Overview of the Immune System

00:00 Dr Mike

Welcome to another episode of Dr Matt

and Dr Mike's medical podcast. I'm your host Dr Mike Todorovic and I'm joined by my co-host that boasts the best roast and that is Dr Matt

hew Barton. Hello Michael. You're a vegetarian so you probably don't boast the best roast.

00:45 Dr Matt

That's why you can roast vegetables. What a loser! Why is your crowd still here?

00:54 Dr Mike

Yeah I paid them a lot of money. Today we're talking about — we're just going to jump straight into it. What do you think? Go for it. Well do you want to — how are you?

01:02 Dr Matt

Are you good? I'm well. I'm well. Good. What's new? Not a lot. Having an extra child is a lot more work. Yeah. Yeah. Are you going to have three? No. You told me. You told me this. You warned me didn't you? I did. You're like, oh wait do you have a second?

01:19 Dr Mike

Yeah and then I said wait do you have a third? Wait do you have a fifth? I've got a couple of mates who have four kids. That's — I just — But apparently foursies and three. Yeah but you've got to buy a new car. As soon as you get four kids you need a van. That's true. You do. Do they have vans? Yeah. Okay. Yeah. One of my mates has that new Kia Carnival. Is that what it's called? Yeah.

01:45 Dr Matt

That's great. That's huge. It's like an eight-seater car. It's like a bus. So — How are you doing?

01:52 Dr Mike

Well thanks for asking. No problem.

01:54 Dr Matt

You never ask. I always ask you. You never ask me. That's because I'm not off screen. Well I kind of off screen. No. Off screen you never ask me either. No I do. Then you spend an hour explaining and I'm oversaturated and then I don't want to go through it again on here and I don't want to subject the listeners to it.

02:09 Dr Mike

All right. Fair. Okay. Look no one's listening because they want to hear how we are as human beings. No one cares about us personally. We're just robots. That's right. We're just information machines to you animals. You don't care about us. Anyway dear listeners disregard everything I just said. Today we're talking about the immune system. We're going to do an overview of the immune system and I just want to preface that by saying the immune system is bloody difficult. Yeah. Very complicated. I think that probably the smartest people on the planet are immunologists and people that deal with the way that the immune system functions and all of the very specific niche small slight changes defects. I mean it is.

02:56 Dr Matt

I think we saw that quite evident in the pandemic which are we still in? Yeah. And that illustrates how difficult it is. So you've got the best minds on the planet trying to understand a virus but the virus is constantly changing. Yeah. And so this is the difficulty right?

03:15 Dr Mike

And not just that but the way everybody responds to that virus is different. Yes. Some people are asymptomatic others die. Correct. Correct. So I mean that's very different.

03:27 Dr Matt

And then we actually seen all the ramifications now of being infected like the long COVID syndromes which probably a lot of it is driven by your immune system right? So not so much the virus it's what your immune system has done in response to the virus which has now caused a host of downstream effects anything from brain, heart, kidney, liver.

03:53 Dr Mike

Well I think one of the big what they've been saying regarding COVID is that it's a vascular disease. You know it affects the vessels and obviously every tissue of the body has blood vessels. Yeah. But your receptors and your abundance of certain types of cells and chemicals differs from person to person and therefore some people will be affected differently and so some might be more affected neurologically with the nervous tissue. Some might be more affected renally. Some might be more affected systemically with the and some might not be affected heavily at all. And so I think that's one of the reasons why COVID has been a real tricky beast.

04:31 Dr Matt

Very difficult. And I think also this is probably the first time in human history where we've been doing to a degree science experiments in real time that the public is part of. Yeah. And people knowing this information is sometimes not great. Well when you have not great. I'm not like that I want to keep we should keep people in the dark.

04:56 Dr Mike

But when you have non-specialised people trying to make sense of specialised information it doesn't work. Right. I mean if I went to my mechanics I know nothing about cars. If I walked into my mechanics and got him to explain exactly what he was doing and why he was doing it there would be many things I wouldn't understand and many things I'd misinterpret. And that's simply because I don't have the content knowledge to make sense of it. And I think that's one of the things that's happened. Like you said involving the population in dealing with COVID and being part of vaccine trials and getting people vaccinated and all these types of things. It's the immune system is probably one of the most complex parts of the body and we're trying to get the public involved in understanding it. Right. And they're not trained to understand it.

05:45 Dr Matt

It's not their fault. And then even just the understanding of science and the process that science goes through. Yeah. It's not like you do one experiments and now you have a definitive outcome that is like written in stone. Yeah. And then you have the data and so working in a system now that we have a pandemic where everyone's affected and it's in an emergency situation. And then scientists or medicos are being asked that you have to be definitive with this and then you have the media trying to be definitive with this. That's right. And then when things change which what science does. Yeah.

06:23 Dr Mike

People feel that they lose trust in the process. Exactly. And we have a lot of data in this. And we've got one experiment that we're doing, for example. We have a paper that we're publishing. It's actually a paper that we're publishing. And it's a paper that is actually published. It's a paper that's actually published in the literature. Right. And every every scientific experiment that we perform in paper, we publish is relevant in the context of that experiment and is in a way and it's probably not the right term to use, but for that experiment that's what happened. And if you do it more often and with larger numbers, then you become more confident in the answer. But you still don't really ever say that definitively this is the case, particularly when it comes to the human body. It's very tricky. And like you said, I think that's the problem that has risen where people have started to distrust science and scientists. Yeah, is because they're like, oh, you said this and now you did that. And now you've said this.

07:25 Dr Matt

It's just like, yeah, because science changes all the time. And also because the virus is changing, you know, that's true. All the early evidence was done on the Wuhan version. And now we're so far down beyond Omicron, which is almost a different virus. Right. That's right. And so it's you can't kind of change things in real time. Yeah, that's right.

07:45 Dr Mike

So, you know, just that is highlighting some of the difficulties associated with the immune system. So hopefully with this overview, we can help people sort of have a basic understanding of how the immune system works and also delve a little bit deeper as to the various aspects and components of the immune system so that you can apply this information either in your own life or within your study. Yeah. Right. So I think this episode, everybody will be able to understand in some way or another and apply some information. But there's a lot. And we'll try to illustrate in a kind of a real life example. Yes. So to begin, let's define the immune system. And so I would say that the immune system is a complex network of cells, tissues, organs that work together. Molecules. Molecules that all work together to protect the body against harmful agents. And these agents could be living bacterial. They could be viral, which isn't necessarily living fungal parasitic. It could even be just abnormal cells of your body.

08:59 Dr Matt

Yes. And I think that's important to state that the immune system also will provide surveillance to your own self. And if there is question questionable cells, whether they are dysfunctional or whether they are maybe on the brink of becoming cancer like, the immune system will remove them. Yeah. But there's also things that happen in the body that's not necessarily cellular, but could be just debris or toxins. I know you don't like that term.

09:33 Dr Mike

Well, if it is a toxin, then that's that's absolutely fine. And you can have toxins from bacteria, for example, and you can have metabolic. Can you say metabolic toxins? Well, you know, you would say metabolic byproducts that have accumulated to toxic quantities. Okay. All right. Right. So, you know, so you could say that. But I think at the end of the day, the immune system is the body's way of dealing with something that could harm the body, whether it's an invading pathogen, which is something external where there could be living, nonliving.

10:05 Dr Matt

And that might include bacteria, viruses, fungi, parasites, or it could be abnormal cells, or it could be misshapen, damaged, dying cells, anything that at the end of the day called debris of cells could damage or harm the body. So I think it's also an interesting point to add there is you may not want to say rid in the body of microorganisms, because we now know how important having a bio biota or a microbiome is now. Right. So you don't want to more cells of other things than we are ourselves. So you don't want our immune system to make us sterile. So we do have to live with these. And we shouldn't say pathogens, because pathogens are disease causing microorganisms.

10:54 Dr Mike

So we should just say we want to live with other microorganisms, but we need to have that balance between having a neighborhood of microorganisms, but not allowing the dodgy ones in. That's right. We live in a biome. And the biome is not just us. It is bacteria. It is viral. It is fungal. It is parasitic. We have all of these organisms on us right now, and they aren't necessarily pathogenic. However, you can have organisms that live on and in you that may not be pathogenic in the environment or in the local environment that they live in on your body in the quantity that they live in. But if they become overabundant or they decide to move home and go from your skin to your blood, for example, then yes. Or your surveillance system has kind of weakened. Yeah. To let them do this, then yes, then it can be damaging. And that would be called opportunistic. Yes. And that happens. I mean, for example, we've got staff on us at all times. Staphylococcus aureus, right? I thought you meant dog. No, sorry, not staffees. But we've got staff aureus on us at all times. And it's not necessarily a problem until you have too much or it's in the wrong spot. So again, we need to be very mindful of that. And our own genome, our DNA is filled with old dead viruses. And in actual fact, by saying dead makes it sound like they don't work. We've got a whole bunch of viruses, ancient viruses embedded in our genome that we require for survival. So we've even taken some of these pathogenic organisms, if you could call a virus an organism, and have incorporated it into our DNA and have used it and wouldn't be around today without it. So again, it's bloody complex. So when we talk about this, we're going to use some analogies. And Matt and I sat down for the first time. Wait, before we do that, can I just summarize the immune system in my mnemonic? Yes, but just let me quickly just say that Matt and I sat down for probably the longest time period ever together to discuss a podcast. Five minutes. Which is about five, 10 minutes to talk about how are we going to frame this episode. And so we think we've figured we haven't practiced it. But we think we've figured out a good overall analogy to use. But before we jump into that analogy, please go ahead.

