune response to the presence of pathogens. Because the microbiome uses the exact same signals that are present in chronic low grade inflammation to try to signal the immune system. And if that signal is really loud and that signal is present all over the body, then the signal from the microbiome that a pathogen is there gets completely lost in that milieu. So it's no surprise that the mortality rates for something like COVID-19, that people are being exposed to, are really high among people that have chronic low grade inflammation. So the non pre-existing mortality rate is around 1%. Which compared to something like the flu...

The rate is around one percent, which compared to something like the flu is in itself is high, and this is among symptomatic people. So these are among people that are symptomatic. This number is lower when you just take the population as a whole and include people that are asymptomatic. So among symptomatic people, it's about one percent.

But among people with cardiovascular disease, it's ten times higher, the mortality rate. Among people with diabetes the mortality rate is seven times higher. Among chronic respiratory disease, hypertension, cancer, five to six times higher.

So that chronic inflammatory signal that is going on in the body is dampening the immune system's ability to understand that this new pathogen is there and control it and sequester it in a reasonable amount of time so that the pathogen doesn't cause huge amounts of damage within the system. So that is the really important part here.

Again, if you've listened to my talks before, even though we're talking about the immune system right now, the microbiome is the key to reducing the chronic low-grade inflammation in these conditions as well. The microbiome plays such an important role because leaky gut is the biggest driver of the chronic low-grade inflammation signal from these comorbidities.

So that is a really important thing that people need to really understand as we talk about resilience. When we talk about resilience of our immune system, it's not just about loading yourself up with vitamin C and zinc and so on. Those things are important for immune function, but it's about dampening and reducing the loud overbearing alarm calls from these inflammatory cytokines that are going on in the body due to the chronic low-grade inflammation that is so persistent within the US population. That is a really important part of it.

So let's jump to some quick conclusions. A healthy, diverse microbiome provides critical signaling and energetics for the immune system to elicit a proper immune response. You cannot elicit a proper immune response without a healthy, diverse microbiome.

Higher pathogen load clearly disrupts the immune response. There's studies that show that when you have higher pathobiome with relative abundances higher than the commensal bacteria, you will have disrupted immune responses because the pathogens do not want to trigger the immune system. So they have ways of working around immune stimulation, immune triggering, and of course they will not signal the immune system when other pathogens show up as well. So pathogens tend to do a good job becoming friends with one another to allow the existence of each other within the system.

A disrupted microbiome leads to improper and attenuated immune response. This is seen very clearly in studies on antibiotic damage to the microbiota, to in the case of immunotherapy when you use antibiotics first, there's lots and lots of indications that disrupted and dysbiotic gut leads to improper and ineffective immune response.

A disrupted microbiome is also the most prevalent source of chronic low-grade inflammation. So you're getting a double whammy here. If you have severe dysbiosis, you likely have high degrees or higher degrees of chronic low-grade inflammation, and when you have higher degrees of chronic low-grade inflammation the signals from the microbiome to the immune system are drowned out and lost anyway. That increases the susceptibility to more profound infection when you encounter a new pathogen, because the control mechanisms to stop the pathogen early on are not working and are not functioning appropriately.

Immune-support ingredients, things like vitamin C, D and zinc, are important for immune function, but they cannot overcome a dysfunctional microbiome. So it has to be used in conjunction with things that modulate the microbiome. This is the thing that I keep trying to understand with even just my friends and family that ask me thousands of questions about all this stuff. People will feel that-

PART 2 OF 3 ENDS [00:50:04]

Michael Roesslein:

I'm sure you haven't become more popular at all in the last day or so.

Kiran Krishnan:

Right. The most popular man.

Michael Roesslein:

Hey Kiran, we haven't talked in forever. How are you doing? How's the family. I've got a couple questions for you.

Kiran Krishnan:

Yes. Do you have two hours, please?

Michael Roesslein:

Yeah. Can you please talk to me until next Wednesday.

Kiran Krishnan:

The think I keep emphasizing to them is you absolutely should be making sure your vitamin D levels are adequate, your zinc and vitamin C and all that. But they also will not overcome the dysfunction that's driven by dysbiosis in the immune system. So you have to fix dysbiosis as well. You cannot just walk around loaded up with vitamin C thinking that you're supporting your immune system adequately enough. You have to think about the whole picture of how the immune system responds.

The success of preventative measures, things like vaccines, people talk a lot about vaccines, and of course the powers that be mentioned the vaccine is going to be a big savior. But again, a vaccine is not the illicitor. It doesn't create the immune response. The microbiome still has to be the thing that elicits the immune response to the presence of the vaccine.

