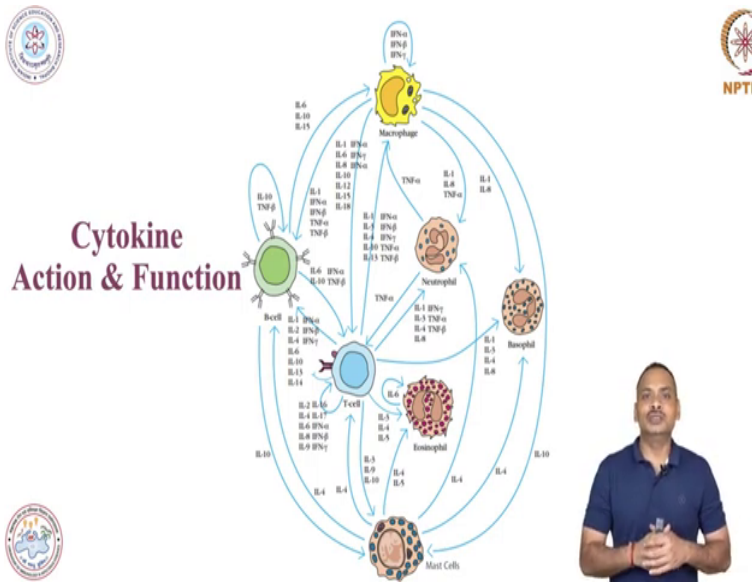
Host-Pathogen Interaction (Immunology)
Prof. Himanshu Kumar
Laboratory of Immunology and Infectious Disease Biology
Department of Biological Sciences
Indian Institute of Science Education and Research (IISER) - Bhopal

Lecture – 23
Cytokine Function and other Immune Mediators

Hi, in previous session we have discussed about the cytokine and we have learned about how it works? And now we will continue with some aspects of some more aspects of Cytokine. I will show you how this cytokine network is how complex it is in immune system? And then I will discuss about some innate cytokines as well as adaptive immune cytokine and then we will talk about other immune mediator.

So, other immune mediators are basically non-conventional molecules means generally the cytokines are protein molecules or glycoprotein. But there are some non-protein molecules are also there which plays a very important role in communication among the immune cells. And there are some set of molecules which is basically produced after splitting of some of molecule which is playing an important role in immunity. So, we will discuss all those things.

(Refer Slide Time: 01:39)



So, here you can see the complex network of cytokine here you can you can realize it is a quite complicated. So, here you can also see there are some cytokine which is produced by the same cells and acting on the same cell. For example, if you see on top there is a

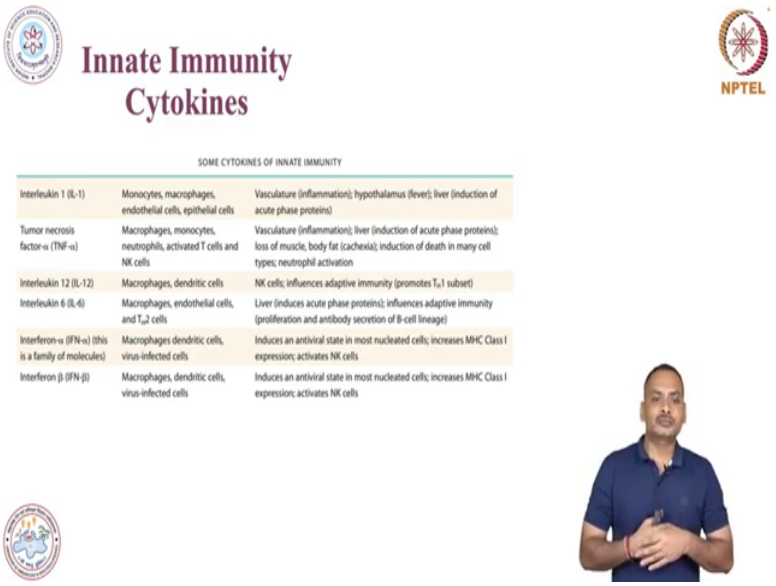
macrophages and the macrophages is producing the interferon alpha, beta, and gamma and it is acting on the same cells that is macrophages.

Similarly, if you see there is a cytokine known as IL-10 which is produced by the B cells and it is also acting on the B cells. Another is IL-6 if you see the eosinophils IL-6 are produced by the eosinophil and acting on the eosinophil. T cells produce a various cytokine and these cytokines are produced by the cells, T cells that particular subtype of T cells and it is acting on same cell type.

