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 – 20
Cells of Immune System and its role in Host Defense-NK and NKT Cells

Hi, in previous session, we have discussed different kinds of dendritic cells and macrophages, we learned about their function and we also learned how these different kinds of dendritic cells play a very important role in various aspects of immunity. And the key point of that previous lecture is that dendritic cells are very important and antigendegen presenting cells. The follicular dendritic cells they play a very important role in B cell development and B cell mediated immune responses.

And there is a one more type of dendritic cells that is plasma cytoid dendritic cells and these plasmacytoid dendritic cells plays a very important role in virus infection. We have also discussed macrophages various kind of macrophages and it is role and finally, we had discussed about how these reactive nitrogen species and oxygen species are generated and I also give you some idea about the importance of one of nitrogen species that is nitric oxide in a non-immunological function.

So, in this session we will take up two major cells, one is NK cell and another is NKT cells. So, NK cell and NKT cells they are one of very important component of immunity.

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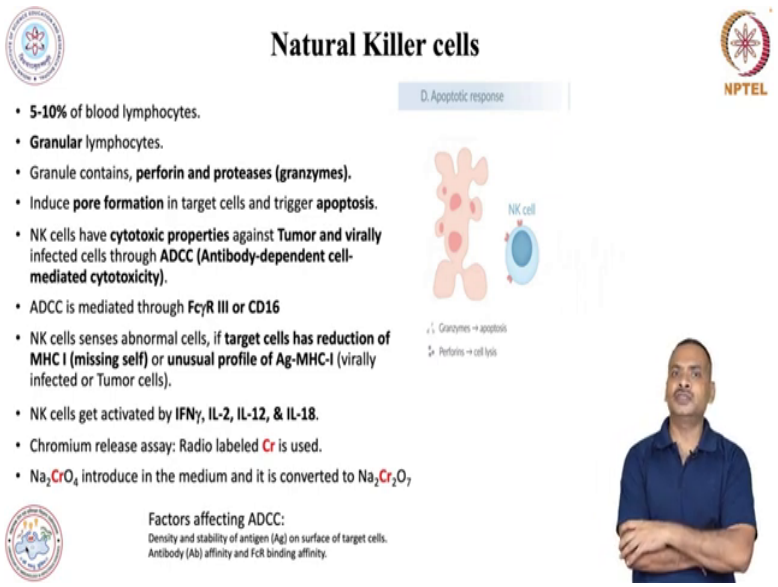

And basically, these cells are present in blood and this constituted about 5 to 10 percent of blood lymphocytes. And this also has a packet of granules and they are granular lymphocyte. They have some ~~granulicity~~granularity. And these granules are very important for their function, as you can see in subsequent thing. So, these granules basically contain two very important ~~and~~ set of molecules one is perforin and another is this contain various kind of proteases.

And we also call it as a granzymes. And this perforin and granzymes is very much essential in order to kill the target cells. So, when the NK cell get activated then they basically forms a pore in target cells and they deliver all these contents of this granule which is mainly consists of granzyme and this granzyme is transferred into the target cell and that will trigger apoptosis.

And this pore formation is mainly taken place by this protein known as perforin as I told you in previous step. Basically, this NK cells are playing very important role or cytotoxic role, I will say cytotoxic role to or against virally infected cells and tumour cells. So, they basically kill the virally infected cell and induce a through apoptosis and they also kill the tumour cell.

As I have told you in some of previous session that in our body there is a always some transformation of self. But that does not result to the tumour or cancer because our immune system is intact and our immune system is keep on checking these kinds of cells. And these cells basically express if you remember my initial lectures, these cells keep on scanning and then they scan for modified cells.

If there is some modify itself then these cells will come in action and basically kill those cells. So, the NK cells are playing very important role in against tumour cell and they are also playing a very important role in virus infection. Please note that once the cells are infected by viruses then there is no choice except to kill that cell. You cannot kill the virus inside the cell. The best way is you kill the cell then virally infected cells.

So, in that way you can prevent the viruses spread in the host and you can also restrict the number of viruses. If you kill the virally infected cell, you will reduce the virus. And that will also result to the reduction of a viral replication. Otherwise, what will happen this? When the cell are infected with virus then after finishing the replication cycle, they will be liberated in outside the cell.

And then these newly found viral particles will infect other healthy cells. In that way, this viral infection will propagate. So, NK cells play a very important role and how it plays a very important role? By a very unique and sophisticated mechanism which we call it as a ADCC. ADCC is antibody dependent cell mediated cytotoxicity. So, this needs antibody. If we do not have antibody the NK cell mediated killing will be not so, efficient.

