A MEETING WITH THE MACROPHAGE

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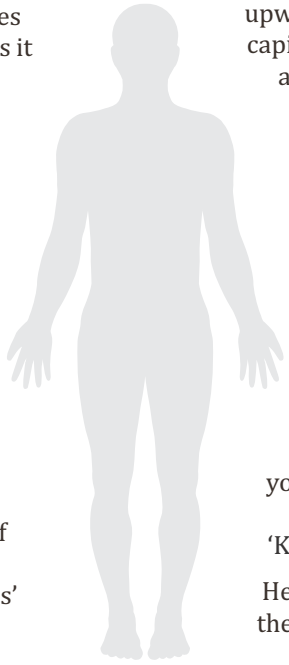
The human body is an eternal battleground. We are constantly meeting with invaders of all kinds and all sizes. Did you know that our bodies have private armies that fight against disease? What are the different units in this army? How do they function? How do they get to the frontline almost instantaneously? These questions and many more are answered in this first-hand account by a soldier (cell) in the human immune system.

"Enter at your own peril, through the bolted door where impossible things may happen, that the world has never seen before!"

- Theme song of 'Dexter's Laboratory' animated television series

Have you ever wondered what goes on inside your own body - how is it that you can gulp down some orange juice and feel the cool waves of freshness coursing down your throat, read this line, and think about the next IPL cricket match, all at the same time? Scientists have discovered that 75% of the cells in our bodies are bacterial, and only 25% are human. Does this make us more bacterium than human? What is it that really makes us who we are? Let us find out at least some answers.

Today, I'll introduce you to a friend of mine. We call him 'big M', but I guess you can call him 'Macrophage'. In the world of the human body, he makes up a small portion of white blood cells or 'leucocytes' that are part of your body's defence system. You can talk to him yourself. All you have to do is travel down your trachea, also called your 'wind pipe', until you reach one of your lungs (let's turn right at the cross-roads). The road ends at an alveolus or 'air sac', which is the destination for the oxygen you breathe. From there, turn upwards and squeeze out through the capillaries (tiny blood vessels that line the alveoli and carry away the oxygen to other parts of your body), travel through the soft pink tissue until you reach the sternum. The sternum is the giant bone that is in the centre of your chest, holding the ribs together and forming the main pillar of the rib cage. Knock on the sternum twice, and ask for the blood monocyte. He'll come, for sure. I have informed him, in advance, that you are going to pay him a visit; he is a good friend of big M, and will take you to see him.



'Knock knock'

Hello there! How nice to see you. You want the blood monocyte? Why, here he is before

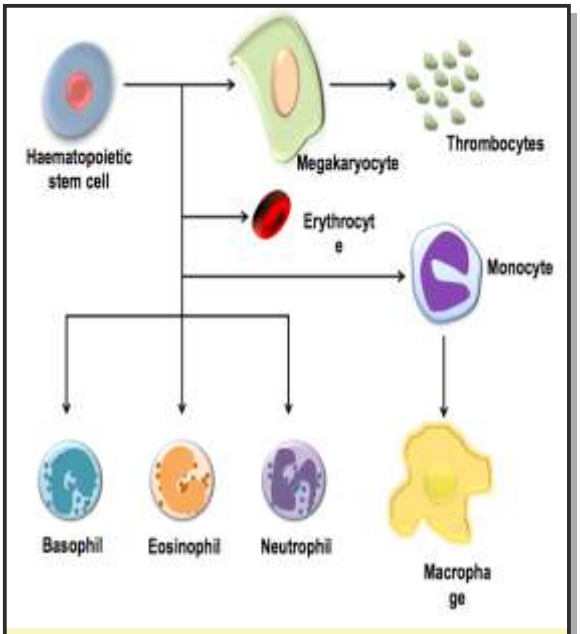
you, in the flesh, or should I say, in the protoplasm! Of course Sir, it is me that I'm talking about. My name is monocyte, and I'm honoured that you have travelled all the way to the sternum to see me. I live further down, past the hard bone tissue, right at the centre, where the walls are soft, the blood nice and warm, and everything is a bright red. We call it 'the marrow'. You must pardon the dreary colour choice, everything in here is red. This, as you know, is because all the red blood cells in the blood stream are produced here. Well, not only here, but in other bone marrows all over the body. This happens to be one of our larger factories, where the process of 'haematopoiesis' takes place. It is a horribly complicated word for a horribly complicated thing. Haematopoiesis (pronounced heem-ato-po-es-sis) is the process where our fathers, amazingly versatile cells called 'multipotential haematopoeitic stem cells' underwent a series of orderly cell divisions (one cell becoming two) and cell differentiations (one type of cell - such as a stem cell - becoming another type of cell - such as a leucocyte) to produce myself, and all my kin. Together, we are called blood cells. We, blood cells, are divided into several categories, naturally because we carry out several different functions.

