Inflammation's Ties to Fasting, Cancer and Covid – Dr. Miriam Merad with Dave Asprey – #783

Announcer:

Bulletproof Radio, a state of high performance.

Dave Asprey:

You're listening to Bulletproof Radio with Dave Asprey. Today's show is going to be exciting because we're talking about inflammation, which is one of my favorite subjects, which happens when your body doesn't do a good job of combining air and food to make electrons. Instead, it does something wrong and you get inflammation. But we're going to talk with a major researcher about how inflammation is related to fasting, to cancer, even to COVID. And our guest today it Dr. Miriam Merad, who's an internationally acclaimed physician-scientist at Mount Sinai, who leads the Precision Immunology Institute at the Icahn School of Medicine. Fortunately, that's called PrIISM, is the acronym for that, so I can say that. And PrIISM integrates immunological programs looking at biology, medicine, tech, physics, math, and computational biology.

Dave:

This is, basically, a really smart person, and if that didn't convince you, she's a professor in cancer immunology and founded the Human Immune Monitoring Center at Mount Sinai. This is likely the world's most sophisticated research center, because of single-cell technology that they're using to look at what immune cells are doing to all major human diseases and treatment responses. Basically, you want to know how your immune system works, this is the person to talk to. Dr. Merad, welcome to the show.

Dr. Miriam Merad:

Thank you for having me.

Dave:

Wow. You've done so much in your career. I mean, this is really high-level stuff. You've written more than 200 papers in big visibility journals, and people have cited your work thousands of times. How did you get here? Why the fascination with this one little immune thing with all the thing you could have done with your, obviously, big brain? Just explain, why?

Miriam:

Well, interest in that system. Interest based on the fact that we, as a human species, are alive today because we were able to survive millions of years of exposure to threats, whether they were infectious threats, like viruses, many different types of microbes, not only viruses, but also extreme fatigue, but also extreme weather. And the realization that we didn't have doctors at that time, right? The only reason we were able to survive, all those of us that survive are those that had an immune system that protected them. It is our best doctor. And, in fact, there is, I realize, a children's book calling the immune system is your best doctor, it's exactly that. It is.

Miriam:

And yet, I realized when I was being trained as a cancer doctor, which is my clinical training, that we were not exploiting that. We do not know, yet, how to exploit or to maximize our knowledge of the

immune system. Now it is being exploited, we treat cancer and inflammation, and I'll talk about COVID maybe during this show, but the fascination is that there is so much to discover about that system and to use to treat most human diseases. And my fascination continued to grow. In fact, I turned 50 a year ago, and, actually, I never talk about my age, but now, I use it to say I am as excited or even more excited as I was 20 years ago when I really decided to become a cancer immunologist.

Dave:

It feels like we're making exponential improvements in our knowledge, largely because of that computational biology thing. Because there's so much more that we can see now, and I'm so excited, because I see this bright future where we're going to know 10 times more in a couple years than we know now, and it seems like it's just growing and growing. But it sounds like your primary motivator, this was an unexplored territory and you wanted to go explore and area that we just didn't know. And so, curiosity, maybe, it sounds like that's the real driver for you.

Miriam:

I'll tell you a little thing that happened during my career where I was being trained as a cancer physician and all my patients were dying. I was trained in France, hence my accent, so I'm sorry [inaudible 00:04:16].

Dave:

No need to apologize.

Miriam:

It's just very strong and it's not going to go away. But I was sad, I was very attached. I wanted to be a physician and I wanted to treat patients, as I come from a family of physicians, and I spent my childhood in the hospital waiting for parents. I loved that atmosphere. I loved the hospital. I was on the floor, and I would study some of my patients lesions, and so I went to the microscope with an attending, and I look at this lesion and I realized that in cancer there were more immune cells than were cancer cells, so I asked the attending, "Why do we call it a cancer lesion? I mean, there is much more than cancer cells in that lesion." And, to me, it was a revelation of there is a group of cells that are there, maybe to fight, but they were not able to fight to eliminate it completely. What if we unleash them?

Miriam:

And this is how everything started. Yes, curiosity about why there were these immune cells there. And what I thought initially, maybe naively, as being a legion full of cancer cells that were destroying our body, now there was a reaction, there was some cell that was trying to stop it and they were unable to do so. So what if we were able to unleash that response? And this is what's happening now, 20 years later.

Dave:

It's so amazing. Sometimes you look at something, and sometimes you look at the environment that it's in. And the whole idea behind biohacking was that, change the environment, change the biology, because it seems to listen. And you had this similar thinking, earlier on, about, "Okay, what's causing it? Maybe it's around it?" And looking at the body as a system. And, in my own path, having lost 100 pounds, having had chronic inflammation for much of my life, learning how to tackle that as a hacker, saying, "I don't know everything going on, but if I change the inputs, I can look at the outputs and see

what works, and we can get there." But I feel like you're the person who's now opening the box up and looking inside and saying, "Ah, it was that pathway, it was this."