So, ADCCs are basically mediated by antigen specific antibodies. And there is a receptor for this antibody over the NK cells. And these antibodies basically bind with this receptor and then that will trigger the ADCC and this receptor is basically Fc gamma R III. So, basically the antibody which triggers this ADCC is IgGG it is a kind of antibody there are several kinds of antibody.

And this antibody basically binds with this receptor and then it ~~initiate~~initiates ADCC I have a one, nice animation which will help you in understanding this ADCC. So then the simple question arises that how this NK cell distinguish the correct cell and not correct cell? Because the correct cells are normal cell there we have all normal cell and uncorrect cell is, it could be a virally infected cell or it could be tumour cell.

So, how this NK cell distinguishes so, basically in NK cell there is an activation receptor and there is an inhibitor receptor. So, these activation and inhibitor receptor basically there is a some balance and if this balance is disrupt then this NK cell get activated. I will take all these

details when I will take the viruses. So, here just for your information there could be a change in expression of MHC class I molecule.

And this MHC class I molecule if you remember my previous sessions, I have told you that this MHC class I molecule is present on all nucleated cells of the host. So, if there is a reduction in number of this MHC class I molecule on target cell then that will activate the NK cell. Another way is that there will be unusual profile of antigen MHC class I molecule, particularly, it is true for both virus and tumour cell.

So, these are the features which basically NK cell sense or screen and if the cell find that this there is a reduction in MHC molecule or there is a unusual profile of antigen and MHC class I molecule then that will get activated and kill the target cells. So, in case I will get activated by interferon gamma besides this, there is a IL-2 IL-12 and IL-18. And this is a kind of signature of activated NK cells.

And here I would like to tell that these NK cells are also used in some or other kind of therapeutic. And this is basically achieved by if you isolate the NK cells and treat with some cytokines, cytokine or lymphokine then they get activated. Here one example is that there is a cell known as LAK cells, this LAK cells are lymphokine activated killer cells. And this lymphokine activated killer cells basically, are the NK cells are treated with IL-2 and then this NK cells get activated.

These natural killer cells get activated and this is used for some cancer therapy. To best of my knowledge this kind of cells are not generated in vivo condition, it is a ex vivo condition, we activate and then infuse and then we see some phenotype. This we also use in our experiments when we are using mice. So, now, there is a simple question that how we can measure the NK cell activity? Whether they have a killing capacity or not.

So, we do one experiment which we called it as a chromium release assay. This chromium release assay is a very simple experiment here we provide the target cells with some chromium salt. Here you can see that sodium chromate we provide or Na 2 Cr O 7. We put this molecule in the media over there this chromium is radio labelled. And once it will taken up by the cell this will be converted into the Na 2 Cr 2 O 7.

And this cannot come out of the cell and when you put NK cells over there then we will see there is a death of cell target cell and there will be a release of this radioactive chromium. And in that way, we can assess the NK cell activity so, this is a one very simple experiment this is a very gold standard experiment. However, these days, we since you know that radioactivity, has a lot of problem we do not use radioactivity.

So, we have some another way what we can do? We have a very sensitive assays for lactate dehydrogenase. So, probably you know that lactate dehydrogenase is quite abundant in the cell. So, if the NK cell will kill the target cell then there will be a release of lactate dehydrogenase enzyme in the supite. And if we measure those lactate dehydrogenase enzyme amount by giving appropriate, substrate or chromogenic substrate.

Then we can calculate the killing capacity of NK cells. So, basically NK cells are we can test the NK cell activity by these two ways. Now, we do not use the chromium release assay, although this is a very good experiment but we do not use. Now, we use the lactate dehydrogenase because this anybody can do it and you do not need a special facility. You do not need any special kind approval for those conducting those experiments.

So, there are some factors which basically affect the NK cell activity that is density and stability of antigen on the surface of target cells. And antibody affinity so, as you can understand, there is an involvement of antibody. So, if the affinity is weak, the NK cell activity will be not so, good. Here I have a one short video which you can see how the NK cells works?

(Video Starts: 15:33) Referred to as NK cells these lymphocytes, also business SC receptors on their surface which bind to the antibody leading to natural killer cell activation, a natural killer cell releases perforin a protein similar to the membrane attack complex that inserts into the plasma membrane and causes target cell lysis natural killer cells also release granzymes, a group of proteins that initiate apoptosis caused by type **(()) (16:03)**. **(Video Ends: 16:04)**

So, I hope you understand this ADCC phenomena very well and now let us move on another very important cell type which we call it as NKT cells.