So, this is a very good example of autocrine action, there is a paracrine action here rest of all communication between the cell to cell or communication for development of particular immune response, you can see in this complex network. So, this is quite complex and it will take time to remember or to learn these things. So, you need not to remember all this cytokine which cytokine is produced by which cells?

But as you go in the immunology course when you take or when you study say for example macrophage then you will study all those macrophages associated cytokines, at that time you will remember. However, you do not need to memorize all these network, when you do? When you study those particular cell and their response, you will automatically learn or when you will do research in that field. Then you will automatically remember, you need not to mug up these networks.

(Refer Slide Time: 04:08)



Now, I will talk about some innate immune cytokines. So, here you can see the there is a cytokine like IL-1, TNF- alpha, IL-12, IL-6, interferons so, when I say interferon this is type I interferon or which under type I interferon there are two major interference that is interferon alpha and interferon beta. So, these are the innate cytokine, a key innate cytokine do not take it these are the only cytokines.

There are some other molecules are also there which is playing important role in innate immune responses. So, for example IL-1 is produced by a variety of cells, as you can see it is produced by monocyte, macrophages, endothelial cell, epithelial cell. Please remember, endothelial and epithelial cells are non-immune cells but they produce cytokines. So and they basically induce inflammation, they can also be responsible for the development of fever in the individual.

And they will also act on the liver in order to synthesize the acute phase proteins which will cause the acute phase response. So, like IL-1 this acute phase response is also induced by other cytokines. As you can see the TNF alpha can also induce the acute phase response. So, as well as this will also induced by the IL-6. So, these cytokines basically overall play a very important role in order to eliminate the pathogen without any pre-education of the immune system.

Adaptive immunes response is little different so, they in first when the individual is infected first time then the adaptive immune response or adaptive immune cells get educated in that sense means they will develop a antigen specific immune response. And when there will be a second infection of same pathogen then this will be quickly eliminated so, here I just broadly discussed about the innate immune cytokines.

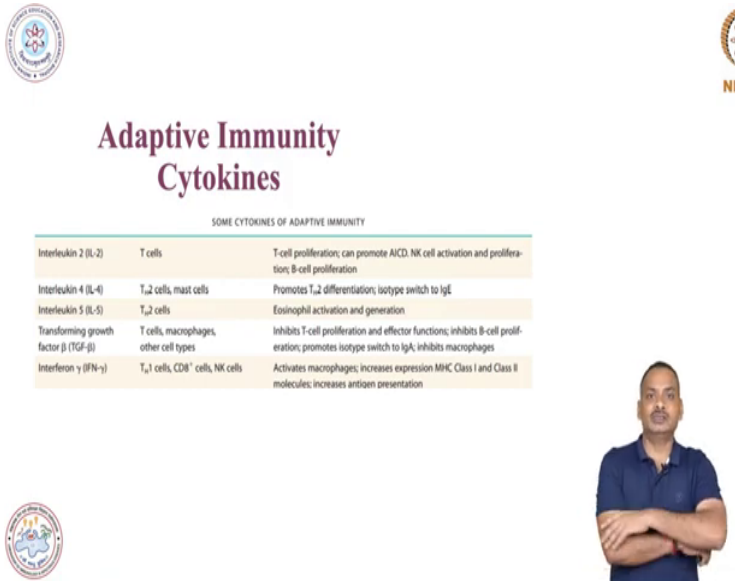
And among that these innate immune cytokines there are two major categories if you see very broadly, one is inflammatory cytokine and another is type I interferon. So, inflammatory cytokines are in a very simpler way they are inducing inflammation. And inflammation is basically inviting the immune cell at the site of infection that is the role of inflammation. And this is positive role and negative role.

You know that will result to the development of disease. Another is innate immune cells are producing the type one interference. So, these type one interferons are playing very important

role during virus infection they interfere the viral replication and they have anti-proliferative activity. So, when the interferon will be produced then that will restrict the cell division, anti-proliferative they will stop the cell division.

They can also act on variety of immune cells which includes the innate immune cell as well as adaptive immune cells. Innate immune cells such as natural killer cells, adaptive immune cells like a B cells and T cells. So, here I just broadly discussed about the innate immune cytokine.

(Refer Slide Time: 08:31)



There are adaptive immune cytokines and among that IL-2 is playing a very important role and it is very much necessary. If you see the IL-2 then our immunity is developed in such a way that there is a various kind of receptor for IL-2, high affinity, low affinity and medium affinity. Why nature devised so many kinds of receptors? The reason is very simple this has a huge effect and this huge effect can be fine-tuned by making various kind of receptor.