The vaccine itself is not a medicine. The vaccine itself is not immunity. You can inject an antigen into your system, the immune system has to be functioning properly in order for your immune system to actually respond to that antigen that's being injected and then elicit immunity against it.

That's one of the reasons in my view that the flu vaccine doesn't work very well in general, because number one, you're injecting it into someone's arm, which is not where you typically sample influenza type of viruses. They come through the respiratory mucosa.

Then the second part is if you don't have the adequate immune response to the presence of that antigen, you are not going to build immunity against it no matter how many times you take that injection. So that's a really important part to understand ,is our ability to be resilient and actually develop some sort of immunity against the new pathogen and all the existing pathogens that we encounter, come from an appropriately functioning microbiome.

Simple measures can make a big difference in your microbiome. Many of you who've heard me talk about this before have heard me emphasize this. Diversifying your diet, lowering stress, because remember stress increases barrier dysfunction and leaky gut. Stress also increases the replication and the infectivity of latent viruses like cytomegalovirus, herpes simplex virus, Epstein-Barr virus. Those viruses, they respond when your stress hormones are high and they start to proliferate because they understand that the immune system is now under pressure and doesn't function as well under the stress condition.

So them being opportunistic, latent pathogens will start proliferating in that condition. Because they're proliferating then, they then start attacking your immune cells themselves. They attack B cells and T cells. So that compromises your immunity in a very significant way. So stress can compromise your microbiome, lead to more chronic, low-grade inflammation and directly compromise your immunity in a very significant way.

I know it's hard to talk about stress right now because there's lots of things that are stressing people out. Getting outdoors is really important. I know we're all supposed to stay in as much as we can, but if you can go out into nature, that's really the key. Because there are enough studies that show more exposure to outside environments, especially natural environments. I'm not talking about going and walking down the sidewalk having the same effect.

Going out into a place where you can do a hike or going out into a natural environment, that gives you exposure to microbes that actually increase the diversity in your microbiome and improve immune function.

Using a spore-based research probiotic, we've got a bunch of studies that we've been doing, two recently published on the improvement of the HIPAA protection using the spores, modulation of the immune response, the upregulation of certain aspects of the immune system, and of course these spores, like I mentioned before, have direct antiviral type of effects to help the immune system with supporting that kind of healthy response against pathogens.

Focus on leaky gut solutions, because remember leaky gut is the biggest source of chronic low-grade inflammation and chronic low-grade inflammation drowns out the signals from the microbiome to alerting the immune system to the presence of pathogens. So if leaky gut is present, that's going to become a serious comorbidity to reducing the impact and the functionality of the immune system.

You have to bring down inflammation. So whether that's an antiinflammatory diet for you, behaviors that reduce inflammation, compounds, taking things like garlic and curcumin and all that, all of those things can help with bringing down that inflammation and that drowning out signal that occurs in the body in general.

Prebiotics like oligosaccharides can have a major impact on immune function, one, through the creation of butyrate and other short-chain fatty acids, but there are studies that show directly the impact of prebiotics on immune support against viral infections, and they're really quite profound. So prebiotics really help, especially oligosaccharides, really help with providing signaling capability for the microbiome to inform the immune system of the presence of pathogens.

Things like polyphenols, omega fatty acids, can be powerful support tools. Omega fatty acids of course for dampening inflammatory response locally in the gut, especially if it tends to have higher EPA and higher DPA. Polyphenols act as a very potent prebiotic for the microbiota by increasing diversity, dampening inflammatory response in the microbiota itself.

Then facilitating the production of things like urolithin, which helps produce new cells, removes damaged mitochondria or damaged cells that occur. The damage occurs through infection and so on. So polyphenols can be really a important tool for your microbiome to help your immune system and help the body recover and also elicit an appropriate response to the presence pathogens. So I think that's the last slide. Maybe I'll leave it here for now.

Michael Roesslein:

Yeah. You can leave it there. I have bad news and hopefully good news.

Kiran Krishnan:

Okay.

Michael Roesslein:

So my bad news is that I'm out of time. It's an hour 40, and I don't have unlimited time tonight unfortunately. I should have expected your presentation to go that long because I know better and we've done this before.

Kiran Krishnan:

You know how we do it.

Michael Roesslein:

But the good news is your call because I would like to, once we're done with this, perhaps we could try to figure out a time where next week we could do the Q&A.

Kiran Krishnan:

Yeah. I would love to so that.

