Host-Pathogen Interaction (Immunology)
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Lecture – 27
Application of Cytokines in Therapies and Research

Hi, so in previous session, I have discussed about the interferons therapy and in this session we will take up the Cytokines, mainly inflammatory cytokines.

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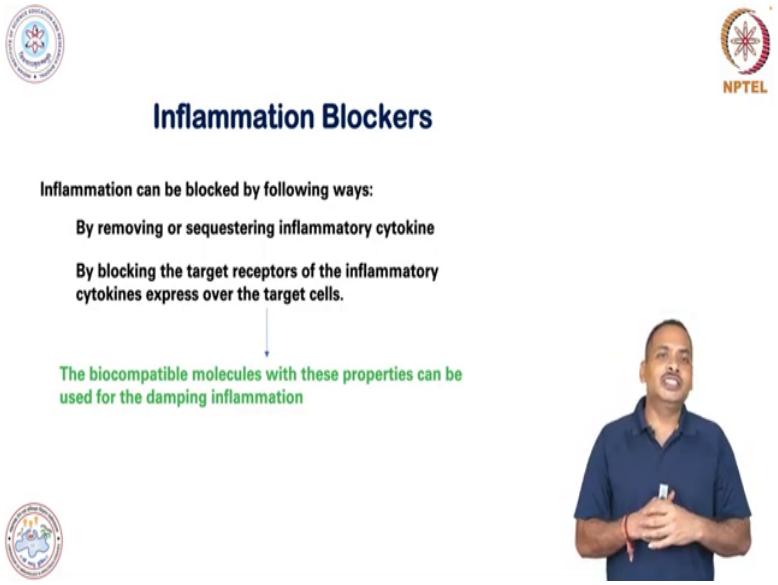

So, you know that inflammation is mediated by a variety of cytokines such as IL-6, TNF, IL-1 beta and other cytokines of adaptive immunity. So, how we can; so, in many diseases there is the basis of disease is inflammation as I have explained you in previous session when I discussed about the inflammation. So, limited amount of inflammation is good for wound healing, recovery from the disease.

But in some scenario these inflammation is quite persistent and it stays for quite a long time. So, in that situation that result to the development of disease or we call it as a immunopathogenesis, immune mediated development of disease. So, in those scenarios what we have to do is? We have to remove that substance which is inducing inflammation this could be a one approach.

Another approach is if the substance is we are not able to remove then this substance is inducing the production of inflammatory cytokine. So, if we somehow sequester this inflammatory cytokine before it is inducing it is biological effect then that is another approach in order to treat the disease. So, this all these things the inflammation can be blocked by as I told you by removing or sequestering this inflammatory cytokines.

And another way is by blocking to bind with the target which is the cytokine receptor which is present on respective target cells. So, if we do this thing then we can overcome the inflammation. And for that we need to make some biocompatible molecules with these property means either this will sequester in physiological condition or there will be some way by which we can make some kind of decoy.

Decoy means probably you might have seen in some movies that when the fighter plane is attacked by some missile then the pilot senses there is some attack of some missile is coming to destroy the aeroplane. So what the pilot is doing? There are several ways by which these missile work. One is that this missile senses the heat, so, you can understand the fighter plane is a source of huge heat. So, we call it as a heat seeking missile.

And there are some missile which is metal seeking so, there is a huge metal. So, basically fighter plane basically is a metal and this missile is looking at that metal and then it is hitting the aircraft and destroying. So, in this scenario what the fighter pilot is doing they release some flares in order to for example, if it is a heat seeking missile so, they will release some flares whose temperature is more than that the aircraft.

And then this missile will go and hit those flares and in that way the missile can be destroyed. So, similarly the similar approach is also there either we can sequester the cytokine or we can make a decoy. Decoy means we will make some receptor which will just bind but there will be no signalling. So, these are the key approaches by which one can reduce the inflammation.