Dave:

And given that deep knowledge you have, what brought you to my attention was the paper you published in Cell in August of 2019, Dietary Intake Regulates the Circulating Inflammatory Monocyte Pool. Basically, fasting reduces inflammation and improves chronic disease. I was doing my research for my book on fasting that's just coming out, and I was like, "Oh, this is amazing." Very recent research. What did you find around infections and fasting?

Miriam:

It's interesting this study. I was always interested in diet, because all immunologists are interested in food, because this is an influx of foreign agents to our body. The immunologists study response to foreign attack, right? All of us are, at some point in our career, have been interested or exposed to people studying human response to the microbiome and food allergy and tolerance to food antigen and how does our body understand how to react or not to react against this food, a lot of stuff that are being brought to us from the outside world, right? The big puzzle of the immune system is to be able to recognize what's dangerous from what's not dangerous. And when it doesn't know how to recognize that, it leads to severe disease including inflammation and auto-immune disease, et cetera.

Miriam:

I was interested in how the immune system respond to these, but while many of my colleagues were looking at the gut and the intestine, I looked at the systemic response. Again, this high-level view of the body's system, right? Everything is connected. And it's the source of immune cells, which is our bone marrow. Bone marrow is a source of immune cells. When you have an infection, when you have COVID, for example, it is something we are studying very carefully now, it's the bone marrow that's going to provide some effector cells, an army of cells that are going to the site of infection. I was asking whether the bone marrow was sensing something, right? And maybe we were not going to find anything. With a fellow of mine, the first author of the paper, who's now leading his own laboratory at [Charité 00:08:53] in Berlin. Big [inaudible 00:08:56] institution. And he's going to be working full force on this.

Miriam:

We ask this question, it is, "Okay, are we sensing foods at this systemic level?" And, indeed, this was the case. We were fasting animals, mice, and each time we're introducing some food, the bone marrow were releasing these monocyte. And monocyte are inflammatory cells that are released when there is an infection. So we thought, "Wow, the bone marrow is sensing that we are eating, so eating is a threat." And, in fact, when you think about it, it's true. When you eat, you can ingest something that can be dangerous to yourself. We have to be in a position to defend ourselves. And who is the army of the human body? It is the immune system. The immune system was being mobilized. And what struck me is that, in fact, mice eat all the time, because the way we cage them, well we house them, I hope animal activists are not listening too much, but they are very useful with these studies, I can tell you that.

Dave:

If any animal activists are offended that we're making the world a better place, with mice, you guys are free to unsubscribe. There, solved.

Miriam:

But then, we try to be as humane as possible.

Dave:

Of course.

Miriam:

There is access to food all the time, right? And then, it made us realize, my fellow was telling me, "Well..." he was being very interested in fasting, but I was thinking, at some point, the discussion was around, "When did humans start to eat so often? Why did we start to have these three dinner course?" And, in fact, in America we eat even more than that. And I'm a big snacker, so I snack all the time. Why do we eat so often? When you think about humanity, we started, we were eating when we were hungry. We would eat and we would walk and exercise. When we are hungry we get food in response to hunger, which is not the case anymore.

Miriam:

And then, we started to really think about whether this constant exposure to food is making our body believe that there is potential constant threat and that somehow we change that physiology that rheostat. That usually is, okay you have [inaudible 00:11:28] of food every two days, this is how early humans were doing, and then you have this [inaudible 00:11:34] and you can cope with that, but here there was this constant release of immune cells and inflammatory cells and we wonder whether this is contributing, maybe, to many inflammatory disease, such as atherosclerosis, which always now occurs to all of us with age. All of us are going to develop atherosclerosis. It's extraordinary. Is it, really, maybe a response to these new dietary habits that we developed not physiological reasons, maybe for social reasons, and we were wondering whether this needs to be revisited.

Dave:

Wow. What's happening there is the body says, "There's some foreign stuff inside of me, because you chewed it up and did that." And it says, "I've got to use similar mechanisms to break that down that I used to break down other things that might be inflammatory in the body, excess protein inside of cells, autophagy processes." And if you're a chronic eater, it's similar to having a chronic infection, which would raise your white blood cells and show, in lab work, that you have these problems. Yet, if you, occasionally, don't eat for a while, then all of that chronic inflammation goes away and then the systems that were doing that can either recover, so your immune system is better, or they can go to repair work elsewhere in the body. Am I saying that right?

Miriam:

Yeah, it's exactly that. It's extraordinary when you think of it, extraordinary to the point where I started now to fast a bit. I changed my habit completely, where I stopped snacking, because it was so clear and reproducible, that somehow if you eat less, you have less inflammation.

Dave:

I got to the point, when I weighed 300 pounds, where I was so inflamed, I could tell by whether I would get blisters from walking, sometimes even a few hundred yards. My toes would get blisters, which is a very large inflammatory problem. And just the pain and the energy level in my brain, so I started finding

things before I knew as much biology as I do now. Where I could say, "If I eat, I'm always more inflamed than if I don't eat." And it, of course, depends on what you eat, as well. A plate of French fries is different than eating an egg or something. They're just fundamentally different. Now we know so much to say, there's a case for having nothing or substantially nothing, you probably can coffee and tea and stuff like that, according to some evidence I found.