Michael Roesslein:

And to go into some details. Because you put on here, you have stuff about probiotics and leaky gut solutions and prebiotics and all that and you guys have a lot of solutions for that. I just saw your new study. I think you posted or email went out today on the combination of the megaspore and the prebiotic relating to something awesome. I don't remember.

Kiran Krishnan:

Short-chain fatty acids.

Michael Roesslein:

Oh yeah. Short chain fatty acid in obese [crosstalk] mice.

Kiran Krishnan:

Diversity also.

Michael Roesslein:

So maybe we can chat offline and figure out the soonest time that we could get back on and do Q&A and then talk some specifics around the products and the research. Then I'll put together a little guide to other steps people can take. I can take this slide and maybe we'll make a little here's your steps you can take.

Because I've got ... So I typed this in the chat. You probably didn't see it. But as soon as I went to start trying to copy over all the questions from the email and the Facebook and the chat boxes and everything, I usually put them into one Word doc that I have because I have a huge monitor here. So I can have this open on one side and I could have a Word doc open on the other side and I could read the questions off in an organized fashion.

My Microsoft license expired at the exact time that this webinar started. So it wouldn't-

Kiran Krishnan:

They get you somehow.

Michael Roesslein:

Yeah. Back to Bill Gates. I opened up the Microsoft Word and it's like, screw you, you can't use this. Here's this 27 step thing you have to go through to turn it back on. So I spent a lot of the time writing this. Let's exit your screen.

We'll come back to the slides. Can you turn off your share screen?

Kiran Krishnan:

Oh yeah. Sorry. Let's see ...

Michael Roesslein:

That's a great slide. Did you just put this presentation together recently?

Kiran Krishnan:

Today, yeah, just between lunch and now. I was like, you know what? This is important enough. I got to do it.

Michael Roesslein:

Oh, no big deal. That was only the best microbiome immune system presentation that I've seen.

Kiran Krishnan:

Thank you.

Michael Roesslein:

So I'm going to have to watch it like four times, because I was doing this.

Kiran Krishnan:

Oh yeah.

Michael Roesslein:

I have this many questions. So these are from the chat and they're from the Q&A box, and some of the email that I got. There's about 30 questions on here, so this would probably be about an equal duration webinar that we could do just on the Q&A, and maybe getting into some more specifics.

Some of the questions are more specific related to your product. Some of them are just a fine point questions on some of the stuff you went over, and then some of them are related to other immune simple questions. So let's do that.

Kiran Krishnan:

Yeah.

Michael Roesslein:

I see a lot of really happy people in the chat box, fire hose information once again. Yeah. That's kind of how we roll. That's why we give you guys recordings. So to the most popular question is, is there going to be recording? Yes.

Kiran Krishnan:

Yeah.

Michael Roesslein:

We usually will get that out ... Today is ... What day is this? Wednesday? Is there days anymore? Do we still do days. Today is Wednesday. So Friday, we'll probably get it out Friday with a transcription. Then I will talk to Kiran when we're done here and try to figure out time soon that we can do a part 2 with a Q&A and some specifics around research, around products, because there's a lot of questions there too.

Kiran Krishnan:

Yeah, and we were able to capture most of these questions. Even I was able to just-

Michael Roesslein:

I've got them all.

Kiran Krishnan:

Copy them too. Okay.

Michael Roesslein:

I either answered them, there was a couple of them in the Q&A that I answered.

Kiran Krishnan:

Yeah.

Michael Roesslein:

Then I, hold on, yeah, and then I copied all of them into there's three that I'm just going to take a screenshot of right here in the Q&A that I have not written down, which would have been the smarter way to go the whole time. But I always think of the smart answers after I've done all the work.

I have all the questions recorded.

Kiran Krishnan:

Okay. Awesome.

Michael Roesslein:

So I can send them to you so that you can be somewhat prepared for them. Will our email questions be able to be answered next week? Yes. I have all the email questions, the Facebook questions, the chat box questions and the Q&A questions from this, I think, onto all of these, onto these pieces of paper. So I'll get them to Kiran.

We will let you know as soon as we know when we can hang out again, and we will get into that. I apologize. I should have booked three hours knowing better.

Kiran Krishnan:

You know, we've only done this 40 times Michael.

Michael Roesslein:

Yeah. And it's weird to have a webinar ending and it's light out where you are.

Kiran Krishnan:

Right.

Michael Roesslein:

Summer's happening.

Kiran Krishnan:

Yeah.

Michael Roesslein:

I feel like, oh, we're ending so early, but it's almost two hours. So thank you everyone. Man, everybody's super love. I don't know if you have the chat box open, but everybody's very excited.