'Thrombocytes' or platelets derive their name from *thrombos*, the Greek word for blood clot. They are the tiniest of blood cells, and are only 20% of the size of red blood cells. Platelets disperse throughout the entire blood stream, ready to form blood clots wherever blood vessels are damaged. This is very important to prevent the loss of blood when there is a wound, or to prevent leakage of blood into the surrounding tissue, in case blood vessels spring leaks.

'Erythrocytes' are red blood cells. These cells are produced in huge numbers, and it is because of them that the entire body is red. Without them, every tissue in the human body would be white, or yellow, or straw coloured in places where there are many fat cells. Did you know that at any given time, the body contains approximately 20-30 trillion red blood cells? That is 20 followed by 12 zeroes! Haemoglobin, found inside red blood cells, binds iron, which gives a red colouration when it is bound with oxygen. In fact, this bond between iron and oxygen is the way that oxygen is transported from the alveolar capillaries that you saw in the lungs to all other parts of the body. Many diseases occur in the human body when these red blood cells cannot accumulate haemoglobin optimally, leading to a deficiency in oxygen throughout the body.

Oh my, look at the time! I've been rambling, I really do apologize. I still have so much to tell you before we meet big M. You see, big M is a man of business; he does not like questions if he thinks that the answers are trivial. Most of the people who come here to talk to him are scientists working on larger problems in healthcare and disease. Just the other day, there was this PhD student who wanted to know how big M detects the *E. coli* lipopolysaccharide! I myself have no idea what that means, but, big M - he knows everything! So before we actually meet him, I'll have to tell you all about him and the rest of my brethren. The last thing we want is for you to ask him who he is when you meet him!

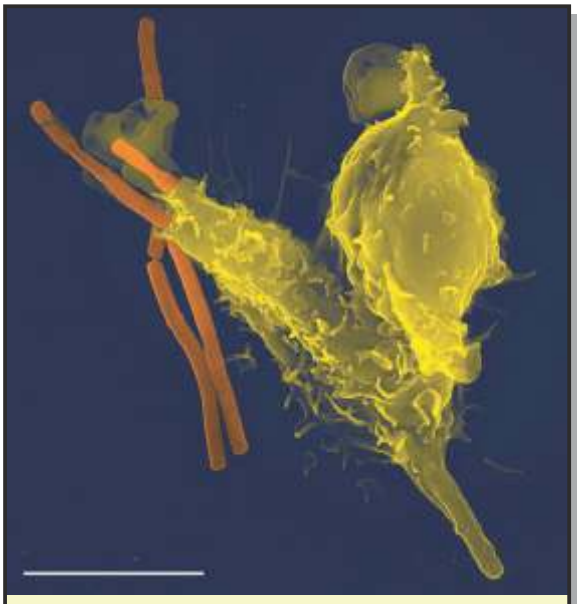
Big M is part of a family of defence cells, called white blood cells. You could think of him as my elder brother, which is why most people ask me to take them to him. The other cells won't do it, because they are afraid of his 'cytotoxic' potential; I'll tell you what that means as we go along. Our family tree has myeloid leucocytes as well as lymphocytes; all on the paternal side (remember our fathers, the multipotential haematopoeitic stem cells?)! The myeloid (my-ee-loyd) leucocytes include the monocyte - that is me, Big M - the macrophage, and our three cousins - the neutrophil, the eosinophil and the basophil. Our family, I am proud to say, has been the first line of defence for the body since the day it was born. We



The process of haematopoiesis – where the parental haematopoietic stem cells divide and differentiate to give rise to all the other cells found in the blood

have had help from elite forces called lymphocytes, but that has only been during serious battles, when we were being overpowered. Can you imagine living on the borders of this land, so far away from home, always waiting and watching, and expecting an attack at any moment? Well, that is the life we lead.