13:23 Dr Matt

This is just me summarizing what the immune system does in a few dot point words. Okay.

13:29 Dr Mike

And what do you call them? Your five Rs. Matthew's five Rs of the immune system. Yeah. Is that what it's now trademarked as? Let's trademark it. Matthews. Ladies and gentlemen, may I give you. No, that's not right. Ladies and gentlemen, let me introduce to you the five Rs. No, ladies and gentlemen, how much of this should I cut?

13:49 Dr Matt

Ladies and gentlemen, Dr. Matthew Barton and his five Rs of the immune system. I got applause today. Okay, great. For once. So first R, it needs to recognize. It needs to recognize. It was going to be redhead. It needs to recognize those shady characters. So both outward or also inward, it needs to react to this. So when it when it recognizes it needs to be able to react to it in a favorable way, it needs to remove. Okay, so it needs to get them out of the picture, usually destroying them. It needs to repair. And that's probably the additional thing we could have said at the start. The immune system is also important not only for, you know, killing things off and removing debris, but also facilitating healing.

14:42 Dr Mike

It sets the scene. Yeah.

14:44 Dr Matt

And then finally to remember.

14:46 Dr Mike

So what are the five? Just what are the five Rs? Recognize, react, remove, repair and remember. Wow. How's that everyone? Are you proud of Matt? Because I'm not. Never have been, never will be.

15:02 Dr Matt

All right. So that's that's a scene.

15:04 Dr Mike

It does. So it does a lot of things for us. We are going to now set another scene. This scene, Matthew, is a military battlefield. We are in a war. In a war, yes. And this war is going to have soldiers. It's going to have infantrymen. It's going to have various units within the military. It's going to have generals and lieutenants. And it's going to have grunts and it's going to have front linesmen and it's going to have very specific individuals like the Navy SEALs or here in Australia. And equipment they use. And the equipment they use. And we're going to tie it all together to build this beautiful understanding of the immune system. Firstly, I think it's fair to say that you can broadly divide the immune system up into what we call the innate division and the adaptive division. Now, the innate division is also known as the non-specific aspect of the immune system. Yep. And the adaptive division is the specific aspect. What this is referring to broadly is that the innate or non-specific, it's various cells, chemicals, structures and functions of the body that will deal with these pathogens or issues of the body non-specifically. It doesn't care whether it's a bacteria or a virus or just a damaged cell. It really doesn't care what it is. It's going to deal with it the same way regardless. And so that's why it's called non-specific or innate. Yep.

16:42 Dr Matt

The adaptive… And the way it reacts to it is very fast.

16:46 Dr Mike

Very true. So it acts within seconds, hours. It's the first line of defence. Compare that to the adaptive. Now, this is the specific arm. It has a way of recognising specific pathogens. So it knows whether not just whether it's a bacteria or a virus, but it knows what type of bacteria it is and what type of virus it is and whether it's seen it before. So it has memory. It can develop memory and it can retain and maintain that memory.

17:16 Dr Matt

Yeah. And I think I'll add there when you say recognisers, it's recognising a piece of that foreign agent, right? That's right. Which is an antigen. And it's important to note here that this is as close as it can be to infinite. So…

17:33 Dr Mike

As an infinite… It can recognise theoretically an infinite number. Why can't we say the word infinite today?

17:41 Dr Matt

Infinite. Infinite. Amount of antigens. Yes. So these are the pieces of clothing or articles or something that recognises something foreign or damaged.

17:50 Dr Mike

I'll give you an example. When we're at work, if I say, hey, Matt, I'm going to come to the Gold Coast campus, I'll see you there. If I'm walking and you're in the distance, I recognise your red hair. That's your antigen. That's my antigen. Right?

18:04 Dr Matt

It's like your flag that you wave that says, I am Matt Barton. So now you know specifically that's me.

18:09 Dr Mike

Yes. So at some point when I scalp you, I'll be able to take that red hair and show it to somebody else and they go, oh, that's Matt. Yeah. It was Matt. All right. So let's first focus on the innate. Yes. Of the immune system. So non-specific, doesn't have memory. The very first part of this, again, if we're thinking about the military, this is going to be the external defences. So this is going to be the things keeping everything out. So this would be the first line of defence? This is the first line of defence. This is, let's just say, you're trying to keep your city under control. You don't want any of the invading enemies getting into your city. And you know that the enemy is fast approaching. So what do you do, right? If the enemy is fast approaching, what do you sort of set up? What do you get ready to stop them from first invading?

18:59 Dr Matt

Yeah, they put all those temporary barriers up with sandbags and razor wire and things like that, right? Yeah. It makes it very difficult for invading armies to get into.

19:10 Dr Mike

So the first thing, like you said, is these walls. And so we've got walls of our body, which is called the epidermis, which is our skin, which is made up of epithelia, which is one of the four tissues of the body. Epithelia, nervous, connective and muscle. So epithelia is the protective lining. And the protective lining of our skin, the epithelia, is called stratified squamous, which is many layers of these flat pancake shaped dead cells. And that's like just creating this fast brick wall or sandbagged wall surrounding the city. Easy. First line of defense. But there's other things.

19:51 Dr Matt

Yeah, there's other vulnerabilities where the army can get into.

19:55 Dr Mike

Well, that's the invading army. That's right.

19:58 Dr Matt

Exactly right. And so let's just say they get to the wall. So you'd say your body as a surface, I'd be guessing here, but let's say something like 98% of your body is wrapped up in skin. So it's a pretty good barrier. But there are a couple of vulnerable points where you can get entry into the body. Eyes, mouth. Yeah, all the orifices basically. So ears, eyes, nose, mouth, rectum. Yeah. I mean, yeah, that'll do. Let's keep it like that. So now we go into mucous membranes, which are areas that have still like a wall, something to it, but it's now got fluid associated with it.

20:37 Dr Mike

So because the army that's protecting the city, they know these are vulnerable, vulnerable spots because this is where the army, their own army enters and leaves. Yeah. Right. And this is where some of the citizens can enter and leave. So you need you can't just wall off everything. Otherwise, how do you get food in? That's right. Right. How do you get waste out? Just like the body. Right. So what they do is they go, OK, these are vulnerable spots. What can we do to make this less vulnerable? And what the body does is it creates these mucous membranes and they have fluids and these fluids often have enzymes that just make it not and not a great environment for anybody come or any thing. Pathogen coming in. So, for example, you've got your saliva and your saliva will have multitude of enzymes inside. So do your tears as well. And, you know, they've got various enzymes that can start to break things down. So, for example, you've got your tears, you've got your saliva, you've got the mucous membranes inside of your nose. All of them have enzymes and the pH is a bit off, which means it's not a great environment to survive. You've also got sebaceous glands and sweat glands on your skin, which release oils and release very salty sweat. And again, it's not a great environment for anything to survive. Yeah. So you sort of removing all the all the factors that make it tenable for survival. So it's like salting the land of the enemy. It's just like, well, I'm not going to have any there's not going to be any food for you. And your sebaceous oil glands secrete unsaturated fatty acids, which bacteria don't really like to eat. You also secrete a lot of sweat, which can wash things away as well. So, again, it's just like making the land untenable for the survival. Does that make sense? It does. But you've also got things like hair and cilia, which can trap things. That could be maybe like the razor wire. Yes, the razor wire on top of the fences. And they get stuck in it. Yes. And then you can sort of just pluck it out and throw it away.

22:51 Dr Matt

And so that's. So within the fluid also, you could throw in some mines. So, you know, hell in the waterways, they'd throw those floating mines. And then if the ships try to get, they'll just blow up. Yes. Tears, saliva, any other mucus, maybe also in the general tract. The vagina and the urethra, they would have these kind of.

23:14 Dr Mike

Lysosomes. Yeah. Blow it apart. That's right. Yeah. I think that's a good one. And also, if it gets in, let's say it gets through and it gets into your gut, for example, your stomach, I should say, the pH is going to be between one to three. Right. So, again, there's some water land mines there. You're just going to disintegrate. Yeah, you're not going to do too well in the stomach. So what we've got as our first line of defense here, it's nonspecific. It doesn't care what is invading it, but you've got the epidermis and the skin, which are the walls. You've got the hair and the cilia, which is going to be like the barbed wire fence. You're going to have the saliva. You're going to have the tears. And these are going to be things like, you know, salting the fields or not allowing for the environment to be good enough to survive on or having water mines or land mines present to just blow things apart. That's the external barriers that we first have. But the thing is, we know that enemies can invade through those external barriers. And sometimes you need to fight head on, fight face to face. And this is where we start to meet the internal defenses of the body. Again, they're innate, they're nonspecific. But now we need to talk about the fighters, the warriors, the soldiers.

24:27 Dr Matt

So now we go into the second line of defense. Yeah. And these are the cells. Yeah. So now we're talking about the soldiers. Still innate, still nonspecific. Yep.

24:37 Dr Mike

In place of the soldiers, these are the cells. Yes, that's right. So the very first line of defense is the grunts. These are just the general soldiers of the army. We could call them in this context the phagocytes. So phagocytes, phage means to eat, site means cells. And there's a couple of different types of phagocytes.

