Host-Pathogen Interaction (Immunology)
Prof. Himanshu Kumar
Laboratory of Immunology and Infectious Disease Biology
Department of Biological Sciences
Indian Institute of Science Education and Research (IISER) – Bhopal

Lecture – 18
Cells of Immune System and its role in Host Defense-Dendritic Cells

Hi, so, in previous lecture we have discussed about the blood cells which contain various immune cells and among all those cells we have discussed about the granulocytes. And if you remember we have discussed about neutrophil in great length. We have looked at various mutations which is basically taking place in the one of very important enzyme known as NADPH oxidase and that result to the development of several congenital diseases.

Then we have taken the eosinophils and we have discussed basophils and we also discussed mast cell which is not present in the blood but it is present in various tissues. And today we will move on in same series and we will first discuss about dendritic cells. So, dendritic cells are very important in immunity and today you will see how the dendritic cells playing a very important role in linking between innate and adaptive immunity.

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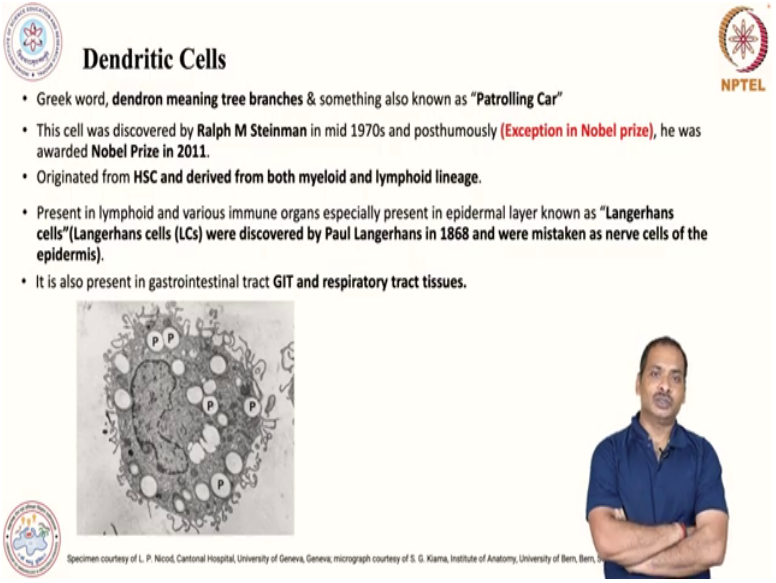

So, let us begin with dendritic, so, dendritic cells, why we call it as a dendritic cells? Because this is derived from a Greek word dendron, meaning branches of tree and due to this cell got this name when it was first observed then they found out that this has a branching like a

structure. In fact, they were confused with neuronal cells. If you remember the structure of neuronal cells, they have two major component.

One is the aExon which has a myeling sheath, and another part is having a soma or body part of the neuron which has dendrons. There are projections which is like a branch. So, this dendritic cells looks like the neuronal cell and there is a one class of dendritic cells which I will discuss shortly after a while. When it was discovered then they thought that this is a neuronal cell.

These dendritic cells are also known as a patrolling car. This is because of their function. So, these dendritic cells basically perform the function of a patrolling car. They keep on scanning our different barriers the for example in a skin and they keep on scanning. And if there is a some intrusion of some pathogen then that will be sensed by the dendritic cells. And then they will elicitate appropriate immune response which I will explain you later in this session.

And they are something if you want to understand it is very simple it is for example, some city or some country they have a fence and you can consider the fence as a skin. And if some intruder or some terrorist enter in the in the fence then they will this terrorist will come with various kind of weapons like a various kind of guns, bullet and all those things and this dendritic cells can sense.

And if the dendritic cells can sense and elicitate appropriate response then they will try to eliminate that. However, these dendritic cells if it is not capable to eliminate this antigen then what it will do it will inform some kind of headquarter. Where there is a specialized soldiers or specialized weapons, are there. For example, if the terrorist or it is a big group of terrorists then that needs different kinds of tech to overcome?

And if it is a say, a few terrorists but they have a very advanced weapon and all those things that needs a another type of a weapon in order to clear. Similarly, these dendritic cells, if they are not able to clear the pathogen what they will do? They will inform the headquarter. Now, you may think that what is the headquarter so, headquarter is nothing it is a lymph node, the nearest lymph node. Over there, all kinds of cells are available.

Initially, they will alarm also when they will see the pathogen. They will also induce a kind of alarm and they will try to invite the nearby immune cell in order to take care of that pathogen. However, if it is not able to do it then this information will go to the headquarters that is lymph node and then over there and some sample of this antigen will also go over there and then there will be a development of appropriate immune response.