So, IL-2 is mainly produced by the T cells, IL-4, IL-5 and TGF beta and all these are produced by another cells, mainly IL-4 and IL-5 is produced by Th~~-H-~~2 cells which plays a very important role in in development of humeoral response or parasite during parasite infection allergy. So, this this IL-4 and IL-5 is basically produced by Th2~~-H~~ cells and they facilitate or if you see it is playing a very important role in a very important biological phenomena known as class switching.

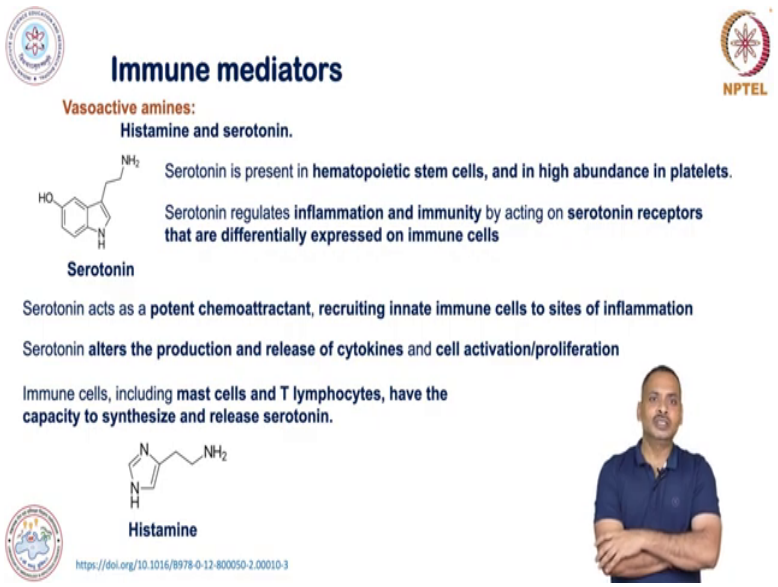
Class switching is present in ~~an~~ antibody synthesis, class switching in a very simple way so, generally B cells produce first one type of antibody, there are five types of antibody among five, four we know their function. So, class switching is from one type to another type and the synthesis of one type of antibody to another type of antibody, we call it as a class switching. These can also act on eosinophil, eosinophil activation or generation of eosinophils.

TGF beta is basically produced by T cells, macrophages and some another immune cells and they play again wide range of role like class switching to IgG~~G~~A, inhibit macrophages and it inhibits the T cell proliferation. Another is interferon gamma, interferon gamma is basically produced by many activated adaptive immune cells, like Th ~~H~~ 1 cell, CD8 T cells, natural killer cells.

And basically, they activate the macrophages and enhance the expression of MHC class II molecules, as well as MHC class I molecule. In addition, they also enhance the expression of some adhesion molecule. So, when we will take up the T cells at that time you will learn, what is the role of adhesion~~addition~~ molecule? Basically, this antigen and MHC class I or class II and surface molecule is presented to the T cells and over there will this is a one kind of interaction.

But in order to activate the T cells, you need additional stimulation and that additional stimulation is provided by the adhesion molecules. These adhesion molecules will there will be a ligand for these adhesion molecule over the T cells. And then collectively there will be a appropriate response or appropriate activation and then these T cells will get activated. So, for all those things there is a need of appropriate adaptive immune cytokines.

(Refer Slide Time: 12:44)



Now, let us move to the various different kinds of immune mediators and you probably aware about there are two major or these are the two molecules which plays a very important role in regulation of immunity. Not only immunity, you will see they play a very important role in another biological processes for example, they act on smooth muscles, they act on a mucous gland and so on.

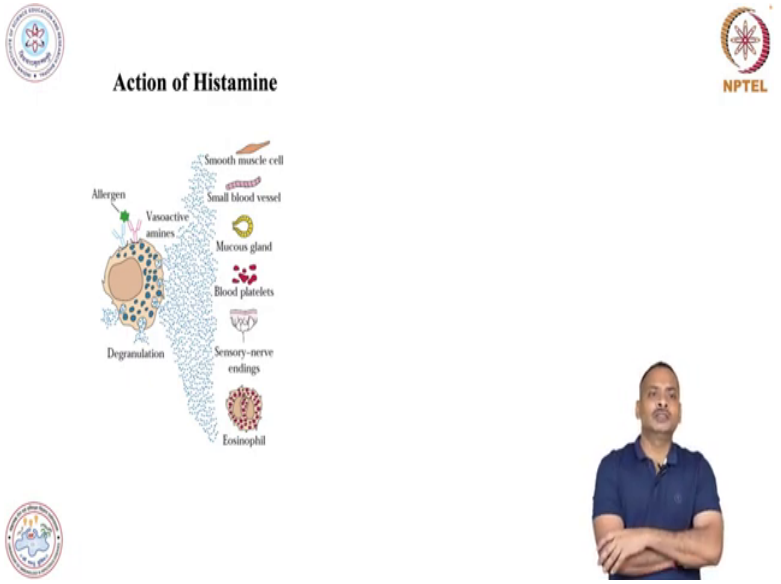
So, let us take up this another immune mediator the first is vasoactive amines and here the two major molecules are come in action one is histamine and another is serotonin. So, about histamine we have learned in great length, when we had taken the mast cell, eosinophils and basophils. So, let us first discuss about the serotonin so, serotonin as you can see that this is a vasoactive amine and this has a variety of function.