Dave:

But what I found in your paper, that was interesting, you were looking at the immune system's response to acute infections versus fasting. And what, I believe, the paper said was that your chronic inflammation would go down when you fasted, but it wouldn't affect your ability to fight off a virus or a bacteria.

Miriam:

Yeah, that was a very important finding, I have to say. Because the goal of this immune system is to protect us against infection, right? What's the point of having a reduced level of circulating inflamed cells, if we are not able to protect ourselves, right? It was very important to us to really realize whether, somehow, there was a connection between this level of inflammatory cells and our protective ability or whether, in fact, even better not to have all the circulating immune cells and not really interfere with our ability to react and respond and release the immune cells when needed. We've done this experiment where we did many different type of infection and we saw absolutely no difference.

Miriam:

It was very important for us to really understand whether we compromising anything. Now, one thing I wanted to highlight is we were looking at intermittent fasting. It means that we were looking at mice that were not eating for 16 hours, no sorry, mice were either four hours or 12 hours and also some volunteers that were not eating for 18 hours. We were not studying cachexia. Cachexia is something very different, and we know that this harms the immune system. It is very important to make this difference. It's that if someone starves for many days, he is immunocompromised.

Dave:

A long fast, you're saying, versus an intermittent fast?

Miriam:

Yes, exactly. Intermittent fasting, is very, very different than this long-term fasting that can really compromise your immune system, however, I can tell you for a fact now, we've done it enough that we are sure that if you do this intermittent fasting, we absolutely didn't affect our ability to fight acute infection. And maybe we can talk about chronic inflammation also, but acute infection was not compromised and we did improve chronic inflammation.

Dave:

In humans, chronic inflammation is tied to cancer, it's tied to cardiovascular disease, it's probably caused by diabetes, but may also cause diabetes. And if you look at Alzheimer's Disease, yep, inflammation. All the big killers of people, the fuse is lit by chronic inflammation, which is one of the reasons I think I need to write a book on how to do an intermittent fast without being hungry so it can be achievable. But I came across two studies that are interesting in respect to the immune system and fasting that I wanted to ask you about. And this is just as I was writing a chapter on, funny enough, immunity and fasting.

Dave:

One of them showed that fasting worked really well for bacterial infections and survival goes way up when you fast a human or an animal during a bacterial infection. But during a viral infection, having higher levels of blood glucose, not excessively high, but just the normal from eating, enhanced survival. That was probably a mouse study. So they were actually looking at, essentially, bacteria, you want to be in a ketogenic state from fasting, and viruses, you might want to have some glucose ready to power some systems that are necessary to give you resilience against the virus. Any commentary on those findings?

Miriam:

Yeah, these are very interesting studies, done by a very good friend of mine. It's a little bit complex, and I think there is maybe more to look at. And in this study, in particular, there was prolonged fasting, the animals were fasting for a prolonged period of time, and he was looking at how this was affecting our ability mark a different pathway, indeed, you use different pathway for different infection. We looked at something a little bit different, and I think it's right, but we were looking at two different systems, and I think it's important to make these differences. And he was not looking at intermittent fasting, he was looking at prolonged.

Dave:

Yeah, longer fasting. Correct. To get into ketosis, two days, plus.

Miriam:

Ketogenic diet. These are different processes that requires, I think, very serious work in animals, but also in human beings. If you want to look at long starvation or a longer period of fasting, you have to be quite careful at really measuring exactly the response mechanisms that you are going to induce. Well, there were some ketogenic pathway that were starting to be induced, but nothing was extreme. It seems to us that what we're doing is putting someone in some type of good physiological state, where nothing was suffering to the point where you were using ketogenesis to produce. You were just reducing, somehow, some of the metabolic state.

Dave:

So it was before ketosis kicks in. If women, at least human women, do an every other day intermittent fast for 16 to 18 hours, they'll get a slight rise in ketones over the course of the week, but they're not in full-on ketosis, they'll have 0.1, 0.2, 0.3, but not much more. And I'm so happy you're pointing out that difference. The best practice for humans, if you're going to be fasting for multiple days, you rest. You actually lay down, you journal, you reflect. But if you're going to try and do that and then go exercise and all, you are going to not have enough cortisol present in order to fight off an infection. It is nuanced, it's very heavily nuanced, and you're one of the first to look at intermittent fasting in immune response, specifically, which is why it's really cool, but this isn't a keto conversation, this is a no food in my gut conversation, right?

Miriam:

That's right. Exactly. And it's important that we don't take this lightly, right? Because there have been a flurry of malnourishment, where people are starving themselves, and I'm a bit anxious about this, that somehow food is the enemy. Well, food is not the enemy. I come from North Africa, and I can tell you there's a lot of part of Africa that's dying, because they don't have enough food, right?

Dave:

Yeah, food's important.