So that is why these cells are also called as a patrolling car. This this cell was first discovered in mid 1970's and it is about 1973 by a very talented scientist, his name is Ralph M Steinman. And he also initially mistaken or he was also get confused after looking at this structure, so, this cell was discovered by him and then later on throughout his life. He characterized these cells and they he also tried to use this cells for various therapeutic and for his this remarkable work, he was awarded a Nobel Prize.

And there is a some unfortunate stories associated with this Nobel Prize. This is a first time in where the Nobel Prize was given after his death. And actually, this this Nobel Prize was already decided to give him but dude. He had a pancreatic cancer and three days before announcement of this Nobel Prize. He was, he was unfortunately passed away but this is first time in history in case of Nobel Prize, this is not happened earlier.

Nobel Prize were not given posthumously. But in his case, it was considered because this Noble family did not receive this news. And finally, when, when they received this news, they decided that this, the prizee will go to his wife and his kids, So, this is a kind of exception and he got this Nobel Prize in 2011, along with two more scientists. Their name is Bruce Butler and another is Julie Hoffman.

I will discuss about their work when I will take the pattern recognition receptor. So, this dendritic cells are basically derived from hematopoetic stem cell. If you remember my previous sessions and there is a two lineage of hematopoetic stem cell, one is myeloid lineage and another is lymphoid lineage. So, this dendritic cells are derived from both myeloid lineage, as well as lymphoid lineage.

So, the these cells can come from any of these origin. The lymphoid cell, the dendritic cells which is present in the skin, is known as langerhans cells. I think I may discussed earlier if not then the cells, the dendritic cells which is present in the skin, we call it as a langerhans

cells and this was discovered quite early quite early means before this 1970's. But it was not very well characterized and it was discovered by Paul Langerhans and it is discovered in 1868 and he was also confused that this is a neuronal cell.

And therefore, it was not very well characterized at that time, it was discovered in the epidermis. So, this dendritic cells are present throughout our system and especially the linings. Linings of the body it is a inner lining, all mucosal surfaces as well as outer lining the skin surfaces. As I have explained you, there is a Langerhans cell which is dendritic cells and it is also present in mucosal surfaces such as gastrointestinal tract, respiratory tract and they again play a very important role in defense.

Here you can see a transmission, electron micrograph of dendritic cells and these dendritic cells are fed with polystyrene beads. Here you can see the white region which is denoted by P. So, these cells can also phagocytose and here you can see lot of projections and these projections are basically the ~~dendrions~~dendrons. The projections and these projections plays a very important role in adaptive immunity.

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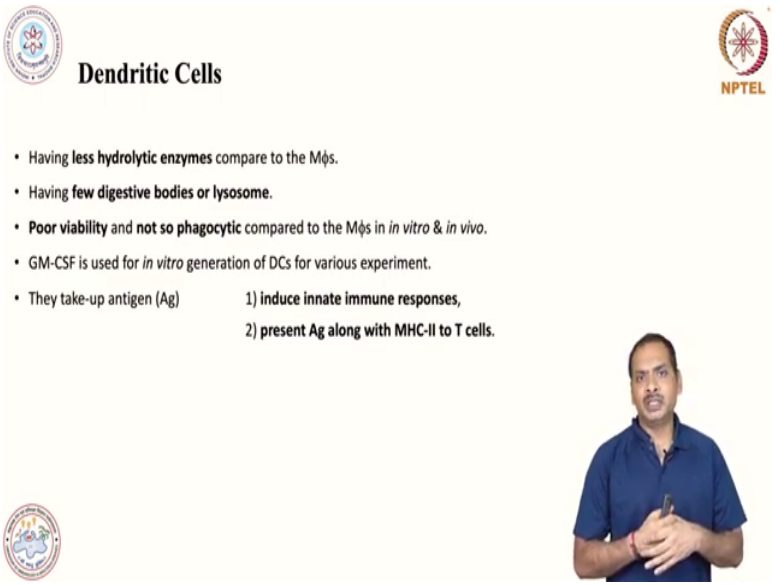

So, dendritic cells are having less hydrolytic enzyme compared to the macrophages. We will discuss in probably next session about the macrophages and you will realize that they have a relatively less hydrolytic enzyme. You know there are variety of hydrolases present in the phagosome or well and this this get activated when there is a fusion of phagosome and lysosomes.