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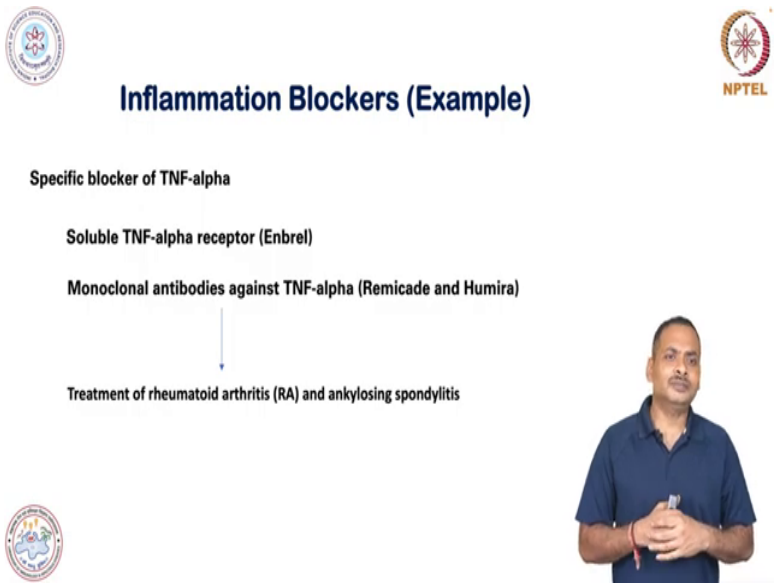

And of course, since we are using in biological condition all we need to consider all those possible side effects. It should not interfere with normal physiology but it should do the job properly, it should have a very high affinity with that cytokine. So, this is basically enabled by the most biocompatible molecule is this monoclonal antibody so, let us I will give you some examples here.

So, there is a specific blockers of TNF-alpha, you know that TNF-alpha is also inflammatory cytokine. So, there is a soluble TNF-alpha receptor, the name of drug is or the molecule which is available in the market is Enbrel. So, this soluble receptor is something like that the flares which is released by the fighter pilot and this missile is just hitting these flare and the missile get destroyed.

So, this soluble TNF-alpha receptor is something like that. There is a some monoclonal antibody against TNF-alpha so the body is producing lot of TNF-alpha. Then another way is that this TNF-alpha, we will make some monoclonal antibody which will specifically bind with this TNF-alpha with high affinity and then this will be removed. So, these are the best approach by which you can reduce the effect of TNF-alpha.

And this is quite successful in many scenarios, like it is used in the treatment of rheumatoid arthritis, ankylosing spondylitis so, this is very effective.

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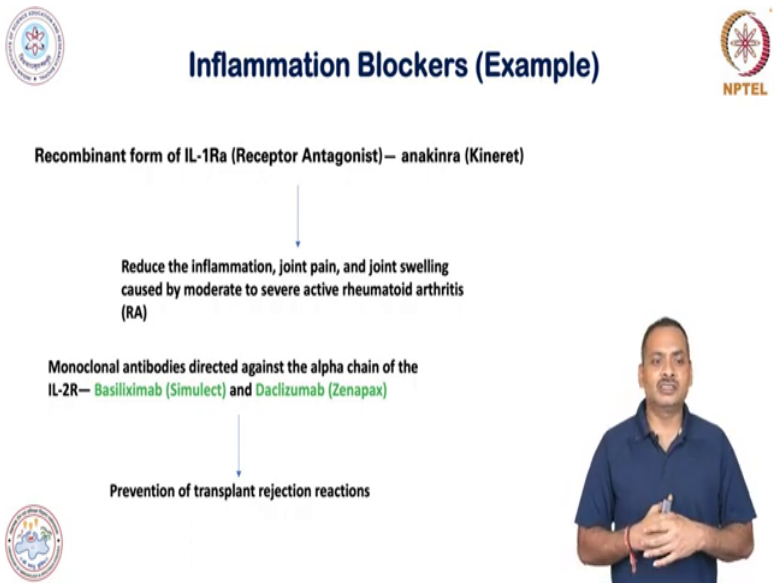

Another example which I can share with you is the use of recombinant form of IL-1 receptor antagonist, it is a similar approach as you have seen there is a soluble TNF-alpha receptor. So, this is much more effective because this is an antagonist it is not enhancing the biological property, it is rather it is reducing the biological property. So, this is also used in clinic and this reduces the inflammation, joint pain, joint swelling caused by this moderate or severe active rheumatoid arthritis.

So, another example is monoclonal antibodies directed against alpha chain of IL-2 receptor. And there are some monoclonal antibody which is already in the clinic this is basiliximab and daclizumab these are basically the monoclonal antibodies. So, these monoclonal antibody can bind with this IL-2 and then that will reduce the effect of IL-2. Just for your information so, IL-2 is a; if you remember, I have told you in when I initiated the cytokine session.

So, IL-2 is a cytokine which act by all three ways or three manners autocrine, paracrine and endocrine manner. And this cytokine is very much important for T cell activity and there are different kinds of receptor for IL-2. There are three kinds of IL-2 receptor, one is IL-2 alpha receptor, IL-2 beta receptor and IL-2 gamma receptor and these receptors the combination of these receptor gives the different affinity to the IL-2.