Miriam:

Food is important. And usually these people die of infection before dying of extreme fatigue or organ failure. A lot of infection kicks in, and so showing that the immune system needs that glucose also to be able to fight. But it doesn't need this constant exposure, and it needs [inaudible 00:21:27]. I think you talked about repair earlier, like when we need probably to sleep, so a lot of the repair mechanisms that occur during our sleep. I think you need periods of prolonged fasting, the prolonged meaning during the day, where your system is at rest, so that you put things in equilibrium. Now, how much more we can push that, I think we need very serious measurement of different processes and systems to make sure that we are going to recommend the right combination.

Miriam:

But, right now, this is not what we've done. I'm an immunologist, I will continue to study inflammation. I will not be studying diet extensively, but there are many fellows that will specialize in, really, food. In fact, I'm recruiting, hopefully, also a whole team to study that in the institute soon.

Dave:

Ah, you're recruiting a team to study food. It's going to be world changing to do that. I have found, through trial and error and lots of research in my new book, there's five categories of food that drive systemic inflammation, but not always the same in all people. You have to have a computational biology approach, because if only one-third of people have the genes that make them susceptible to a certain class of food, it won't come out in normal study, at least it won't come out very well, unless you're measuring those and looking at the subpopulations. And you're like, "Oh, wow. There wasn't an effect on the whole population, but on a third of the population, it was a 90% effect." And that seems like the world we're in around fasting and, specifically, around different foods.

Miriam:

Different food and different people, I think what you highlight is absolutely correct. It's that, somehow, we are not all equal, right? So we have to really understand that it's important to stratify people, and this stratification comes from teamwork with computational and quantitative immunologies and quantitative biologies. And we can be put, potentially, in groups that share the same patterns. And now, we can, we have the state of knowledge to say, "Well, this group of people should..." We know that this is the case, for example, in African-American being more susceptible to some disease and not others, because they have differences in some gene organization, same with Asian people, and same with Ashkenazi Jew. There is some ethnic groups that have different type of gene organization, that we can now identify, and sometimes it's spontaneous mutation. I agree with you, it is complex, but we are at a stage where we can now try to understand complexity.

Dave:

This is something that I've really been looking forward to asking you. You have this great set of knowledge and information and you've constructed these models in your head about inflammation. You mentioned that you went from being a frequent snacker, until you started intermittent fasting. What do you normally eat?

Miriam:

Well, I used to adore breakfast and have croissant [inaudible 00:24:48]. I spent a lot of my life in France.

Dave:

Of course.

Miriam:

Either a croissant or I could also eat a scone in the morning-

Dave:

Made with real butter at least, right?

Miriam:

Yes, exactly. And then, I will have lunch with a salad, and then evening I will have dinner with the family. Usually, two dishes, one dish of meat, usually white meat, I have to say, and salad. Now, what I decided to do is to skip the breakfast, so I don't have breakfast anymore, which was terrible for me, it was very, very hard. But I skip breakfast, and I now often also skip lunch. I was a very frequent snacker and I thought that this was going to be impossible. Initially, I did it for the study that we've done in the lab. No, initially, the lab told me, "Well, do you want to be a volunteer? 18 hours of fasting." I was like, "Absolutely not." And then, I tried it because they all tried it, as some point. I'm not a pussy, so I did it.

Miriam:

And, in fact, I realized that I felt better. I had more energy than before. Well, I never lunched too much, also, I have to say, but the breakfast was a big deal for me. And I skipped that breakfast and I was not tired. And, in fact, I can tell you, today I had a little thing, a little falafel bite at 2:00 p.m. and then I didn't have anything. Now, we know that inflammatory response makes you tired. We know that, right? When you have flu, that inflammation is what makes you tired. When you have a vaccine, it's that bit of inflammation that makes you tired, sometimes. So an inflammatory response, an injury, like a little injury in your hands, that will make you even feel a bit tired. That inflammation is associated with tiredness, because there is a release of inflammatory molecule that can sometimes cross the blood-brain barrier.

Dave:

I think almost always they cross the blood... inflammatory cytokines enter the brain and they make you slow. So you whack your elbow and you get a bruise and you're less sharp that day, right? Okay.

Miriam:

We believe that this renewed energy that I felt was, in fact, due to the fact that I didn't have this burst of inflammation. Now, since then, I love it. And, in fact, I feel tired if I have breakfast.

Dave:

Wow. Coming from a French background, that's even more impressive, because croissants, baguettes, all the good stuff, lots of butter and maybe some cheese.

Miriam:

[inaudible 00:27:28] baguette... What I don't want to say, because I think it's very important for the audience to realize, that happiness matters, right? It matters even to your immune system. We know that when you are sad, you also respond to it. There is a very strong connection between nociceptors, so some receptors of pain and the immune system. And there is strong correlation and there is a lot of work on that. Happiness is also, potentially, contributing to your well-being. Right? If a croissant is what makes you extremely happy in life, well, probably make sure you are not going to sacrifice too much. And, me, I realized I saw thought that this was super important to me, but, in fact, it's not. But once a week, I have that croissant in the morning, because I want to enjoy it, right?