24:59 Dr Matt

But their job is to go in and indiscriminately destroy. And so the majority here would be the infantry, right? The riflemen. The rifle people. Yep. So this is the neutrophils. The rifle people, yeah. The neutrophils. Yep. And the vast majority of these cells are from this type. Neutrophils. So somewhere over the range of 40 to 60% of white blood cells. Because these are white blood cells, right? Yes, called leukocytes. Can we say this now? Yep. These are these white cites cells. So this is a form of blood cell neutrophils. These are the grunts. These are the rifle people.

25:37 Dr Mike

And 40 to 60% of white blood cells that you can create in your body would be of this type. Yes. And if we think about the white blood cells, the leukocytes, there's a mnemonic you can use to remember them. Which is, and we're going to talk about all of these leukocytes. Never let monkeys eat bananas. And it goes in order of most abundant to least abundant. So never is neutrophils. Yep. Let lymphocytes. Monkeys. Monocytes. Eat. Sonophils. Eosinophils. Bananas. Aesophil. That's right. So these are the white blood cells. Now the thing is, of these five, the lymphocytes are the T and B cells, which are part of the adaptive immune system. So park that one and we'll talk about it a bit later. But we will talk about neutrophils, monocytes, eosinophils and basophils because they're part of the sentinate nonspecific. Now you perfectly said the very first white blood cell that comes in when there is something invading is the neutrophils. They're the rifle people. They're the front line of defense. They're coming in. And because they're what we call phagocytic, their job is to simply engulf and destroy. So the process of phagocytosis, which is what neutrophils do, is basically it engulfs it, brings it inside, destroys it inside of itself and breaks it down

27:01 Dr Matt

and basically recycles the parts of it. Yeah, and then itself as well. And itself. They're not lasting very long. They're really only lasting probably hours.

27:10 Dr Mike

It's a good point. So they self-sacrifice. A lot. And when they get the enemy and destroy them and they themselves die, you've got the remains of them laying across the battlefield. This is pus. It's pus. After you get an infection.

27:25 Dr Matt

Yeah, particularly infection that you can see, right? So if it's on skin or maybe in your nose, mouth, this is you basically see the remnants of neutrophils probably killing bacteria. Yeah. And themselves dying in lumps everywhere, which is the pus. Great. Glad you said lumps. So in addition to the… The one thing I will add here, why we call them these strange names.

27:50 Dr Mike

What do you mean? As in like neutrophil? Yeah, go on.

27:53 Dr Matt

Is… Well, neutrophil, asinophil, basophil, they are in reference to phil, philic, which means to love. Oh, sorry. I've got a cousin called Phil and I just thought it was named after him. To like the stain that they are stained with. So neutrophil, they like a neutral stain. The stain that would stain the neutrophil… Histologically. Histologically would be of a neutral pH. So you're talking about all the boring stuff. That's right. But I've got to say it. Because otherwise people won't wonder why they have these strange names.

28:27 Dr Mike

So when you stain it with something boring and neutral, neutrophils light up. What about basophils?

28:34 Dr Matt

Basic. So a… A basic stain. A basic stain. So it's something beyond 7 pH. All right. Eosinophils? Well, eosinophil is like a specific stain called eosin.

28:45 Dr Mike

Which purple? Pink. Pink. Okay. I'm colorblind. And what's the last one? Monosite.

28:52 Dr Matt

Monosite. That's just a cell with a single nucleus.

28:57 Dr Mike

Right. So it's all different. Well, the other ones… One's about the stain it likes, the other one's about the acidity, the other one's about what it looks like inside and then… Basically it's all histological appearances. Let's keep it to that. And let's leave it at that. That's right.

29:14 Dr Matt

Because that's boring. The histologist will hate us. But anyway, we've said it. We've said it.

29:19 Dr Mike

We love you though. Yes. We love you. You can hate our guts. That's fine. So neutrophils, first line of defense. But they're not the only phagocytic cells that come in straight away. There's a lot.

29:29 Dr Matt

So the second lot are macrophages, which just mean big eaters. And they technically aren't macrophages to begin with. So they're not born that way, Michael.

29:38 Dr Mike

Well, not the first type called the wandering macrophages. The wandering macrophages are actually monocytes. Yeah. Right. And so we've spoken about neutrophils now. Let's talk about monocytes. You said they're the ones that when you stain them, they've got the big circle on the inside, right? Which is the nucleus. It's the nucleus. So what the monocytes do is they're floating through the bloodstream. And then when they get to the site of infection where they're like, oh, this is where the enemy has broken through the walls, they jump to that battle site. So they jump out of the blood vessel and start migrating towards the area of concern. Yep. In the tissue. And here it starts to change and it changes its appearance into a macrophage, which is a big eater. And now it stays there and engulfs and eats and destroys. And what would this be as a military personnel? So this is going to be like the scouts. OK. So they're sort of walking. They're sort of looking for danger. That's right. They're roaming the battlefield and going over there. I'm going over there. And as soon as the scout gets onto the battlefield, they pull their rifle out. They're a rifleman now. OK. Right. So then they start to fight.

30:42 Dr Matt

Take them out. But you also mentioned that the macrophages have also been strategically located as fixed macrophages.

30:50 Dr Mike

So they're put in certain locations in the body that are likely to encounter dodgy things. Yes. So the monocytes are the wandering. They're just the scouts. They float through. But you're right. There's going to be some where the general has said, look, you guys, I want you to remain in the jungle and you stay there and wait for the enemy. You guys are going to remain in the desert. You're going to remain in an urban environment. Right. And they just sit there and they wait. They've got the snipers ready and they're sitting and waiting for the enemy. They're fixed macrophages. And so you can have the cup for cells. So they're in the liver. Cup for cells of the liver. You can have the microglia. So that's a central nervous system of the central nervous system. You can have this.

31:35 Dr Matt

Well, this is going to be one in the alveoli. So alveol and the jungle ones. They're right at the bottom. Yeah. Of the very wet humid environment. That's right. And so they're really the last form of defense in your respiratory tract. They're right at the bottom of the alveoli is hanging out just in case it gets right to the bottom.

31:55 Dr Mike

That's right. So basically pick a tissue of the body. You're going to have some fixed macrophages there and they've got the sniper and they're ready. Again, they don't care what's coming as long as it's something that shouldn't be there. And then they'll pick it off.

32:07 Dr Matt

So there's another one just to add here, which I'm not sure it technically is a macrophage, but there's a term or a cell called a dendritic cell. Yes. And so they also located in the under the epidermis. So in the dermis layer and also in the mucosa. And they're going to be very important because they're basically the bridge between the innate and the adaptive. So they're going to play a really important role in identifying the enemy. But you could probably just say that they're just a form of macrophage as well. Right.

32:41 Dr Mike

Yeah. Or a faggicide at least. I would call it a fixed macrophage. Yeah. Yeah. So then so they're those basically the grunts. Right. And we've you know, but we've got other cells that are present. We haven't spoken about the eosinophils or the basophils. Now they're less abundant, but they have very specific roles in the innate aspect of the immune system.

33:04 Dr Matt

The way you should think about the and correct me if I'm wrong, the eosinophils and the basophils is the eosinophils are white blood cells that are really good at helping kill off parasitic infections. Yes, I think that would be probably slightly more dominant of the eosinophils. Yeah. And then the basophils are very good at allergic responses. This is where it becomes difficult because the sonophils will also be allergies. Yes. Overlap with all of these cell types.

33:32 Dr Mike

But if we're going to just sort of make it easier to understand eosinophils, they're there for the parasitic infections and the basophils are there for the allergic response based infections.

33:42 Dr Matt

So with the sonophils, the parasites we could give an example to. Like a tank coming in. Yeah, like worms. So helminths, which is what we term it in microbiology.

33:53 Dr Mike

It's funny because when we played the game worms, they were wearing helmets. So these are helminths.

33:59 Dr Matt

That's right. So the sonophils, yeah, like the tank, what would you call them? Anti-missile. That's right. Shooting missiles. These are, well, technically, sonophils are filled with granules. So they are called, you know, in, again, histology, they would be called a granulocyte. And when they are activated, they spill their granules over there. Let's say in this case, over the worm, which is like shooting missiles into the tank.

34:27 Dr Mike

That's right. Yeah. Okay. So the basophils, right?

34:31 Dr Matt

So basophils, you can probably talk with mast cells. So mast cells are a bit like what you said with the wandering versus the fixed. So which one's which here? The fixed are the mast cells. So they're like a fixed basophil. Yep.

34:46 Dr Mike

And the basophil is wandering a bit. Okay. And when they come across sort of like, you know. An injury. Yeah. Or, I mean, I could be wrong with my analogy here, but let's just say the enemy has thrown out some sort of chemical warfare, right? Agent Orange or something. When that chemical hits these soldiers, they're now primed to respond and react. So the way they will react is they're carrying their flamethrowers with them. Basophils are wandering with their flamethrowers and mast cells, they're sitting crouching with their flamethrowers. And then when the enemy comes by with their chemical agents to trigger them, again, the allergen, they start flamethrowing. They can't see them. All they see is the chemical. They just, oh, this chemical, that means the enemy is nearby. And they flamethrow that area. Now, what happens when you start to flamethrow an area? It starts to heat up and you get inflammation.

35:43 Dr Matt

Yeah. So I think this is a good indication. What we're trying to do here is the basophils and the mast cells are really important cells to initiate inflammation. Yes. And inflammation is a physiological process that's part of the immune system that's nonspecific, but it's a now it's a physiology. It's a process. Yeah. Why do we have inflammation? Well, it's a good it's a good thing to have to notify the body when it has been injured for the first time.