My cousin, the neutrophil, is like your foot soldier on the outside. He is the first to enter into a skirmish, and sadly, his family counts as the first to give their lives to protect the body. Have you seen pus - the thick sticky white fluid that oozes out of an open wound or a gash? Well, that is

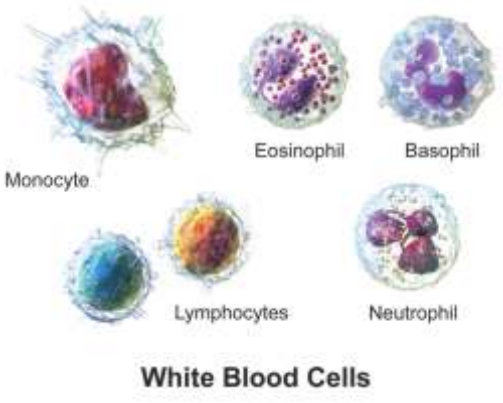


Neutrophil Engulfing Anthrax Bacteria

Volker Brinkmann – (November 2005). "Neutrophil engulfing Bacillus anthracis". PloS Pathogens 1 (3): Cover page. DOI:10.1371. Retrieved on 2009-01-04. Neutrophil engulfing anthrax bacteria, taken with a Leo 1550 scanning electron microscope. Scale bar is 5 micrometers. Creative Commons Attribution 2.5 Generic

formed by neutrophils dying in huge numbers, taking the enemy forces with them. Be very careful when you get a wound that starts oozing pus, because that means that the neutrophils have started dying and the body has to call the second line of troops. Keep the wound clean, wash it with antiseptic, otherwise the invaders may travel further inside our borders.

Have you ever wondered what kinds of enemies invade our home? Almost every invader you can think of wants food and shelter! If you give them an inch, they'll take a mile. Just the other day we met a huge nematode worm that had entered as tiny eggs in food. The food was not cooked properly, and the worm eggs survived (this happens mostly in meat, like pork and beef; and green leafy vegetables that are grown in dirty water). That was when my brother eosinophil swung into action. Armed with proteins that are highly toxic to worm parasites, he ejected toxic vesicles (small sacks containing poisonous stuff!) which exploded like hand grenades, at the worms, killing them instantly. He was awarded the medal of valour, and given a 2 hour vacation (2 hours is pretty long in the life of small cells like us)! Of course, there are those in my family who don't have such heroic tasks, and are few in number. I am talking of eosinophil's brother, the basophil. There are so few basophils here, and their numbers are always lower than the eosinophils and the neutrophils. The basophils however,



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perform a very important function. They act as 'messengers of inflammation'. An inflammation is like an SOS signal or a 1-0-0 call to the police control centre. Whenever your body gets itchy or red in places, with swelling or heat, or even whenever you have a runny nose and a horrible cold, you should know that cousin basophil is doing his job and rallying the forces of the body to battle against disease.

Well, I think we have almost completed a brief tour of my family tree! It is as well, because we have almost reached the liver, where big M awaits