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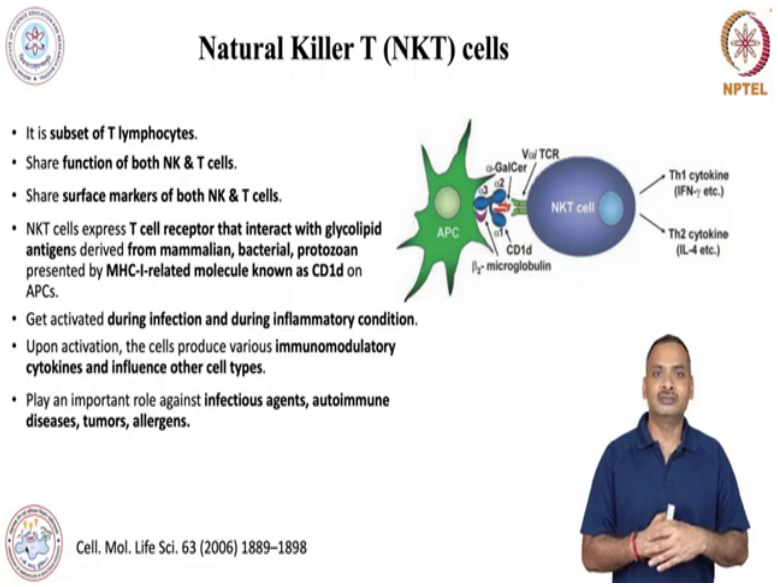

It is a natural killer T cells and this natural killer T cells plays a very important role in recognizing non-conventional antigen. Basically, this NKT cells are a subset of T cells and this subset of T cells plays a very important role against non-conventional antigen. And what is that? Before that I will explain there are some properties, so, basically, these NKT cells share function of both NK cell as well as T cell.

They also share surface marker of both NK cell and T cells. So, NKT cells basically express T cell receptor that interact with that non-conventional antigen generally conventional antigen is protein antigen. Here it is a non-conventional antigen and these non-conventional antigens are glycolipid antigen. As you know that the pathogen do have a lipid and lipid derivative and these molecules also need to be taken care by the immunity.

So, NKT cells are the key player against this non-conventional antigen or lipid or lipid derivative antigen. And all these lipid and lipid derivative antigens are present on variety of pathogens, such as bacteria, protozoa and they are also present in fungi. If I say bacteria, one of the very important bacteria is mycobacterium tuberculosis. This mycobacterium tuberculosis is it is outer covering, is rich in variety of lipid and sugar derivatives.

Probably you might heard the name of molecule known as LAM, lipoarabinomannan, so, these lipoarabinomannan are also presented along with one of MHC class I molecule derivative molecule or it is a similar to MHC class I molecule known as CD1d molecule. Here it is shown and these lipid derivative molecules are presented to the NKT cell and then there will be a activation of immune responses.

So, overall the lipid antigen is presented by a family of molecule known as CD1d which is similar to the MHC class I to the NKT cells. And then NKT cells get activated and induce the appropriate immune response. So, this NKT cell get activated during various infection as I have explained you microbial infection and it is also get activated during inflammatory processes or inflammation condition.

And as I told you when this NKT cell get activated, they produce a variety of immunomodulatory molecules, the cytokines they can activate some population of immune cell and so and so forth as I have explained you previously several times. They play a very important role against infectious diseases, autoimmune diseases, tumour, allergen. If there is some allergen will be there NKT cell can activate and it will induce some immune response.

So, here I am showing you in this schematic that how this NKT cells play a very important role in modulation of immune response. Here you can see that NKT cell present alpha galactosylceramide and lipid. This is a basically a derivative of sugar and lipid and this is presented to the NKT cells and upon activation of NKT cell it can induce Th1 cytokine, for example, interferon gamma and or it can also induce Th2 immune response, such as production of IL-4.

So, Th1 and Th2 response I will explain you in more detail in upcoming session. Here I will stop with this NK and NKT cells and in next session I will take the last component of immune cell that is B cells, T cells and I will also discuss about one very important a group of molecule or a kind of nomenclature which is very important to understand in immunity known as cluster of differentiation.

You are seeing lot of CD1 and CD various number so, we will discuss how this CD things came up and how it is helpful in understanding the immunology? Thank you.