36:13 Dr Mike

Inflammation is like hanging out with Matt in the short term. It's great. But over time, it's pretty annoying and detrimental. And yeah, you've got to get rid of it. And so inflammation is also part of the innate nonspecific immune system.

36:29 Dr Matt

So we can sort of talk about it now if you like. Yeah. So anything that potentially can cause tissue injury to vascularize, which is pretty much everything except cartilage, which is not a huge amount of tissue in the body. But you're right. I'm like a shark. All right. So what it will do is initiate this process. And so an example, what the mast cells and the basophils are doing here, because again, they're granules. They will do a process called degranulation. And one really common granule that they will release is histamine. And so they just say that the flame in the flame throw is histamine. That's right. So it's spilling all this histamine into the tissue. And that's in the tissue is all these blood vessels and the blood vessels start dilating, meaning more blood will come to the area. So the area becomes hyperemic, which means lots of blood flow. And it becomes really leaky. So a lot of plasma leaks out into that area now, which is going to be important for also bringing all those soldiers into the into the area, which is.

37:33 Dr Mike

Well, think about it. When you get the flame thrower and you start to flame throw a jungle, everyone's going to look in that direction. Something's going on over there. Let's get over there.

37:42 Dr Matt

And so then you've got more neutrophils and monocytes and macrophages coming to that area to help fight that infection. So the other thing that flooding the area does is it dilutes it all.

37:53 Dr Mike

So when you spoke about all those chemicals and all those destructive agents to the tissue, put an exudate or edema into that area floods it, dilutes it and allows it to be a more favourable environment for repairing. Yeah, that's a good point. When we talk about inflammation, what are the cardinal signs? So any time you have inflammation, so any time you have damage to vascularized tissue, inflammation will occur.

38:19 Dr Matt

But we know that inflammation ticks three or four different boxes, which are red, redness, heat, heat, swelling, pain. Right. Now, usually with those, at least for the last two, pain and swelling, it will add a fifth, which is loss of function or decrease. Use. So wherever that inflamed tissue is, it's likely that you don't want to use it anymore.

38:45 Dr Mike

So you could say there's five cardinal signs and all of these basically come off the back of increased vascular permeability. So the leakiness of the vessel and and vasodilation, which is really due to this histamine. Now, you could, if you wanted to, and I think we should add a couple of other chemicals here, which are released when those cells are damaged. So, for example, when the basophils and the mast cells start to flamethrow and you're fighting the enemy, other tissue will be damaged during that time. And these tissues are going to release bradykinins and prostaglandins.

39:24 Dr Matt

Yeah. And all these are made from cell membranes. So pretty much any cell with a cell membrane, which is every cell, has the potential to make these products that you just spoke of.

39:36 Dr Mike

Particularly prostaglandins made from arachidonic acid, which comes from the fatty bilayer. And prostaglandins do what histamine does pretty much very, very similarly, but probably more abundant. And prostaglandins are ubiquitous. They're everywhere in the body, but they don't just play an inflammatory role. There's actually a subset of prostaglandins that are activated in times of inflammation that do vasodilation and increase vascular permeability. But there are prostaglandins in the body that play housekeeping. Very important housekeeping.

40:09 Dr Matt

Yes, allows for the kidneys to work, allows for the gut to produce a mucus barrier, a whole bunch of stuff. And that's important to note because if you try to use drugs to diminish inflammation, if it's not selective, you can start to knock off these housekeeping effects. And that's where you get the big side effects of anti-inflammatories, specifically the non-steroid anti-inflammatories. NSAIDs. Like aspirin, like ibuprofen.

40:39 Dr Mike

Diclofenac, celicoxib. They stop prostaglandins. But if you have too much of it, you stop the housekeeping functions of prostaglandins. So you can get ulcers in your stomach and kidney function issues. Yeah. Okay. All right. So we've spoken about those granular sites, the eosinophils and the basophils and the mast cells. There's another cell type we need to talk about here that comes into play. Very sneaky cell type. It's got a cool name. The NK cell. What does NK cell stand for?

41:10 Dr Matt

Atro-killer. Atro-killer. Yeah.

41:13 Dr Mike

That's all they're made for.

41:14 Dr Matt

Remember that movie? Woody Halston? I know of it.

41:16 Dr Mike

Natural born killers. It's disturbing. But anyway, so you've got the natural killer cells. Interesting for those ones, they've actually come from the lineage of lymphocytes. Which are T and B cells. Correct. But they're specific.

41:30 Dr Matt

That's right. But these aren't. These aren't. Right. So these are guys started from a different area of the military and they're defected, I don't know if defected is the correct term, but let's just go with that. They're defected to the innate system. So they've left one arm of the military and moved to another.

41:48 Dr Mike

I see these as mercenaries. They're sort of out for themselves, right? And they're pretty ruthless. And what they do is when they see an enemy, they basically will very quietly go up to them and stab, stab, stab. So these are the ones that. You know what's Futurama? You know the robot that stabs? All he does is stab. He's sort of like this miswired robot and he stabs, stab, stab, stab, stab, stab. So that's the NK cell is stabbing the robot.

42:15 Dr Matt

I like to think, you know, those ones that just dress up in full camo and they just lie in the ground. Yeah, they've got the camo under the eyes and they just. Yeah, yeah, yeah. They're just waiting around. And then once. And well, this is important to note here. With your cells in your body, you have certain things that identify you as self. Yeah. And an important receptor that does this is called the MHC1. The major is the compatibility complex. This is a type one. OK. So this would be your like swipe card that would tell your immune system that this is you. Don't kill you as in your own cells. Right. This is your identification. That's right. But if anyone's foreign, they don't have this identification.

42:59 Dr Mike

Like in every movie where they try, you know, where the US military tries to get into a Russian base and they need to fake the ID. Correct. But if they don't have the ID, they're in trouble.

43:10 Dr Matt

OK, so. So this is the what we do our own cells. OK, so the natural the NKs, the natural killers, are just looking out whether they have the identification or not. Right. And if they they're lying on the ground in full camo and they see a person walking past, they see this guy doesn't have any MHC1. And stabby stab stab stab stab. Can't behind put holes through it with a knife. Good preference. So it actually has enzymes that act like the knife and just put holes all over it, which is not going to be very good for that outcome. Or if it's in a difficult situation where you can't make noise. Right. Because the person is going to scream if you stab them. So you put cyanide tablets into the mouth and close their mouth.

43:53 Dr Mike

Oh, and then they will disintegrate from the inside. And so that's called grands arms. So the NK cells have knives called preference, which put holes in them and they just leak out changes the concentration gradient from inside to the outside and they just leak out and die. But in other moments, it might want to give them grands arms to destroy them from the inside and induce something called apoptosis. Which is Greek for when the leaves fall off the trees in autumn. It's lovely. Beautiful. So stunning. Anyway, back to the violence. So this is different to necrosis. We need to I think it's important to sort of state necrosis is when basically the walls just break off and the cell sort of dies out in the open and it can be damaging to other cells around it. Right. Necrosis.

44:39 Dr Matt

So like one necrotic cell could possibly induce another necrotic cell because of the chemicals that releases and makes the environment inhospitable. That's right. All the all the gut. So this is more talking about your own cell depth here rather than microorganisms. So if you were to have to go through, let's say there was a situation in this analogy where a whole lot of your cells were compromised and they needed to be destructed. If they were able to be done in a controlled manner. So if the I don't know some military personnel came in and said, look, guys, you're really not well here. You've been infected. We want you to take one for the team and self destruct. Yeah, they can do that in a very controlled demolition way. You know how when you do it, the demolition and it's nicely orchestrated and it falls down with no damage to the neighborhood. Yes. That's apoptosis. Yeah. OK. But if it's done very quickly, so there's a lot of destruction quickly and the cells don't have the ability to kill themselves in a controlled manner. They're just going to explode everywhere. And the inside of cells is going to go everywhere through the inside of the cell has a lot of chemicals that's dangerous and toxic to the environment. This could be anything from lots of calcium to even things like ATP or even bits of DNA or lots of potassium. This is harmful for the neighborhood environment. So necrosis is an uncontrolled cell death where it just bursts and can damage the environment and cause more inflammation. And apoptosis is a controlled cell death that happens from the inside and it basically just is self controlled, doesn't damage the environment. Yeah. And a good example of that of necrosis, just to illustrate something clinically, if you were to have a heart attack, so a myocardial infarction where a whole segment of your heart was to die quickly and this would be a result of running out of blood. So you have a blockage in a pipe, a blood pipe, a whole section of heart. Do we call them blood pipes? Arteries, coronal arteries, coronary arteries. So a whole section of the heart dies, but it dies so quickly that it just bursts everywhere. And all the bits of the, this is going to be the cardiomyocytes, burst into the blood and clinicians actually measure this. And this is a way that we know that a person's had a heart attack. We look at these levels in the blood. This is called troponin, which is just a protein inside muscles and we know that creatine kinase, which is an enzyme in muscle and they can go, oh, looks like you've had some necrosis. Yeah. But this is likely in your heart because you've had other symptoms like chest pain and ECG changes.