Miriam:

It's also measures, right? If you have very good habit and then you have some pleasure, you can also alternate. We could study that even at the cellular level to see whether we change anything if we do change this habit, so all those things can be done. And I'm hoping that the team [inaudible 00:28:50] will be studying this level of detail, both in animal, but also in people.

Dave:

I really hope so. The recommendations in Fast This Way, and I've been recommending intermittent fasting for 10 years, people have lost a million pounds based on my nutritional stuff with the Bulletproof diet, and intermittent fasting just emerged from my own path and very early research on it. But what I found was that, especially for women, that oftentimes intermittent fasting every single day, an 18 hour fast every single day, after months of that, it would lead to problems. It would lead to sleep disturbances, it would lead to hormone irregularities, it would lead to hair loss, which is kind of like going to long without food, so you get the negative effects. And probably immune suppression, too, I would guess, is a part of that. But what it comes out to for people who are staring fasting, especially women, sometimes three or four days a week or even working up to five days a week.

Dave:

But the advice in the book, which is so funny you said this, Saturday morning, have the pancakes, probably make them gluten-free, that's going to be better, but do that even in the morning, which isn't the best time to eat carbs, but it's because of the joy, because of the social stuff, and because you want the body to know that sometimes there's just stupid amounts of sugar available, so it can invest in glial cells, it can invest in brain maintenance, and that if you're always in keto or you're always fasting, and you never give yourself a break, you never foods you love, it's not how to do it. And you've intuited that and you've gotten it from your science, but it's funny saying, "Oh yeah, Saturday morning." It just lines up so perfectly, and for you it's a croissant. All right.

Miriam:

Not studied extensively, but it will be even interesting to study whether it can be beneficial, as you've said by sometimes changing, in fact, exposure.

Dave:

I believe that the way we will probably be able to study it is this thing on my arm, a continuous glucose monitor. This is from Levels Health and I'm an advisor and investor in the company and it's so cool, because then we can actually see at least what was the post-prandial spike in blood sugar, which is probably correlated very highly with inflammatory cytokines, because we know HbA1c goes up. I think we'll do some computational stuff where we can reliably predict cytokines based on this, and something

else, and then we'll be able to get data from hundreds of thousands of people who record when they eat their croissants, and it's such a brave, new, amazing world for doing research on people. On people, not mice.

Miriam:

Absolutely.

Dave:

Now, I mentioned glial cells, these are the unsung heroes of the brain, where we have these neurons, which are the rock stars everyone knows about, except their supporting staff in the immune system in the brain likes glucose more than it like ketones, even though neurons like ketones better. You've gone way deeper on that, you talk about dendritic cells and macrophage biology. Can you talk about dendrites and macrophages and glial cells and help listeners understand why those matter, and what the effect of food and inflammation is on those?

Miriam:

Yeah. Well, those cells, dendritic cells and macrophage, and I'll talk on the glial cells in a minute. But glial and macrophage are cells that are present in every organ. Let's talk about macrophage. And macrophage are present in every organ, including the brain, and in the brain they are called microglia. In the brain there's two types of glial cells, there the microglia and astrocytes. And the microglia are macrophages and, really, the goal of the cell type is two-fold. The first is to constantly clean damaged cells. Each time the cell is dying, because even neurons can get damage and can die, and there is, in fact, some neurogenesis always ongoing, some neuron proliferate despite the dogma that neurons will never regenerate. There is some ongoing neurogenesis, even in adult brain. The macrophage constantly eat damaged cells. They know when something is damaged, they eat it. They are vacuum cleaners in our organs.

Miriam:

In an organ where there is high cell turnover, such as the skin or the gut, the epithelial cells are turning over constantly, and if you didn't have a vacuum cleaner, then you'll have all of these death cells accumulating and it would interfere with the organ function. Macrophage is a key, key cell type. And, in fact, several groups have shown that these macrophage were already present in primitive organism, so in very, very small organism. There is this dogma in biology that if something is conserved between different species it means that they relevant. Otherwise, we would have gotten rid of them, right? Darwin principle. These macrophage were already present in very small organisms, so clearly they are doing something that is essential in organ homeostasis, you're maintaining the organ in a good state.

Miriam:

But what macrophage also do, and they share this function with dendritic cells, is that they also have acquired this possibility to recognize a threat. They have threat receptors on their surface, and they are the one, we call them also sentinels. I call sentinels more than dendritic cells, I'll come back to this in a minute. Both cell types can recognize when there is a threat. They are the only one that can do that. They are the one that tell the adaptive immune system the noble cells, the T cell and the B cell that makes antibodies, something is wrong, they act against it. They are the one that tell the bone marrow, "Please send us granulocyte, neutrophil, to come and help fight the infection." They are the one that really ring that alarm and tell everyone there is fire. Very, very important cell type. So that is two

functions, they eat damaged cells all the time, and then they decide when to react and when not to react.