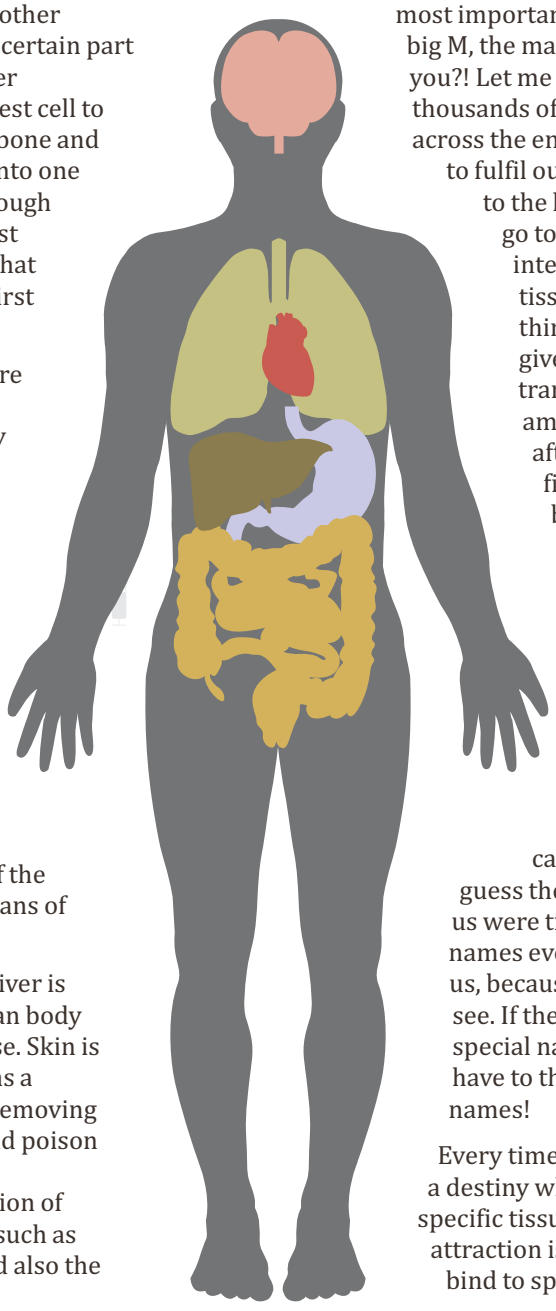
us. I have modestly left out a description of my own humble self, the monocyte. It won't be an exaggeration to say that I am the largest of all the cells in the blood. The head office has entrusted me with two responsibilities, which is more than what most of my cousins can handle! We, monocytes, can change our nature at a moment's notice. On a normal day, I look just as you see me now, clear and transparent, without any defined shape (like an amoeba, another parasite that brother neutrophil constantly fights against). This 'shapeless shape' of mine is very useful in squeezing through tight places like blood vessels, and navigating through tightly packed tissues. Whenever brother basophil raises an alarm in a certain part of the body (do you remember inflammation?), I am the fastest cell to reach his calls. Dashing past bone and cartilage and fat, squeezing into one vessel and squeezing out through another, I can find the shortest path to any part of the body that needs my help, which is my first function.

My second function is far more interesting. Once I reach the site of inflammation, I use my powers of bodily transformation to do something quite amazing, if I do say so myself! I won't tell you about it just yet. Instead I'm going to give you a live demonstration once we reach our destination. Just behind that large membrane, called the diaphragm (di-a-fram), is where we are going, to one of the most important and vital organs of the body - the liver.

In case you didn't know, the liver is the largest organ of the human body (apart from the skin, of course. Skin is just everywhere!). It performs a myriad of functions such as removing harmful substances that could poison the body (a process called 'detoxification'), metabolization of various components of food such as carbohydrates and lipids, and also the synthesis of cholesterol and other proteins and hormones. In fact, during the first trimester of the foetus (the first three months of a baby's life inside the womb), the liver even produces red blood cells (which as you now know, is produced in the bone marrow of adults, where you met me)!

Ah! We have reached at last!

BEHOLD! IT IS I YOU HAVE TRAVELLED SO FAR TO MEET! As you can see, I have been growing bigger and bigger ever since we have entered the liver. Using subtle chemical signals present in the liver tissue that only I can see and respond to, I have transformed into one of the body's most important soldiers. I have become big M, the macrophage. Surprised, aren't you?! Let me explain. Every day, thousands of monocytes, like me, journey across the entire span of the human body to fulfil our destinies. Some of us come to the liver as I have done; others go to the bones, the brain, the intestines, and virtually every tissue in the body that you can think of! Some of us are even given different names when we transform into macrophages. I am called a Kupffer cell, named after the German scientist who first found me in the liver. My brother macrophages in the bones and the brain are called osteoclasts and microglia respectively. A few others have no special name, for example, macrophages that reside in the alveoli (remember your journey down the wind pipe into the lung?), are called alveolar macrophages. I guess the scientists who discovered us were tired of thinking up new names every time they spotted one of us, because we are everywhere, you see. If they had to give each of us a special name, I am sure they would have to think of more than twenty names!