So, in case of dendritic cells, this is quite less compared to the macrophages. They have very few digestive bodies or lysosome. You know that lysosome is a place where lot of hydrolytic enzymes are there which can ~~degradate~~degradate any kind of biomolecules. So, they are less they have a poor viability and not so phagocytic compared to the macrophages and poor viability is not only in vivo, it is in vitro also.

So, if you isolate the dendritic cells, as you have seen in my previous session, I told you after during the isolation of PB~~V~~MC there are very few number of dendritic cells. And these dendritic cells are quite short-lived. And therefore, it is very difficult to perform the experiment with human dendritic cells. Why? Because you need to drain lot of blood and that is not practically possible.

But if you want to work with say lymphocytes then it is quite easy. ~~Al~~right If you remember, there is a quite big percentage of cells are present and all those cells are lymphocytes. So, generally we perform the experiment in mice and we can easily prepare these dendritic cells using some factor known as GM-CSF, granulocyte monocyte colony stimulating factor. So, I will explain you how we can make this dendritic cells in the laboratory using mice.

So, what you have to do? You basically take a adult mice and then you can sacrifice by whatever way which is approved by your institute by your institute ethical committee. And then you can take out those long bones. So, long bones when I say basically, I am trying to say the hind limbs bone. And if you have some idea about the bones, there is a pelvic griddle which is basically a hip joint.

And where in this hip joint, there is a bone known as femur, femur attaches with pelvic griddle and then there is a tibia. So, basically what we do? We take the mice we sacrifice as per the guideline of institutional ethical ~~comm~~committee~~unity~~ and then we take out this femur and we also take out the tibia. And if you cut the ends of these two bones then you can get the bone marrow a simple way.

If you want to do the culture of bone marrow cells, you can flush this bone using very fine needle and you can use the syringe with fine needle. And after flushing, you suspend this cells and then you can use these bone marrow cells. In order to make the dendritic cells and

using this method you in addition you need to add this GM-CSF and when you will add this GM-CSF and leave it for say 10 days or 15 days.

Then most of these bone marrow cells will differentiate to the dendritic cells. And then you can use this dendritic cells for various experiment. You can use it for innate immune studies. You can use it for adaptive immune studies whatsoever. So, this way we can make the are dendritic cells in the lab and this is very useful for conducting various experiments. So, basically dendritic cells, they take up the antigen and then they induce the innate immune responses.

When I say innaete immune responses, it means there are two major things which is taking place in the cell. One is that there will be a activation of these dendritic cells mean it will produce more cytokines more inflammatory cytokine. You take the cells and stimulate with any antigen or any appropriate ligand, for example LPS. Then this will produce tons of inflammatory cytokine.

And they will also express the MHC Class 2 molecules and some adhesion molecule. These adhesion~~addition~~ molecule is needed in order to establish appropriate T cell mediated immune response and subsequently B cell response as well. So, this is a when this dendritic cells are activated by some pathogen and then this will induce the innate immune response. So, these are the all innate immune responses which I am talking.

And second, they also present the antigen, along with one molecule which is known as MHC major histocompatibility complex to the T cells and that will basically play a very important role in development of adaptive immunity.

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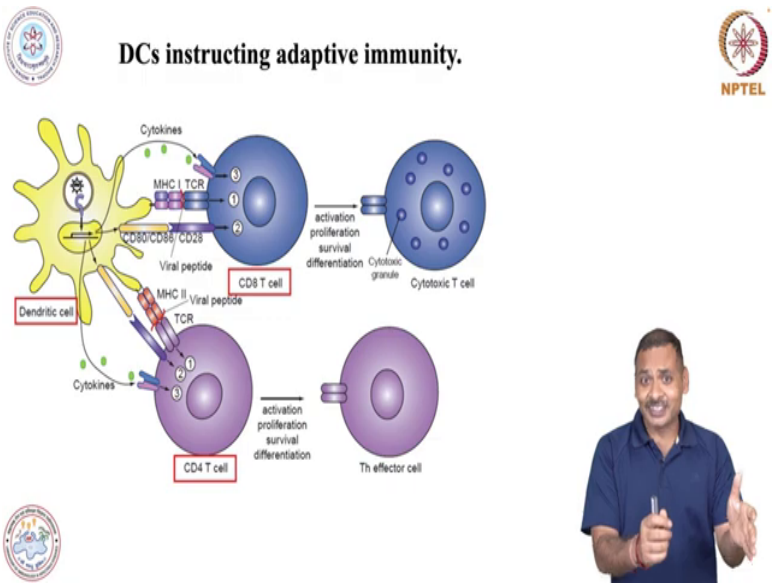

As you can see, the dendritic cells are having a projections and these projections are very important for presenting antigen. So, the dendritic cells basically express MHC Class 2 molecule and that is why we call it as antigen presenting cells. And besides dendritic cells there are other cells which are antigen presenting cells that is macrophages and B cells. And these dendritic cells also express MHC class 1 molecule and as I told you in previous sessions that MHC class 1 molecule is expressed in all nucleated cells.