Kiran Krishnan:

Awesome. Well thank you so much. Yeah. I think people are, there's a lot of anxiety right now. I think eventually we need to get out there. So we're going to be going out, and this particular virus and many of the other viruses we have to deal with as well, aren't going away anytime soon.

The good news to me is that our immune system is well equipped to deal with this. It's well equipped to deal with almost anything it encounters. It has all the mechanisms.

The big point I was really hoping to get across today is how we have to make sure that our ecosystem and the terrain that the immune system functions within, is also adequate to respond to these types of things. The good news with the pandemic virus, for example, is still 80 percent or more people tend to have a very mild type of response, which means that people's immune systems are handling it.

It's pretty clear that the ones that aren't handling it have lots of chronic inflammation. So we can deal with it, and I don't think you need to be afraid. I don't think you need to be anxious about it. I think you just need to be prepared.

One of the best ways you can prepare your immune system to encounter something like this is through shaping that microbiome. Then the other stuff you do as well, the nutrients you take and all that. We could talk about more of those details and things I do, for example, in our next Q&A. But hopefully people got something out of this. I'll send you the PowerPoint, Michael, and [crosstalk]-

Michael Roesslein:

Yeah. People were asking for the slides.

Kiran Krishnan:

I'm happy to share them. Yeah. I'm happy to send them to you so you can [crosstalk].

Michael Roesslein:

Don't worry. Nobody could steal your slides and give that presentation because I would just click from slide to slide and go, here's this slide.

Kiran Krishnan:

And then this looks like-

Michael Roesslein:

Yeah. These people, one of them is wearing a joker hat. He's the boss. Thank you, Tammy. Thank you. Everybody's really fantastic. Blown away. Yeah. Thank you so much.

Kiran Krishnan:

Of course.

Michael Roesslein:

I'm going to have to watch it so many times. I know to us mortals, when it comes to microbiology we're like, "Oh man, that's so much work that he just did," but then people don't realize you love this stuff like this.

Kiran Krishnan:

Totally, yeah. Yeah.

Michael Roesslein:

You didn't have to put together a slide show on immunity and microbiome this afternoon. You got to put together a slide show.

Kiran Krishnan:

Right. Well before I put the slideshow together, when we decided to do this, I decided that I wanted to read up on the most latest papers on this topic. So I probably, between Monday and this afternoon, I probably read maybe like 40 published new publications on this topic, and there's so much rich information. I was just going to come on and talk about it like I do often and that's when I decided I was like what there's too much stuff on here. I need to outline it for people on slides.

So that's why I decided to put the site together and try to give people visuals, because a lot of this is really complicated and the visuals hopefully help understand the processes. Again, when we do the Q&A, we can explain things even deeper, clarify some questions.

I think if any of you go through and watch it again with this first base of level of understanding, it'll start to click and make sense of how things are connected. That's the part I really want you to get. I want you to understand how this response works, what's going on when something enters the body, how your microbiome responds and why that response is so important.and you are in complete control of all of that. So that's the beauty of all of this. You can manage how your immune system works.

Michael Roesslein:

Yeah. A lot of it's under our control, which is great. So everybody, you've probably just got the first view of a presentation that's going to find itself to medical conferences-

Kiran Krishnan:

Yes.

Michael Roesslein:

Once those things start happening again.

Kiran Krishnan:

That's the part I was excited about.

Michael Roesslein:

I know how to multipurpose slides, so I know that doctors are going to be seeing this, but you're going to have a leg up on your doctors. So thank you for doing that for our group.

Kiran Krishnan:

Right.

Michael Roesslein:

That's really special. There's somebody in the chat says, "I'm a clinical microbiologist and this is frontier of our field. Totally awesome material."

Kiran Krishnan:

Awesome.

Michael Roesslein:
So you have a fellow-

Kiran Krishnan:
That's so good to hear.

Michael Roesslein:
Bug nerd in the chat there.

Kiran Krishnan:
I love it.

Michael Roesslein:
And I mean that endearingly.

Kiran Krishnan:
We need more.

Michael Roesslein:
Right. We need to get kids watching these. We'll turn little kids into microbiologists.

Kiran Krishnan:
Excellent.

Michael Roesslein:
Cool. Well, thanks a lot.

Kiran Krishnan:
Thank you Mike.

Michael Roesslein:
We'll talk soon and everybody will be back soon and we will get this finished.

Kiran Krishnan:
Yeah. Take care.

Michael Roesslein:
All right. Thanks.

PART 3 OF 3 ENDS [01:36:14]