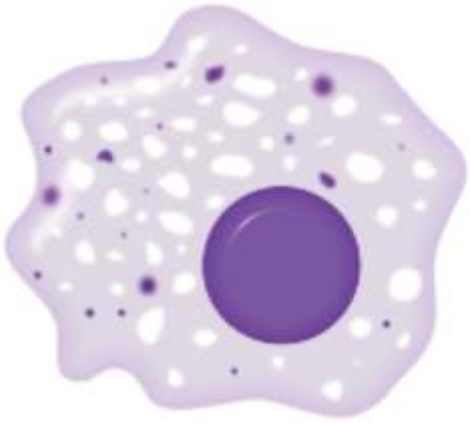


Every time a monocyte is made, he has a destiny which draws him towards a specific tissue in the body. This attraction is through chemicals, which bind to special molecules on our cell

surfaces, called receptors. Whenever we feel the presence of these chemical molecules, we are pulled towards the source of that chemical. In this way, cells in the bone call on monocytes to migrate into the bone tissue, and transform into osteoclasts. Cells in the brain secrete chemicals that welcome monocytes into the brain to become microglia. I was quite young when I felt my first pull. Almost as soon as I was born, I knew that my home was the liver, and my destiny was to safeguard the cells in the liver by transforming into a Kupffer cell.

My job is simple. It is no secret that I am always hungry - look at my waistline! I am here to defend the body against any external agent by doing what I do best, eating everything in my path. My very name means 'big eater', and that is all I do. The liver, you see, is one of our most strategic battle stations against the outside world of bacteria, fungi, parasites and toxins. Here in the liver, we constantly face a barrage of blood-borne pathogens (pathogens are disease causing organisms), mostly from the gut. Just to show our importance, scientists, studying our role, have experimented with removing all the Kupffer cells from the bodies of some lab mice. The results were shocking to them, but quite obvious to me. All the mice died. Which is why we have a saying here, in the immune system (the immune system is the body's army), *"you can live without a femur (the longest bone in the human body, located in the thighs), but you ain't got no chance without a Kupffer in the liver."*

I have a lot of company here, because the liver is the organ with the largest population density of macrophages in the human body. We need to keep our numbers high, of course, because almost everything that enters the body through the blood or the food (and a lot of them do!) head straight to the liver, where we await them. Let me explain the process by which we protect you from all that is harmful and disease causing. As soon as we see a foreign object (a bacterium perhaps), we engulf it in a process called 'phagocytosis' (fag-o-cyto-sis). Once inside us, the invaders don't stand a chance. We trap them inside specialized sacks inside our bodies, called phagosomes. The phagosomes are, then, flooded with a deadly concoction of enzymes and acids that lyse (break open), and



Drawing of a macrophage when fixed and stained by Giemsa dye.

digest virtually every part of the invading specimen! Sometimes when we face a foe that is especially difficult to kill, we produce a harmful mixture of reactive oxygen and nitrogen radicals (molecules that are highly charged and reactive) in a process, called 'oxidative burst'. If our acids don't kill them, the oxidative burst surely will. Of course, the oxidative burst damages us as well, and it is only during really harsh battles that we resort to this suicide bombing strategy. The reactive oxygen and nitrogen radicals explode into the surrounding tissue, killing all the human body cells present nearby. This is why, getting rid of a disease is often tiring, and makes the body weak. Remember to always rest well and fully recover, so that your body has time to repair the damage of the day's battle; because there is a battle being fought by your immune system, almost every day

Now, if you will please excuse me, I have to go eat some bacteria! The narrator will show you the way out. Begone!

Shall we take a roller coaster ride through the nervous system? Or drift lazily down the canals of the heart? Until we meet next time, remember that every second of every day, big M and his friends in the immune system are fighting for you.

Goodbye.

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