And this when, when this antigen is presented along with MHC class 1 molecule then it activates CD8 T cells or cytotoxic T cells. The antigen which is presented along with MHC Class 2 molecule this activate CD4 T cells and when the CD4 T cells get activated then there will be a induction of variety of immune responses. There are various kind of CD4 T cell responses, CD4 T cells also we call it as a Th cells.

And Th cells will be of various kind and there depends on the type of Th cells the responses will be elicitated. For example, the Th1 induces responses which will basically clear the intracellular pathogen the pathogen which is residing inside the macrophages. And Th2 responses they are playing a very important role in induction of antibody and in some scenario it is also playing very important role in development of allergy.

On another hand CD 8 T cells which since the antigen along with MHC class 1 molecule they are also called as a cytotoxic T cells. And these cytotoxic T cells basically play a very important role in a virally infected cells. They basically kill the virally infected cells and we

can get rid of from the virus infection. They are also playing a very important role in against the transformed cells.

Basically, I want to say that they play a very important role against tumour. So, if they see some unusual expression of MHC class 1 molecule and if they see there is a some problem in presentation of antigen then these cytotoxic T cells or CD8 T cells will eliminate those cells. So, this is very, very nice system and here you can see that dendritic cells are key or pivotal in development of a variety of immune responses.

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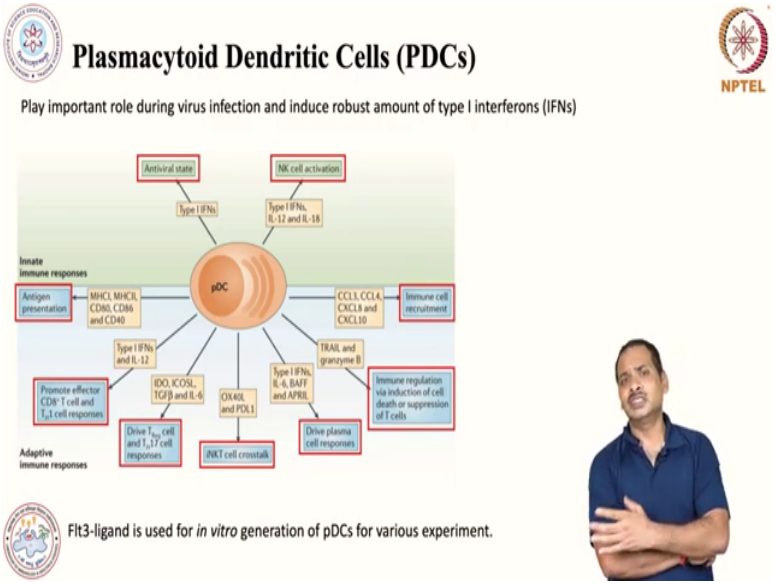

So, since we are talking about the dendritic cells, there are various kind of dendritic cells and one is plasmacytoid dendritic cells. These plasmacytoid dendritic cells are playing extremely important role in virus infection. And upon virus infection these plasmacytoid dendritic cells produce a robust amount of type 1 interferon. This type 1 interferons are very important in stopping the replication of viruses, various kind of viruses.

And they do not only have this property in addition they also have a property they have antiproliferative properties this is also used in some cancer treatment as well particularly associated with liver cancer. Your hepatitis virus infection. There is a virus known as hepatitis B and during that infection, the patient received this type 1 interferon. This type 1 interferon are synthesized and stabilized and we basically call it as a pegylated~~paglated~~ interferon.

And this is used as a therapeutic. So, PDCs produce tons of type 1 interferon during the virus infection. So, please remember PDCs are key player in virus infection, and how it work it

basically make antiviral state. There are so many functions of this type 1 interferon or we call it as a pleiotropic function. And this pleotropic function is creates the antiviral state in the host.

In addition, they also further enhance the antiviral state by activating a very specialized cell which is we call it as a natural killer cells and these natural killer cells are a kind of a very important weapon against the virus and virally infected cells. They play also important role against tumour cell. So, these NK cells are playing a very important role in in both virus, as well as in anti-tumour activity.