Miriam:

And this is why I decided to study them, because when I joined immunology, everyone was studying T cells and B cells and no one cared about these cells, however these cells are the one that tell T cells and B cells what to do. I love them. Now, there is this dendritic cell, there's a little twist to them. It's that they are like macrophage, except that they got rid of the vacuum cleaning function. Their job is only to travel between an organ, so let's say the skin, and draining lymph node. Well, what's in the draining lymph node? In the draining lymph node, you have all these very sophisticated immune cells, the T cells and the B cells that make antibody, the ones that are going to kill and get rid of the CoV-2 virus in COVID-19.

Miriam:

But those are in the lymph nodes, dendritic cells come from the tissue, where the infections start, and they might wait there and tell them what to do. And I think these evolved later during evolution, there a like a sophisticated macrophage, and you find dendritic cells only in larger organisms that have T cells and B cells, because the smaller organism has a very primitive immune system, composed of mostly macrophages and other type of primitive cells throughout the course of evolution. During fasting, you want the cell, the sentinel cells, to really know how to really respond. There is another cell type that I should have put there, which is called monocyte. And monocyte differentiate into macrophages, they are a precursor of macrophage. And those monocyte are the ones that are being released when there is food intake.

Miriam:

Those monocytes are being released, but they know when to start saying something is wrong. They are going there, they are probably mobilized to tissue, your pool of macrophage is going to increase in tissue, because you are constantly eating, so you send more inflammatory cell, you send more macrophage. And somehow, your macrophage pool is increasing in tissue. And this is what worries me about us eating all the time is that you are not supposed to have all of these macrophage pooled in your tissue. Then, somehow, something is going to happen, and, in fact, in lesions, like arthrosclerosis, for example, what you see is this very large pool of macrophage that are being too inflammatory. You are at risk when that pool of sentinel becomes too big of responding in a dysregulated manner.

Miriam:

So we think that somehow that pool of macrophage in tissue is affected by the way we eat. Of course, we have to study this a bit longer and a bit more and there are many studies now that are ongoing to look at that in a bit more detail. We are just scratching the surface. I can go on and on. You have to modulate [crosstalk 00:38:31].

Dave:

I mean, that's a whole lesson in immune biology from a world leader in the space, which is awesome. I want to take it in the direction of understanding what inflammation does for CoV-2. Because you've been looking at why do some people get really sick and why do most people not get really sick. What's going on there? What have you discovered?

Miriam:

I love these studies, but I have to say it's very complex. But I'm going to tell you a few things that we've found. What's so surprising, somehow striking, is that COVID-19 is very heterogeneous. You have people who have no symptoms, and I'm sure among some of your friends you've seen that or you've observed that. Some have very little symptoms, some are very tired, like if you had flu, but they still can stay at home and don't have to go to the hospital. Very, very tired. And some have to be hospitalized, and some have died, and many have died.

Miriam:

We were very interested in, let's say, among the same group of people with, let's say, the same type of comorbidity... let's forget about comorbidity. Same group of people, let's say, regardless of age, do we find a very different type of outcome? Now, one thing that's very clear is that comorbidity's a big risk factor for COVID-19 disease stability, for developing a severe outcome. And when you look at the comorbidity that are putting you at risk of severe COVID-19, it's quite interesting. Age is one of them, but really the big risk factors are diabetes, hypertension, and obesity, kidney disease a little bit, also. Now, connect all of those four condition really increase inflammation, chronic, you are in a chronic inflammatory state.

Dave:

To repeat those, it was diabetes-

Miriam:

Hypertension.

Dave:

Hypertension, so high blood pressure. Okay.

Miriam:

Sure. I said diabetes. Obesity.

Dave:

Obesity, so being fat. 42% of people, right? Okay.

Miriam:

And age, right?

Dave:

And age, okay.

Miriam:

And chronic kidney disease.

Dave:

Ah, okay.

Miriam:

People who have a dysfunctional kidney. All these diseases, they have one common, strong theme, which is chronic inflammation. To me, aging is really a chronic inflammatory state, and for many reasons that I'd be very happy to explain, because we have a big effort in aging now. It is in this chronic inflammatory state that was common to these patients that, when expose to the virus, will develop a severe outcome. Our hypothesis is that you can see a potential causality there. Now, in this chronic inflammation what you see is this, what we call, accumulation of the cells that I just described to you, these monocyte and macrophages. All of them have excess of monocyte and macrophage in some organ and excess release of, what we call, innate inflammatory molecules. Because these macrophage, when they are in excess there is a problem, right? If they are not being released from the bone marrow, it's very complex. For the bone marrow to release cells in the blood and the blood to cross a blood barrier to enter.

Miriam:

It is regulated. There is a reason why it will do that. When you have an excess of this macrophage, the body thinks that there is a problem and at some point you have, what we call, this chronic inflammation that you have felt when you were overweight. Those macrophages are releasing this inflammatory molecule. So there is a cause to that rise and what you have and what we are finding is that there was a completely dysregulated, what we call, myeloid response, macrophage and monocyte response. And those macrophage, instead of responding in a normal manner, which is, "I am going to tell the body that something is wrong, but then I'm going to stop. I'm not going to continue to call for help." We think that these macrophage were exaggerating the threat.