47:29 Dr Mike

That's right. And if apoptosis occurred, you wouldn't be able to measure those things because they would be self-contained. That's right. All right. So we've spoken about now those NK cells and the fact that they are very tricky sort of things. I want to very quickly talk about the chemicals. So we've spoken about the cells. Let's talk about the chemicals of the innate immune system. And so the chemicals are interesting. The chemicals aren't the soldiers themselves, but the chemicals are ways that the soldiers can leverage the equipment or leverage other individuals to help in the response to fight against the invaders. And there's two major chemical types that we should talk about, the first of which are the complement proteins. There's around about 30 complement proteins and they do what they sound like they do. They complement the immune system and they do this. The way I like to think about the complement proteins is they basically figure out what is needed to help support the defense or the attack. And it might mean more ammo. So they help facilitate more. So they reload the guns, they reload the missiles, they reload all those types of things. Or the mortars. Or the mortars. So that's the complement.

48:44 Dr Matt

Physologically, the complement are a whole lot of inactive proteins in the blood. That's just always there. But when they encounter an environment chemically, that there is something going on, they all snap together. And an example of what they do is once they all join in a big complement process, they then smash holes into bacteria. Yes. And so this is like the mortar, like you said.

49:07 Dr Mike

So we've got the complement proteins and then you've got the cytokines. Now the cytokines simply just means signaling cells, right? And there's many different types. Or signaling cell, cyto.

49:19 Dr Matt

Cyto to do, to tell cells to do things. Yeah. And so it's like calling in support.

49:26 Dr Mike

That's what the cytokines are. And there's heaps of different types of cytokines. Two important ones are interleukins and interferons. But if you think about the cytokines as calling in for support, cytokines are the ones that are called for support. The interleukins is like calling in air support. Interleukins are the chemical messengers that call in other white blood cells.

49:49 Dr Matt

Yes, they're interleukins, I mean, between white. So they're between the white blood cells. So there's specific communications just between the military personnel.

49:58 Dr Mike

That's right. And so they might be saying, hey, I need air support or I need more foot soldiers or I need the special forces to come in. That's what the interleukins do. The interferons though, what do they do?

50:09 Dr Matt

Well, these are specific to viral infected cells. So if a cell is now infected with a virus, so the way that a virus would work, it's an intracellular parasite, unlike a bacteria that's could it could be intracellular, but it's mostly going to be extracellular, meaning it survives outside cells in the interstitial or extracellular fluid. But viruses need to replicate. It needs to dock on to host cell. So it needs to like a moon lander. It has to land onto a cell. It needs to inject its genetic information and it needs to trick the cell to remake a whole lot of viruses.

50:50 Dr Mike

So in the analogy here, it's sort of like the enemy has now infiltrated a particular unit or let's just say or a building. It's just, oh, we had that building. Now the enemy has that building. So what the interferons do, which is a chemical message. Yeah, it goes, oh, they've taken hold of the building.

51:07 Dr Matt

I better let unit F know that this building's been taken over to prepare themselves. Maybe like maybe like someone's waving a flag out like a white flag out the window and just saying we've been taken over.

51:19 Dr Mike

Yeah. So it's messaging. Hey, the neighbor viruses have taken over this cell. Be careful. You might be next. We're done for. Right. So that's interferons. And they can and that way that next group of cells can prepare and make it more difficult for the virus to come in and invade.

51:35 Dr Matt

And it's likely because that cell is now infected that you'll probably get something like a natural killer come along and demolish the building. Yes. So kill it. Kill the whole lot because it's affected. It's going to die anyway.

51:48 Dr Mike

Okay. So Matt, we're going to take a break and have a couple of supported ads and then we'll be right back. So welcome back. Welcome back. We have recently been talking about the innate or non adaptive arm of the immune system. And some of the things that we've been going through very quickly is using our analogy of the military on a battlefield is we spoke about the external defenses. These are going to be the walls. These are going to be the fences, the barbed wire, the sandbags, the trenches, the, you know, the landmines, salting the fields. And this is basically your skin and your mucus membranes. We spoke about some of the cells that are non-specific and these cells include phagocytic cells like neutrophils, fixed macrophages, wandering macrophages. They're sort of like the neutrophils of the first line of defense coming in, the riflemen and then the fixed macrophages sitting there, snipers, wandering macrophages, which are monocytes. They're the scouts determining where an invading pathogen is to turn into a macrophage. Then we had the granular sites and these are the eosinophils to target specific, well, more specifically parasites and basophils, which are allergens and the basophils and the mast cells. And again, basophils wandering, mast cells fixed and they've got the flamethrowers and they promote inflammation once an allergen has been exposed to them. And then we spoke about the natural killer cells, being these camouflaged guys running around with knives, stabby, stabby, stabby. And then the chemicals and we spoke about the complement proteins. They sort of provide more ammo, restock what's needed and then the cytokines calling in for support. And the interferon. We spoke about interferons. Interferons help warn other cells that a virus has infected a unit or a cell. And then the interleukins call in air support. In this case, it was other white blood cells. But don't very quickly, because we're going to be finishing up the innate arm.

54:16 Dr Matt

Don't cytokines also play a role in fever, which is an important physiological response in the innate aspect of the immune system? So cytokines is just a generic term, which basically means to activate cells. But they are released as kind of chemical messages between all the cells that are involved in these injurious processes and microorganisms and so forth. Right. So as these chemicals are being released, they're important to notify white blood cells and so forth to come to the area to try to remove the issue. But that can also not remain locally. It can also go into the blood. And then the blood can go everywhere. OK, so then this can notify distant regions that there is something going on the body like a battle or an invasion. Because are there certain types of cytokines which you haven't spoken about called pyrogens? Yes, pyrogens, which means to generate fire. Like a pyromaniac like yourself goes around lighting fires. So maybe these guys should have the flamethrower. So a good example of a location this is going to go is the hypothalamus. So that's a region of your brain, the diencephalon below the thalamus. And that does a number of things. But one important job it does in this particular context is regulate temperature.

55:38 Dr Mike

So did you say that you've had some sort of invading pathogen? You've had an inflammatory response in a particular area. These cytokines have been released. They've flooded the area, one of them being pyrogens aren't just acting there. They've jumped into the bloodstream and now they've floated up to the brain.

55:57 Dr Matt

And now they're going to have an effect at the hypothalamus. Yeah, and the hypothalamus usually just regulates a set point temperature of your body. The thermostat. The thermostat, which is nicely at 37 degrees Celsius. But when it encounters these chemicals, again through the production of prostaglandin. The prostaglandin changes the set point. So in response to the pyrogen, there's like an intrinsic effect. So this could be an autocrinal signal, which tells itself via prostaglandins turn up the temperature.

56:32 Dr Mike

So the pyrogens increase the release of prostaglandins. And that changes the thermostat. And it shifts it up probably closer to 40 degrees Celsius, which would be 115 Fahrenheit. So the body now, instead of thinking that the normal temperature is 37, it thinks the normal temperature is 40. Correct. So then if it sets it to 40, if you're now 37 degrees, it's going to think you're cold. That's right. So you shiver. That's right. To generate more heat. Generate more heat. Yeah, so that's what shivering does. It's just contraction, relaxation, contraction, relaxation of muscles that generates heat as a byproduct. And so you shiver and then you get hotter. And why is this?

57:15 Dr Matt

Is it just a side effect of inflammation? It is quite beneficial. One thing it does is remember, if we're talking about microorganisms here, they, because we term them now pathogens, which are disease forming, they have generally been selected to live most comfortably or to reproduce most comfortably at 37 degrees Celsius. So they're perfectly suited viruses, bacteria, things like that for your temperature, your physiological temperature. So if you bump up the temperature to 40 degrees, it makes everything they do more difficult. But what about our guys? Well, it's going to be unpleasant.

57:58 Dr Mike

But some enzymes like working better at higher temperatures. That's right.

58:02 Dr Matt

They work faster. And your immune system actually works more efficiently at a higher temperature. Not too hot, but it does make it a bit more efficient.

58:10 Dr Mike

So what you're saying is the whole organism may not like the increased temperature. So the bacteria, the virus or you. But the individual cells may work faster and harder at that temperature. So you're telling me that a fever is a trade off of your increasing the speed and efficiency of the immune system. But at the same time, it's not great for the whole organism, i.e. you. And so there's like this trade off that's happening. And obviously in the short term, fevers can be quite beneficial because it might knock the infection on the head. But if it lasts too long, obviously you'll get too high or it gets too high. Then that's the further detriment of the whole organism. I.e. you. And it might be quite bad. That's right.

59:02 Dr Matt

So people have died of fevers before. Exactly. So particularly for young children, infants, babies, because they've got to develop a neurological system. And you don't want to bring it to 40 degrees and above because those proteins in the central nervous system in the brain will start to denature. And that's going to cause significant problems.

59:22 Dr Mike

So you don't really want to be approaching those temperatures. And young, young individuals, obviously the nervous system hasn't developed properly yet. And so some children can get seizures off the back of fevers as well. And so again, that's not something that you want.

59:41 Dr Matt

That's right. And so because we utilize prostaglandins here, again, the medications that we saw earlier with pain can be utilized for fevers as well. So certain NSAIDs can be used to stop the production of prostaglandins. In this case, in your hypothalamus. A good example here would be paracetamol or acetamefadin.

01:00:01 Dr Mike

Which isn't an anti-inflammatory, but still targets prostaglandins. So if you were to class it…

01:00:08 Dr Matt

Probably more effective in this role.