So, basically serotonin it is interesting that serotonin is present in hematopoietic stem cell and it is present in very high amount in platelets. Basically, it regulates the inflammation and immunity and the serotonin basically act on or act through the serotonin receptor which is differentially expressed over the variety of immune cells. These immune cells have a different levels of expression of this serotonin receptor.

So, this serotonin is produced and then it is acting over the cells. It is a basically a potent chemo attractant so, if there is a high concentration of serotonin at say particular side they basically invite the immune cells, recruit the innate immune cells or other immune cells. And basically, it will help in development of some kind of inflammation serotonin alter the production and release of cytokine.

So, this is small molecule can alter the production of cytokines and hence they can alter the cell activation and cell proliferation. So, immune cells the serotonin is produced by immune cells including mast cells, T lymphocyte and have a capacity to synthesize and release. These cells have this; they can synthesize these serotonin molecules and they can produce. Now, another is histamine I will just quickly brush up about the histamine.

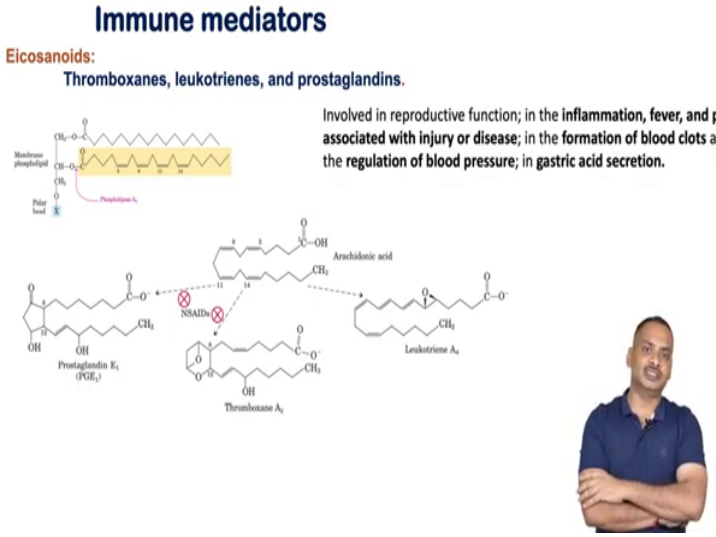
(Refer Slide Time: 16:01)



So, histamine is basically produced by mainly mast cell as well as eosinophil and basophils and they act on various systems. For example, this act on smooth muscles they can act on a small blood vessels and mucous gland, blood platelets they can also act on sensory nerves ending and eosinophils. And you remember that this histamine is a culprit during allergic reaction and that cause type one hypersensitivity which is IgE mediated.

And there is a several drugs which inhibit the synthesis or action of the histamine for example, I have told you in previous session that cetirizine is a molecule which basically act as a competitive inhibitor for this compete with this histamine in order to act on the histamine receptors so, this is all about the histamine.

(Refer Slide Time: 17:22)



Another immune mediator is a eicosanoids, so eicosanoid are lipid immune mediator, it is a lipid based and how this this lipids are coming in action? So, here you can see, there is a this is a membrane phospholipid if you remember and there is a enzyme known as phospholipase A2. So, this basically cleave the second carbon of glycerol and then that will release the mainly arachidonic acid and this arachidonic acid by action of various enzyme this will make some very active immune mediators.

For example, here you can see there is a prostaglandin, prostaglandin E1, there is a thromboxane and leukotrienes. So, all these are very active immune mediators and they are playing very important role in inflammation. And it is very interesting to inform you that there are some drugs which basically inhibit those enzymes which is involved in synthesis of these immune mediator from arachidonic acid.

And there are drugs and these drugs which we call it as a non-steroid anti-inflammatory drugs so, non-steroid anti-inflammatory drugs such as aspirin, you might be using which is also used as a thinning agent for cardiovascular patient. Another example is ibuprofen so, ibuprofen this molecule basically inhibit these the enzymes and these enzymes are cyclooxygenase.