Miriam:

And this is what we are studying now, is why there was this exaggerated response and we think that an abnormal myeloid compartment potentially associated with some vascular damage, because all these conditions also make your vasculature a little bit more leaky. This exaggerated response will increase accumulation of immune cells, because your vasculature is leaky. You tell immune cells, "Please come and help us, but really please come and help, there is a threat here. Please come." And then, suddenly, you have all this excessive inflammation that occurs.

Miriam:

One thing I want to say to the audience, which is very important and it's an important result. All these patients that died of COVID were not dying because of excess virus. All of lesions that we've observed and studied from patients that died of COIVD had been able to get rid of the virus, so there was no virus left, because it's really this excess inflammatory response, strikingly. So the virus triggered something, of course, but the virus was not responsible for organ failure and organ damage. The lung were clear of the virus and they were destroyed by inflamed cells.

Dave:

And do we know which cytokines did that? Was it IL-6, IL-8, TNF, was it IL-1B or 1 beta? What was it?

Miriam:

Okay, so this is where the public often like simple response, right? But you know that these immune cells work through program, right? There is a program that is unleashed. Not only the public likes simple, sometimes even some of our colleagues like simple answers. No simple answers in biology. And,

unfortunately, this is the case. Today, I'm responding to a critique of a paper in a very serious journal, and the guy's telling me, "Find the mechanism." And I'm telling him, "Well, that mechanism is not simple, my dear." It's it not one molecule.

Dave:

It's systems biology. The idea that there must be one is an assumption that is not proven. It's usually more than one. Okay, good.

Miriam:

Exactly. So what happened is that we think IL-6 is involved and we think TNF is involved and IL-1 beta is involved. However, as you may have heard in the press, the initial IL-6 blockade trials were negative. And then, suddenly, even some very close colleague of mine that I love dearly were telling us, "Well, see Miriam, you were completely wrong. IL-6 is not involved." And I said, "Well, we blocked only one cytokine. What we need to do is study what happened in these patients with IL-6 blockade and see whether we affected anything at all or whether, in fact, there were other molecules that are also leading to this injury?" And I don't believe that there is one molecule, there is a group of molecule that need to be targeted.

Miriam:

But what we are looking at, this is a big focus of my group now, and many group all of the world, and I have to say many of us work together on this question, is really trying to find nodes that are important to targets. What are the big nodes there? And there are very interesting results, and we are still testing in patients. I don't know whether you've seen that the IL-6 blockade, in fact, has led to some clinical benefit. There was a paper submitted, [inaudible 00:46:38], but it had a lot of press and there was even a comment about it on The Economist and in The New York Times. I know, it's extraordinary that now The Economist is talking about immunology. I'm very happy about it.

Dave:

You're becoming famous.

Miriam:

Well, my hope is that we will, by doing that, we are not going to try to simplify the message. As long as the lay press understand that it's very important to embrace the complexity and the audience can take it. And just tell them what it is, right? It is complex. Initially, we thought it was one molecule. Now that we can study many molecule at the same time, we realize it's more complex. I believe we can embrace complexity and still have very efficient drug.

Dave:

It's what hacking does, right? The idea is it's going to be a black box and we think we know what's inside there, but we can test if we're hitting enough of the nodes to get the results and then we'll see. In the first couple weeks of COVID. They said, "Well, guys, here's the list of natural compounds that we know radically reduce IL-6," because it's not just pharmaceuticals. There's things like andrographis, all of them, probably because they're plant-based, they also reduce other associated things, like a network effect. And then, I got a nasty letter from a three letter agency saying, "Take down that blog post," so I did. But we do know, [inaudible 00:48:09] if I had an unknown viral infection, well I would address excessive

inflammation, without suppressing the immune response, because that's what all functional medicine doctors have done throughout all of history.

Dave:

And there's herbs, oh, 20% reduction in the duration of symptoms, likely because of this effect, but that doesn't mean it's going to cure any sort of specific virus, but it's building resilience by preventing excess inflammation. What would you do? And you may not even be in a position to answer this, but would you do tomorrow if you had an unknown virus that was causing systemic inflammation? I mean, would you take an Aleve? Would you fast? This is not offering advice for people on what to do, this is you, as an expert in the world saying, "I don't know what's going on." But what's the most likely thing that you'd bet on?

Miriam:

Well, okay. This is the conundrum here, right? You need your immune system to fight that virus. But the excessive response can lead to injury. Big example is COVID. Now, in COVID, what's interesting, and I think the answer for COVID would be simpler, just because we know a lot about it now, is that by the time you have symptoms, you usually have a strong immune response against it, and this is what we have found, my group, and together with many colleagues here at Sinai, by the time they were coming to the hospital, many of the patients had already a strong antibody response, and likely, a strong T cell response. But definitely we measured very good antibody response.

Miriam:

So at that time, I think it's okay to give strong anti-inflammatory, even steroid, because if you have an antibody response, those antibody are not going to go away, they will get rid of the virus, the free virus, and you'll probably have T cell that are going to also help get rid of infected cells and continue to act, and you are going to reduce these inflammatory injury, that inflammation that is telling the immune system, "Keeping bringing effector cells and keep bring more army here to clear the damage." Because at some point the immune system can go in disarray.