01:00:10 Dr Mike

Oh, yeah. It is an anti-piratic, right? So anti-fever drug. Better than probably… So the way I think about it, and it's probably a very gross and possibly incorrect way of thinking about it, is that if, you know, people always go, oh, Ibuprofen or paracetamol? Right? And the way I see it is, well, if it's a fever, paracetamol. If it's inflammatory based, ibuprofen. If you know that the fever is caused through an inflammatory process, probably ibuprofen. But again, it depends. Right? It depends. And it's not necessarily one size fits all.

01:00:50 Dr Matt

Personally, as a father, I would be inclined more for paracetamol for my children as well. It's also tolerated better. I think it's just… Especially for kids. Yeah, that's right. So a few other things here, because we are producing inflammation, in this case from an infectious basis, and we've got all these cytokines going everywhere. There's going to be other side effects of these cytokines, not just from the hypothalamus. I mean, the hypothalamus is producing a fever. It's not a side effect. It's actually a physiological response to a harmful thing that's happening in the body. But you're going to also encounter other physiological responses to this high amount of cytokines. So it will go to muscles and joints and make them start to develop things like myalgia or what's…

01:01:39 Dr Mike

So because it's in the bloodstream, it's going to all these other organs and can have varying effects there. So in the muscles, you can have myalgia, which is muscle pain.

01:01:48 Dr Matt

Okay. Joint pain. Yep. Just generally feeling lethargic and nauseous. Right. And so these are all the common effects, systemic effects of that inflammatory response that can go broadly. And this is also why people see these effects when they, say, become vaccinated. Okay, explain, explain. When you take a vaccine… Because we'll talk about vaccines shortly. Yep. So when you take a vaccine, essentially what it's trying to do is introduce antigens into the body. So you can then adapt to it. And this will be the adaptive immune system. Now, the way that you introduce the antigens could be in a whole array of ways. You could just throw the antigen in.

01:02:31 Dr Mike

So this would be subunit type of antigens, which I think is hepatitis style. So antigen, again, just to… Is the flag of the infectious agent. So it's just a part of that infectious agent. So it could be a protein. It could be a carbohydrate. It could be both. It's just a part of it that can be recognized by the immune system that can go, aha, that doesn't belong to us. That belongs to something else. Let's remember that and let's target it and attack it. That's right. Okay, so keep going.

01:03:00 Dr Matt

So you could use that form. You could throw the dead microorganism in. So this would be a dead virus, as an example. Or you could throw in a very weakened virus. This is a live virus, but a live attenuated virus. Or like we saw with the vaccines from COVID, that was a bit of mRNA. And your own cells are then producing the antigen for us.

01:03:29 Dr Mike

And then we respond to that antigen. You're saying that our own cells take the mRNA from the vaccine, translate it into the amino acid sequence that folds into the protein. The body goes, wait a minute, I just made something that doesn't belong to me. That's right. Let's elicit an immune response. Yep. And so, regardless… Which is amazing, by the way. This technology is amazing. I know people talking a lot of stuff about it. And the general public, there's people that you hear all the time online about, I'm not putting any of that mRNA in me, even though every time you eat food, you're ingesting mRNA. But you're putting it in in a way that your body can make and translate into proteins that then go, oh, I mean, this is awesome, because I know it's a bit of a digression. But you can take cancerous cells, take a sequence of the cancerous cell. Oh, you're talking about the vaccine? Yeah. So in the context of a vaccine, you can take cancerous cell, take the sequence of it that you know won't cause cancer, but the body will recognise as, hey, that shouldn't be there. Make it as an mRNA sequence, inject it in the body, translate it into a protein that, again, isn't cancerous, but the body goes, wait a minute, that's not right. I'm going to make antibodies against you. And what do you know when that cancer arises in your body or if it grows in your body? It's now got antibodies that recognise it and can attack it. So you could potentially have vaccines against cancer through mRNA technology. That is amazing. It's a game changer. Yeah. And I think in the future, if mRNA vaccines become as… More of a mainstay. Yeah, as mainstay as I think they will, not one person will complain about taking a cancer vaccine.

01:05:12 Dr Matt

Anyway. So in any case, regardless of the type of vaccine, what it's doing is introducing something foreign, or at least is picked up as foreign, and your body will start mounting an inflammatory response to it. And it's probably going to be from a combination of those mast cells that will see, hey, you're not supposed to be here, and then the dendritic cells which will gulp it up and then bid the bridge to take it to the adaptive immune system. But in any case, there's going to be inflammation in that area. So if you inject it into your arm, which it usually is, you're going to get local inflammation. So that's going to be red, hot, painful. So that's the local effect. Then your arm in that region is going to mount inflammation. So that's going to be all those flame throwers. Yep. And so now you have a lot of cytokines going into your blood. Some people will get fever, and some people will start to get aches and pains, feel a bit rubbish. And this is because your whole immune system is now ramping up. And you're talking about the productions of maybe half a million cells a second. So that's a lot of energy and things that the body is trying to do. And that's probably why you're feeling tired for a few days. Exactly. It's not that, oh, no, I don't want to take that vaccine because it made me feel crap. It's actually, it's not a, you shouldn't see it as a side effect. You should see it as your immune system is working. That's right. So it's a bit, the example I give as a comparison is, it's like going to the gym and complaining a day or two days later that your muscles saw.

01:06:52 Dr Mike

That's actually good. You want that. Yeah, to a point. But your point's correct.

01:06:58 Dr Matt

All right. But one last thing. And when the cytokines go too much out of control, not in the case of vaccines, just in terms of generically speaking, this could cause a thing called cytokine storm. And we again saw that or heard about that with COVID where in the lung, where the virus is really starting to infiltrate. So usually the COVID virus will come in the nose, mouth, start to take over the cells and slowly make its way down your respiratory tract. And once it gets into your lung tissue and you're really replicating quickly, or the virus is, it's generating a lot of damage, injury, and you get in all these cytokines released. And cytokines is doing the inflammation. So inflammation is great when it's in say a tissue like…

01:07:50 Dr Mike

It's localized. It hasn't gone crazy. But it's helping.

01:07:54 Dr Matt

That's right. It's helping. But not in this case. But if it's in your lung and you're getting all that fluid infiltrating into lung tissue, now your lungs become soggy, full of fluid, and it's not going to do good gas exchange. That's right. And so all of a sudden, you're not getting oxygen into your blood and CO2 out. And then if that continues, this is now moving into serious territory of pneumonia. And this is probably what led to a lot of people dying from it, because it's just you can't get air in.

01:08:25 Dr Mike

Yeah. Good point. Adaptive immune system. Right. So the adaptive immune system, now we alluded to it earlier, that when we look at the leukocytes, the white blood cells, you've got never let monkeys eat bananas. We spoke about the neutrophils. We spoke about the eosinophils. We spoke about the monocytes. We spoke about the basophils. Sorry. But we haven't spoken about the lymphocytes. And there's two types. And with multiple subcategories underneath those two types, which is B cells and T cells. So about 20 to 30% of your white blood cells are lymphocytes. All right. So a significant percentage. Now, these are part of the adaptive arm. So that means they are specific and they have a memory. And that's extremely important. So now we're moving off to start looking at the special forces.

01:09:23 Dr Matt

Yeah. And the other thing I'll just add here, when you say they are specific, they generally mean they've got so much diversity that almost each different type, do you want to call them, are they still soldiers? They are. They are special soldiers. But they're special soldiers. Each one of them have a specific kind of response to a specific antigen, which makes them very diverse.

01:09:50 Dr Mike

Yes. They've been trained in such a way that they know exactly who their enemy is. And if that individual doesn't look like their enemy, they won't attack and destroy. But the thing is, their neighbor or their fellow soldier is trained against somebody else. And then their neighbor is trained against somebody else. And so 99.99%, if not more, of these lymphocytes, T and B cells, they'll never meet their enemy in their lifetime. That's a good point. Right? But all it takes is for that point, 0.001%. And as soon as one of them sees their enemy, they can go, I know that guy. That's right. And then they then call upon their friends and says, hey, he's here. Let's do it. And then they propagate. They make copies of themselves. So that now, instead of having one attack, they've got millions attacking. All right. Let's take a few steps back. Let's talk about the fact that they're called T and B cells. So what is this referring to? Where they mature or where they get their training. All right. So these are special soldiers. When they get trained, they need to be trained at specific training facilities. And so the B cells, where's their specific training facility?

01:11:09 Dr Matt

So basically all the cells that we've spoken about, all the white blood cells full stop are made in bone marrow. They're made from a stem cell. Red bone marrow. Called a hemopoietic stem cell. Right. And then from that, so it's a stem cell, which means it will constantly, every second of the day, thereabouts close enough, will produce offspring. So just over and over and over again. But because it's a stem cell, it's kind of only going to make blood cells. Okay, that's it. Now there's one line of cell that's going to make is the myeloid line. And that's made all the ones that you've already mentioned in the innate system. Okay. So that's the neutrophils, the sonophils, basophils, macrophages, blah, blah, blah. But this line is a lymphoid line. So they will make another lineage called the lymphoids, which are the special service.

01:11:59 Dr Mike

Right. Okay. So which would be what? Navy SEALs in the US or the SAS in Australia, UK, New Zealand. Yep. Right. So Canada, do they have SAS as well? The bounties. I don't know if they're the special services. They're probably special in their own way.

01:12:17 Dr Matt

Okay, they are. They ride moose, right? We're going to get complaints. Okay.

01:12:25 Dr Mike

Anyway, so this is where the special forces, they ride kangaroos. So it's all good.