So, these cyclooxygenase is basically synthesize this prostaglandin, thromboxane or leukotrienes or there are different types of the enzyme, not there are several kinds of cyclooxygenase and then this these molecules are synthesized. So, now you can understand the drug which we commonly use act on lipid mediator which is inducing the inflammation.

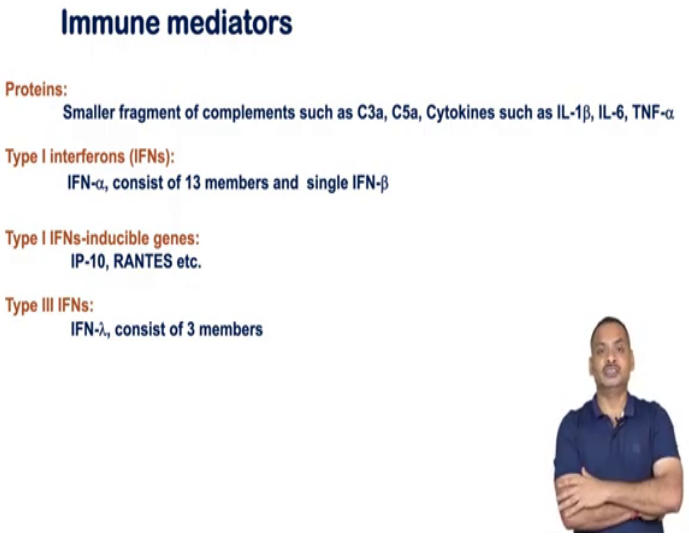
So, basically these lipid mediator has a various way to cause their effect, it basically induce the inflammation this induce the fever pain associated with injury or disease. They are also involved in formation of blood clot and they are also playing a very important role in regulation of blood pressure and gastric secretion. It is not only the little off function they are playing very important role in gastric acid secretion.

(Refer Slide Time: 20:48)

Another immune mediator is a peptide and here I have put this bradykinin. So, bradykinin is it is only nine amino acid; it is a very small stretch of amino acid, small polypeptide. And this has a wide role in immunity, not only in immunity it is playing very important role in blood vascular system or regulation of blood vascular system. So, it is playing very important role in blood pressure regulation, it is a basically a vasodilator.

It also induces or play an important role in inflammatory reactions and you know that inflammation is very important. It elevates the vascular permeability and to cause the vasodilation in some arteries and veins. So, these are the some very important non-conventional immune mediators.

(Refer Slide Time: 21:56)



And now, I will just put some light on the proteins you have studied the cytokines but besides cytokines there are some proteins which is playing a very important role in a immune responses among that one of these is C3a and C3a and C5a this is a smaller fragment of complement. So, complement is a basically a set of protein which is synthesized in liver and plays a very important role against the invading pathogen.

I have told you in previous session they act on invading~~inverting~~ pathogen and they induce three major kind of responses. One is it induces inflammation so, inflammation is mediated through this small fragment of complement that is C3a and C5a. It also induces the opsonisation, opsonisation is so, once this complement is activated it will be deposited over the target microbial pathogen and then this will be readily phagocytes by the macrophages.

And the third function is cytolysis so, basically, they make a hole in the target cell and then there will be a loss of iron and everything and then that will cause the death of that particular microbial pathogen. So, in that way this displays an important role in immunity. So, in great length we have discussed about the cytokine but just I wanted to highlight here about the complement proteins, the fragments of complement protein.

There are type I interferon which I have already explained in great length, here I will add up some more. So, there are thirteen members of interferon alpha and one member of interferon beta. And basically, all these things all these molecules basically take care against the virus infection. There is a type I interferon inducible gene so, when this type I interferon is produced by the immune cells again they act.

And then they activate the huge number of genes and all those genes basically involved in checking this viral replication and we call it as a type I interferon inducible genes for example, IP-10 and RANTES. There is a one more class of molecule which is which recently came in limelight in immunology, particularly viral immunology that is type III interferons so, type III interferons are also called as a interferon lambda.

And they are basically consists of three members lambda 1, lambda 2 and lambda 3. So, maybe now you might have a one simple question there is a type I and type III interferon, where is the type II interferon? So, there is a type II interferon and under type II interferon, interferon gamma comes which is produced by macrophages, T cells and NK cells if you remember. T cells when I say CD4 Th ~~H~~ 1 cells, CD8 T cells.

So, there is a type II interferon also and type II interferon is mainly the adaptive interferon, adaptive immune response interferon. So, with this I am completing the basics of cytokine and other immune mediator. In next session, we will discuss about the inflammation, how inflammation is triggered? What are the signs of inflammation? And all those things thank you, thank you very much.