So, these are the innate immune response. Now, let us look at the adaptive immunity, so, they play a very important role in antigen presentation. Basically, that the PDCs produce type 1 interferon, as well as to some extent of inflammatory cytokine these together, basically activate the DCsdisease. And then over there will be efficient presentation of antigen, they promote a factor, CD8A T cells and Th1 cell responses.

They drive a T-regRex cells. This is the T-Rex is basically the regulatory T cells and there is a T70 cell which plays a very important role in autoimmune kind of a thing which we may discuss later on. And they also induce the induced NMKT cells. And they also produce or enhance or derive the plasma cell response and they are playing important role in immune regulation via induction of death or suppression of T cells.

And this type 1 interferon or the products produced by the PDCs type 1 interferon as well as inflammatory cytokine, it helps in the recruitment of immune cell at the site of infection. So, this is all about the plasma-cytoid dendritic cells. We can also generate this plasma-cytoid dendritic cells in laboratory for conducting various kind of experiments and here we use a one factor or cytokine which you can say that which we call it as a Flt3 ligand.

And this ligand, if you stimulate the bone marrow derives us as I have explained to you if you stimulate the cells with this cytokine then these cells will differentiate to the plasmacytoid dendritic cells.

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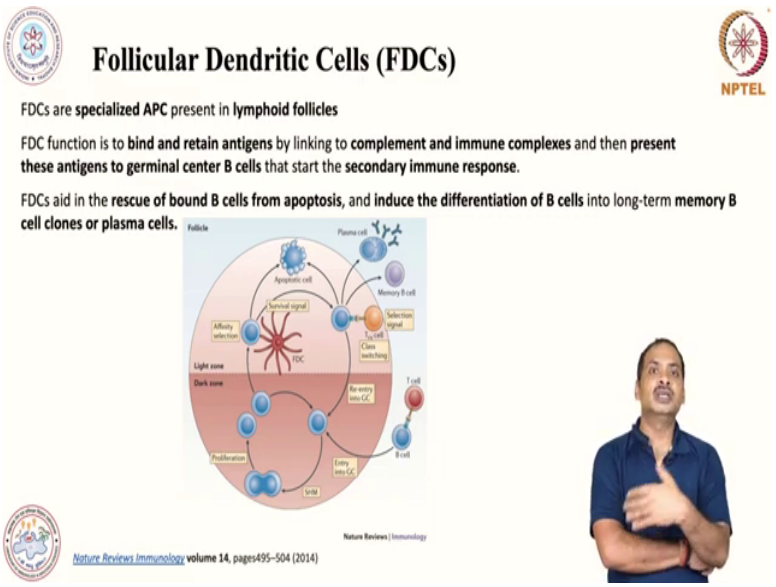

There is a one more dendritic cells which is quite different which we call it as a follicular dendritic cells. FDC, and what is these FDCs? Basically, they are kind of specialized antigen presenting cells and they are basically localized in lymphoid follicles. And basically, they play a very important role in B cell biology, they bind and retain the antigen which is basically linked with immune complex and present these antigen to the germinal centre.

You remember the germinal centre or primary follicle secondary follicle. So, secondary follicles are the germinal centre and basically, they enhance the division of B cells which will basically make the plasma cells. And then this plasma cell will produce a robust amount of antibodies against antigen. They also play an important role in affinity maturation which probably you will not understand at this stage.

So, affinity maturation is a step by which there will be a generation of high affinity antibody against the antigen. So, all those roles are played by the follicular dendritic cells. So, basically FDC is how they play a role in in maintenance of B cells. Once they will bind with B cells, they will rescue this bound B cells from cell death. So, in that way, B cells will survive and then they can further divide to the plasma cell and then they can produce the antibody.

So, they will induce the differentiation of B cells and memory B cells and plasma cells as I have explained to you. So, here you can see that how these FDCs are playing important role in B cell biology, So, FDCs, I do not know. I never prepared the FDCs in lab, so, I cannot say

how to prepare the FDCs. So, in this session I will stop and in this session I will sum up everything.

So, I basically explained the dendritic cells and then plasmacytoid dendritic cells and follicular dendritic cells. Since, all these are dendritic cells that is why I have taken all these cells. And these cells are playing very important role. For example, DC's are playing very important role in both innate and adaptive immune response. PDC’s are playing very important role in antiviral as well as anti-tumour and FDCs are playing very important role in B cell development, maintenance, maturation and so on and so, forth. Thank you.