01:12:31 Dr Matt

So this special services are coming from the lymphoid line. Yep. So regardless of B and T, they're coming from the bone marrow. That's right. So we'll start with the T because it's distinct here. So the T, the reason we've got the T name is they get sent to a training camp. T for training camp, yes. I shouldn't say that. They get sent to a training camp to mature to get kind of, what's the word?

01:13:00 Dr Mike

Special training. Yeah, special training. They've done their basic training in the bone marrow. Yep.

01:13:05 Dr Matt

So they're off to the T, the thymus. For their special training. Special T training, that's right.

01:13:13 Dr Mike

Right. Okay, so the thymus is the T.

01:13:15 Dr Matt

That's right. And that's a gland. No, sorry. It's an organ. It's an organ that's located kind of in your superior metastinum. Yep.

01:13:23 Dr Mike

Above the heart, kind of in the front of the trachea. Pretty big when you're a newborn because you're training a lot of T cells. But as you get older, that thymus pretty much shrivels into non-existence, right? That's right. Like 80-year-olds, you probably can't even see it post-mortem. That would be a fair guess. Yeah. And so, and why is that?

01:13:43 Dr Matt

Is that because all the T cells have been trained? Yeah, I don't actually know. I don't know if there's no more maturity or it's still just to a minute amount. Yeah.

01:13:53 Dr Mike

I'm not sure. I think because all of the, what we can, we'll get there, the clonal expansion is happening in the lymphatic tissue. Okay. Okay. So, basic training for T cells is happening in the bone marrow. They then go to the thymus and they get the special forces training there. Yes. The B cells. So they've got basic training in the bone marrow.

01:14:12 Dr Matt

Where's their special forces training? Well, the B technically was named after a bursa in birds. Really? Yeah. Not bone marrow? No. I can't pronounce the, it's a bursa of some Italian guy's name. I can't remember it. But essentially it was first, probably chickens. It was first identified in, I think chickens. So what, a little sack of the joint? No, no, no, no. I don't think it was, bursa just means purse. Okay. But I think it was just a package location that they figured out. If you, if they remove this structure, the bursa out of chickens, it didn't seem to cause any difference. They're like, and then when they introduced, you know, bacteria or something in them, they're like, oh, they can still kill it off. But they noticed that no longer could kill, no longer could make antibodies. Okay. So they realized by taking this bursa out that they would have no ability to produce antibodies anymore.

01:15:14 Dr Mike

Okay. Now we're not chickens. So where is the training camp for special? Luckily, it still is a location with B. Oh, great. The brain. No, just bone. Oh, bone marrow. They stay there. All right. So the B cells, basic training bone marrow, and then they stay for the special training in the bone marrow as well. The thymus is for the T cells. Correct. All right. So now we've got these specially trained cells. They're trained by, in their specific training, they've been handed a photo of their enemy and says, this is the person that you are after. That's all you want is this person. Anyone else that doesn't look like this, forget about it. And each person will have a different photo. Right. So basically a different antigen recognition site it will have. And if it doesn't come across it, it's basically no enemy. Right. For both T and B cells. What now, if they haven't come across, if neither B or T cells, if they've never come across their quote unquote enemy or antigen, we'd term them naive T and B cells.

01:16:23 Dr Matt

But they're all, once they leave their training camp, they're still all naive. Right. Okay. So basically they could say, yeah, I'm a Navy SEAL, but they've never seen battle. Correct. All right. Correct. But at the camp, they're going through some pretty rigorous training. Of course. So they got a drill sergeant that really works them hard. And so, so when they're trying to identify the antigen, okay, they, they have to be, you know, good enough to know that they can kill them. Right. Okay. So they've got to train them in a way that they are really efficient killers.

01:17:03 Dr Mike

They need to test them. That's right. Make sure. So obviously there's testing that needs to be done.

01:17:07 Dr Matt

That's right. So they get into the point where they know that, yes, I'm as a drill sergeant, I'm confident that in a battle, you'll be able to kill your enemy.

01:17:16 Dr Mike

Well, what if one of the soldiers went, I'm not happy with just one. I want to kill whoever.

01:17:23 Dr Matt

Well, before you get to that point, if they don't meet that criteria, the drill sergeant will just kill them. Well, so they're basically saying, look, look, why can't they just send them home?

01:17:33 Dr Mike

You just haven't met the criteria to be here. You don't deserve to live. You're gone. Okay. Let's just say they send them home in this case, but yes, in the body, they kill it off. Send them home is analogy for. Oh, okay. So, so if it can't get its specific target, it's out. Yes.

01:17:51 Dr Matt

What if it's not just getting its specific target, it decides to just go berserk. That's right. So now if you, if the drill sergeant is too kind of aggressive and you're producing psychopaths that just go around killing people, it could be a danger to its own unit. That's right.

01:18:08 Dr Mike

So they also will get a watery grave. Okay. So that means that it really has a strict stringent selection process.

01:18:17 Dr Matt

And what we mean by that is you don't want to produce B or T cells that will generate water immune diseases. Exactly. And so that's what we're trying to illustrate here.

01:18:26 Dr Mike

Yeah. May have gone a bit too deep into it, but that's okay. So, but exactly. We needed to clarify that. Now we've got these trained T and B cells that haven't seen battle. They're naive. And now they're at headquarters, right? So they're waiting for their orders.

01:18:39 Dr Matt

That's right. So they get sent to strategic locations in the body where they're likely to encounter the enemy. So what are these strategic locations? These locations are, how would you say, like barracks? Yeah. Is that what you meant? Or do you want actual? Oh, I was going to say lymph nodes. Yeah. Lymph nodes or lymphoidal tissue. Yeah. So again, examples, locations pretty close to the battlefront. Yeah. But if an enemy was to escape through, it's, they're most likely to come through these garrisons.

01:19:12 Dr Mike

Okay. So great point. So some of these lymphatic tissues or headquarters where these naive T and B cells are sitting includes at the back of the nose and throat. So your tonsils. Yeah. It's going to be lymphoid tissue in your gastrointestinal tract as well. It's going to be in other areas, axillary under your arm, in your groin, and just placed almost sporadically throughout the body as your lymph nodes. So it's lymph lymphatic tissue or lymphoid tissue and lymph nodes. Yeah. But this is where they sit and they sit to await further orders or further instructions, both T and B cells. And so what can happen is a couple of things. I think we should start with the T cells, right?

01:19:57 Dr Matt

Because yes, we should start with a naive T cell. We should probably say, because as I spoke with the innate, there's usually the one character that's the bridge between the two. Okay.

01:20:08 Dr Mike

So this is the one, this is a cell that's likely to bring an antigen to the barric. Yeah. So you've got your messengers, the people that come in and they're going to say, I just got a message from the president and the message is this and it hands it to a naive T cell. Right. And it's the photograph of the person it's been trained against its entire life. And it says, they're here. And this T cell has to make a decision. It has to go, okay, I recognize this person, I antigen. What am I going to do? Am I going to now can take two parts. It can either become what's called a T helper cell where it starts to manage and facilitate the response. So if it becomes a T helper cell, it can go, okay, I'm going to gather more troops.

01:21:05 Dr Matt

I'm going to show them where to go, tell them where to go and organize the plan. So it becomes like a general.

01:21:10 Dr Mike

Like a general. Or it can become a killer and become a cytotoxic T cell and says, just give me the rifle. I'm going out front, Sarge.

01:21:18 Dr Matt

But these guys are the ultimate snipers. So they are popping a guy off from two kilometers away.

01:21:24 Dr Mike

Yes. That's right. And so it makes that decision. Now, if it goes and says, I'm going to help facilitate the whole thing, it's a helper cell. And these helper cells don't just help other T cells and say, go that way. The helper cells can also help B cells. And so let's just say this specially trained soldier sees the photo and goes, I'm going to become a helper cell. It calls upon T cells and says, all right, I've seen it. It's this looks like this. Make more copies of yourself and go in that direction and go kill it. So is that you talking about the cytotoxic T cells? It calls the cytotoxic T cells to do that. It can also go to the naive B cells and show it to them and say, hey, look at this photo. And again, anyone recognize this? And only one B cell will. It says, yes, Sarge, I can recognize this person. Great. What are you going to do? So now what the naive B cell does is it goes, well, I recognize it now. Give me that photo. As soon as it takes the photo off that that Sarge, the helper T cell, it becomes a plasma cell. The B cell becomes a plasma cell and says, don't worry. I'm going to take this photo or this shirt or sock or whatever for the antigen from the bad guy and give it to my sniffer dog. That's my sniffing. That dog is now the antibody. And it says, recognize this guy. Off you go. Go get it. Go, go, go get it. And not only do you have a lot of dogs. There's a lot of dogs here. Yeah, you've got some millions. And those dogs just run out of the barracks and just go throughout the entire system or field or wherever they are. And they find that bad guy. So they're looking for that one antigen that's going to be part of that microorganism. So the naive B cell will become a plasma cell. Once it recognizes the antigen, it then creates a whole bunch of antibodies off the back of that antigen that are specific for that antigen and send them out into the system. Before we go into the system, remember all of this, all of this training from the naive to so the naive T cell to either the helper cell that facilitates the project or the cytotoxic T cell that goes out and snipes and the naive B cell to turn into a plasma and it all happens in the lymphatic tissue. Or at least most of it happens in lymphatic tissue. And the reason why this is important to say is that if you have, let's say, cut your arm and you've got an infection in your arm, you might find that the lymphatic tissue under your armpits are larger and raised. You can palpate them. You can touch them and they might be sore. The reason why that's the case is because the antigens or the pathogens that have entered your body through the bloodstream will jump into the lymphatic system and it will travel through into those lymph nodes. Carrying the antigen with it and it presents that antigen to the headquarters. Basically that photo that says, hey, this thing is here. Stimulating those cells to turn into more T cells and more B cells is what we call clonal expansion. They make more copies of themselves and the tissue literally gets larger because you're making more copies of those cells, which then will bleed out and not literally, but then will spread out into the bloodstream and start to attack the area. That's right. So it's not just an important point is that you're going to have those messengers bringing that photo in their macrophages. So the antigen presenting cells, antigen presenting cells, which are generally like wandering macrophages or the dendritic cells. Yeah, sorry. Or it could be the dendritic cells that are embedded in the lymph tissue itself. Or you can have the actual invading pathogen get filtered into the lymphatic tissue itself and it recognizes it directly basically.