Miriam:

Now what scares me when I have a new infection, and that's why it's difficult to address your question, if I have an infection that I don't know about, I don't want to compromise my immune system. I want that strong antibody response, because I want to get rid of the virus, so this is where you have to be very careful about how to intervene and maybe this is why some people will be [inaudible 00:50:54]. I was very anxious initially when we were bombarding patients with steroids when they were coming to the hospital, because I thought, "Wow, we are going to put them in an immunocompromised state." And I'm sure that many of these patients don't have a strong antibody response. Well, I don't give clinical advice [inaudible 00:51:10], but then I would have said, "Continue to unleash steroid, absolutely."

Miriam:

You have to be very careful. This is the conundrum that I study, and this is where when I talk to pharmaceutical industry and to funding agencies, this is the conundrum, this is the moonshot of this century, is how you drug the immune system so that you do not compromise or you keep the beneficial effect without compromising our ability to fight infection, the cancer cells, and you prevent the damaging affect, which is excess inflammation. And I draw, usually, a balance and I'll send you some

material if you want, and I said this is the conundrum of the century. We have the knowledge, we can drug it, let's figure out how to continue to make sure we [inaudible 00:52:17] and expand and harness the beneficial effect and control the harmful effect of excess inflammation.

Dave:

And I'm hopeful we get to the point soon where someone shows up at the hospital with whatever inflammatory viral infection, COVID or not, we can look at all their different cytokines, go, "Hmm, this is what's going on." And if you're listening and going, "Wait, what's a cytokine again?" These are inflammatory signaling molecules that happen when you have inflammation. They're like a symphony. Different ones come up at different times. We'll probably be able to say, "Ah, based on this pattern of cytokines, let's use these substances, natural or not, or these practices that may include fasting, to attenuate that response, so you have the right mix of cytokines and you don't have too many of them." And that that will be a very broad spectrum way of treating things, because now we've limited this response. I don't think we have the data for that yet, but it feels like we're getting kind of close. How close are we?

Miriam:

Well, there are some disease where we are closer than others? In this big lung injury disease including [inaudible 00:53:27] or sepsis, for example, we still have a lot to learn. But I have to say, the pandemic is going to really, somehow, enhance that focus and really, I think, there has been not enough attention or funding being put in sepsis. For example, just because of the complexity again. Now, other diseases, for example, when I think about cancer where, imagine a few years ago, too complex to really revive, make sure that we drug cancer immune response. And yet, in cancer, the progress that we have made in 10 years, drugging the immune system of cancer lesions is extraordinary. And, in fact, I will argue that many of the knowledge that brought us to developing this fast COVID vaccine, the mRNA vaccine that Pfizer and Moderna did, it's because of cancer, right?

Miriam:

We made this vaccine, we, the community, were pushing for this type of vaccine really for the cancer community, because it's very difficult to do an infection vaccine, because you will deliver an agent to a healthy individual, so this field is really complicated in terms of drug development. However, cancer there's such a need. All this knowledge was really because of the cancer immunology effort. It's extraordinary. Our field is so active. You cannot imagine how much intellectual strength there is, right now, in really trying to really parse out all these different pathway. When you say, "How close are we?," I think somehow, if we put the same effort that we've put in cancer immunology in really understanding this big lung injury disease, and I think the pandemic is going to just do that, I'm super hopeful. I'm very excited-

Dave:

Awesome.

Miriam:

... right now, because many of these superstar colleague of mine and many of my superstar fellows already had decided to study that. So it's exciting.

Dave:

Well, this is the long-term thing, for listeners, just think about this, it's been pretty messy in 2020, no doubt about it, economically, personally, just society-wise, politically, of course, but the longer-term, one, two, three, four year affects from the level of attention and funding of this are going to make people live longer, regardless of whether or not they get COVID, just because we are cracking more of the code of the human body. And I'm always honored to be able to talk to someone who's actually doing the cracking of the code. Dr. Merad, thank you for being on this episode of Bulletproof Radio and thanks for explaining what's really going on in our immune system, and talking about fasting, even from croissants, but only some of the time.

Miriam:

Sure. My pleasure. Anytime. Thank you.

Dave:

If you guys liked today's episode, you're definitely going to want to read Fast This Way. We don't quite as deep into the science as we went on this episode, but it's got a lot of learning in it. And you also want to join the fasting challenge and training where I'm going to teach you what's in my book for two weeks, for free, because I just want you to try intermittent fasting to experience exactly what Dr. Merad experienced. Wait, you mean I had more energy when I fasted and I saved time and money on breakfast? And when you have more energy you're actually nicer to other people and you can show up in the way you want to, you can make great discoveries, as you're hearing about on the show today. Join me in learning how to fast without pain, go to fastthisway.com and if you haven't ordered the book and you're planning to, please order it now, because early orders make a huge difference for authors like me. Have a beautiful day.