01:25:19 Dr Matt

Yeah, right. So yeah, that's right. So what could happen using our analogy still is one like a naive B cell could be outside the barrack washing its face in the river. And along comes something from the enemy like a hat, like a hat. Yeah. And it takes it up. So this is going to be the antigen takes it up. Does it actually phagocytosis itself, but goes back. That hat's delicious. Yeah, that's right. Goes back into the barrack, but it needs a T cell hill here to activate it.

01:25:51 Dr Mike

Instead of phagocytosis, maybe puts the hat on and walks inside. That's right. T cell is like, wait a minute, I recognize that hat.

01:25:58 Dr Matt

And so that T cell does the same thing as we spoke about earlier with the antigen presenting cell. So the T cell now becomes a helper cell. So it goes from naive to helper and tells the B cell that's wearing the hat. Hey, you need to become plasma plasma cell and make more of those. So the B cell can also play a role as an antigen presenting cell. Have we Matthew confused our audience? Possibly, possibly. But, you know, like you said, like you said at the start, it's complicated.

01:26:31 Dr Mike

And we try to do it in a way that just makes a bit more sense in a different way. We're pretty much covered in aid and adaptive immunity, don't you think?

01:26:39 Dr Matt

Well, you haven't really spoke about what the cytotoxic T cell will do. So this is a sniper. Right. Yeah. So this one, once it has it because it's been made from a particular antigen, it can now go to an advantage point, look out in the battlefield and know exactly now who it's looking for. And so now it's almost like a natural killer cell. Yeah. But it's very selective. It'll only kill that one of the antigen. And so it sits up there with its sniper rifle kilometers away, ready. And once it's locked in, it will radio back to the helper cell. Yeah. The T helper cell and says, General or Sergeant, I've got it. I need to go ahead, Sergeant. You want me to go? And he or she will give a radio back and say, yeah, go for it. And then boom, and the cell's dead. There you go. All right. So that we're almost finished. Oh, and this is the big, probably important part. Oh, OK. Once the battle has finished. Yes. Because we've made so many clones of the T and the B cells. Yes. Right. That's very specific to that antigen. So remember to go from the naive to the huge amount of T and B cells from just that one antigen selected T and B cells. We've made millions and millions of copies of the same cell. Right. Does that make sense? Yep. The battle's now finished. There's no more bacteria. So a lot of them will just get culled off. But then the remaining amount get transferred into retirement. Oh, but as memory cells.

01:28:19 Dr Mike

But won't there be like, I'm too old for retirement anyway. So and what do they do?

01:28:25 Dr Matt

So it's a bit like Tom Cruise in Maverick. You know, 20 years later.

01:28:30 Dr Mike

Or Danny Glover in Lethal Weapon. 20 years later, he comes back.

01:28:33 Dr Matt

I'm getting too old for this shit. So basically what I'm saying is the excess amount of the T and B cells, they get turned into memory cells. Yeah. For just in case down the track we encounter that.

01:28:48 Dr Mike

Oh, yeah. And they're like, we need you back, Maverick. We need you back. That's right. The Russians are coming. Or whatever. Actually, I think in the latest Maverick, they didn't have an enemy. That's right. That's good. Or an enemy. Seeing enemy.

01:29:00 Dr Matt

So the point there is, and this is the crux of the adaptive immune system. The second time you encounter, it's much quicker. Of course. So what you illustrated with an invading army coming in, getting through the first line, the second line, then being phagocytosed, taken to the lymph node, finding the right T cell, selecting for it, clonal expansion, B cells being made into plasma cells, cytotoxic T cells. All this will take two weeks. Right. So it's a long time. Particularly if it's a serious infection, right? You might not have two weeks. So if you've done it once, then you've got all the cavity made for it. And so they're just waiting around as memory cells. The Mounties. That's right. And so if it was to be invaded again, it's going to… A lot faster.

01:29:55 Dr Mike

A lot quicker. Great. Which is what we try and do with vaccinations. We try to prime the immune system to have the memory cells for next time. That's right. Thank you for that, Matty. Very quickly, I just want to do some listener mail and going to read two emails. Please, if you want to send us an email or contact us, you can go to our website, which is drmat.com.au. That's D-R-M-I-K. No, that's my name. That's D-R-M-A-T-T-D-R-M-I-K-E.com.au. And you can send us an email from there. Or just go to or email gubiosciences.com. Tell us if you like the show, give us feedback, you know, questions, all those types of things. And that's what we're doing here very quickly. So I have an email here from Irina. And Irina says, Hello, amazing team. Well, hello, Irina. I am Ira. So I will now call you Ira, Irina. Living in Israel, studying in nursing school year one. Congratulations. I hope you're enjoying it. Until I came to a YouTube channel, I was very lost in the amount of material that is distributed throughout the Internet. Your explanations simply changed the world of learning for me, especially someone diagnosed with ADHD. I feel you there. And as someone whose English is not their native language. Everything is explained in very accessible and understandable English. First of all, thank you for doing this for me and for students like me. Secondly, I would be very happy if you could make a worksheet for all the subjects. Or if there is a good database that you can recommend, I'd be very happy. I don't know if you have material that can be downloaded like PDF or bundles. It would be amazing if there was something like that. Keep up the amazing work, Ira. Thank you so much, Ira. We really appreciate that. What Matt and I are currently working on is a transcript of the podcast. So every podcast episode will have a transcript available. And it will be available on the…as a link on the website itself, or on the podcast, sorry, itself. And you'll be able to access the video of the podcast too. It may not be up straight away, but you can get the transcripts straight away on our website. So if you go to our website, you can click the long form episodes and download the transcripts. We're also building some courses, some mini courses that cover topics like this, where there will be multiple videos, readings, activities, things like that. So watch this space. We will let you know when they are released. Second email, Maddie. So we've got an email here from… Oh, I might read two more very quickly. Tabitha. So Tabitha sends us an email. Firstly, hi Tabitha. Hi, doctor. I love your videos on the human body. I was wondering if you could make one about the anatomy of the pectoral region. It's such a fascinating part of the body, and I think your viewers would love to learn about it. Thanks for considering my request. Think we can do that? I'm surprised you haven't done it. I have looked at the pectoral region as part of scapular movement and also as part of flexion at the shoulder. So I have done a video. It hasn't focused specifically on it, but I've looked at the deltoid, sorry, the pectoral region, looking at pec major, pec minor, origins, insertions and so forth. So there is a video there, but I can do one specifically targeting it. And finally, we have an email here from Robert about intracrine signaling. Let me first say, intracrine signaling was what we spoke about

01:33:33 Dr Matt

in the endocrine system review. Yeah, I said I brought that up and I couldn't explain it.

01:33:37 Dr Mike

Well, you did. You just may not have explained it.

01:33:40 Dr Matt

I came across a term. I didn't really look much further than that, but it is a term that has now been utilized or used within the endocrine physiology space. So as I said, traditionally within endocrinology, there would be the idea of putting the hormone into blood. That's a typical endocrine signaling. Then there would be paracrine, which is in the neighborhood. And then there's autocrine, which we kind of spoke about. That's how B cells and T cells work at communicating with each other and colonal expansion. That's through autocrine. So then intracrine is in the cell rather than on the cell.

01:34:19 Dr Mike

Yes. And from what Robert is saying is that intracrine is confusing and is correct. And the definition is not a direct parallel to the concepts of endocrine, autocrine and paracrine. So basically what Robert states is that under this definition, what basically happens is that the hormones released by a cell, if they are taken back up by that cell, they often undergo intracrine conversion. And so they can change into other various types of chemicals. And a common example of this includes those cholesterol-based hormones, such as testosterone and estradiol and estrogen and so forth. And so he's basically stating that to be a bit more specific. That's what we're referring to here. He says under this definition, intracrine signaling does seem a bit of a pedantic term, but it does raise the important concept that hormones may be modified from their secreted form for specialized needs within the target tissues. Because of intracrine conversion, males have a relatively stable amount of estradiol during the lifespan because it can be produced by intracrine conversion of DHEA or testosterone. Female estradiol is primarily produced by the ovaries and declines sharply during menopause. So I really appreciate that, Robert. These are emails that we love. So please, if there's something that you'd like to elaborate on that we've spoken about or correct Matthew when he's been incorrect, which is quite common. That's right. Quite frequent. Send us an email. You can contact us again on our website, or you can come say hi to me on social media, which is at Dr. Mike Todorovic, at DR MIKE, T-O-D-O-R-O-V-I-C. Matthew, thank you for joining me today. It was a pleasure. And everybody, thank you so much for listening to The Immune System. Thank you.