So, here you can see how nature nicely created this network? So, wherever there is a need of high affinity or more activation of the cell or response there will be expression of high affinity receptor. And wherever there is a need of less than this permutation combination will

change and then there will be a less activation. And where there is a need of intermediate kind of response over there the different combination of receptor will be there.

So, just for your information this alpha receptor is low affinity receptor, beta and gamma is intermediate affinity receptor and when all these three receptors are present then this is a very high affinity receptor. So, this monoclonal antibody basically target the alpha receptor and in that way one can manage the response of IL-2 and this is basically used in various transplantation surgeries.

The patient who received the transplant they basically they are given this IL-2 receptor in this monoclonal antibody, in order to overcome the rejection of transplanted organ this is very important. If we will not give then this organ will be rejected by the recipient and this rejected organ will cause of not only the rejection of organ that will cause another complication. So, this is very, very effective against or making the acceptance of transplanted organ.

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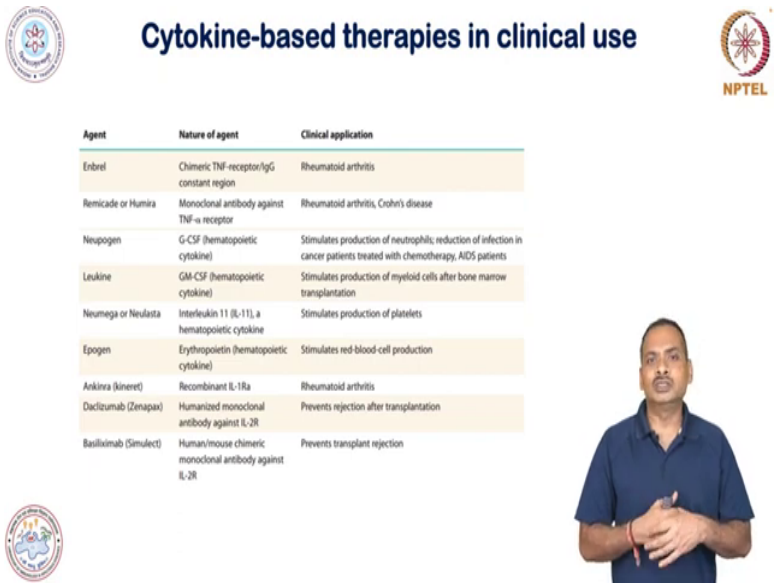

So, these are the list of molecules which is used in the various kind of treatment that is and Enbrel this is a basically chimeric TNF-alpha receptor, it is having a IgG constant region this is a type of one antibody and it is used in rheumatoid arthritis. Remicade or Humira this is monoclonal antibody against TNF-alpha receptor and it is used in rheumatoid arthritis, Crohn's disease this is a again a very complex disease of a gut.

Another is neupogen this is granulocyte colony stimulating factor it is a basically a hematopoietic cytokine. If you remember, I have explained you we use some cytokine in order to make the cells, particular cell type in vitro and today or in this session also I will discuss the same. So, basically G-CSF is used to stimulate the production of neutrophils, reduction of infection in cancer patient.

Because you know; that some cancer patient or most of cancer patients receive the chemotherapy and that will destroy the immune cells. And AIDS patient, as I explained you in previous session AIDS patient has compromised immunity. So, if we treat the patient with G-CSF then the people will be less prone to the infection. Leukine this is GM-CSF, again it is a hematopoietic cytokine stimulate the production of myeloid cells after bone marrow transplantation, it is given after bone marrow transplantation.

Another molecule is a neumega or neulasta this is basically interleukin 11, again it is a hematopoietic cytokine it stimulate the production of platelets. Maybe in worse scenario of dengue infection probably this is given because there is a severe reduction of platelets. So, in a very critical situation probably this is given I do not know I am just guessing. Another is Epogen this is basically a recombinant erythropoietin which stimulate the production of red blood cells.

So, if there is a severe anaemia then they can infuse this cytokine and then they can have the sufficient number of red blood cells. Ankinra this is basically a recombinant IL-1 receptor antagonist, as I have explained you it is used for rheumatoid arthritis. And these two monoclonal antibodies that is daclizumab and basiliximab. So, this is basically humanized monoclonal antibody against IL-2 receptor.

And I will explain you this monoclonal antibody and humanized monoclonal antibody and all those things when we will discuss about the antibody, how it is prepared? So, basically it is used to prevent the rejection after transplantation. So, these are some cytokine which is used in therapy in which is already in clinic.

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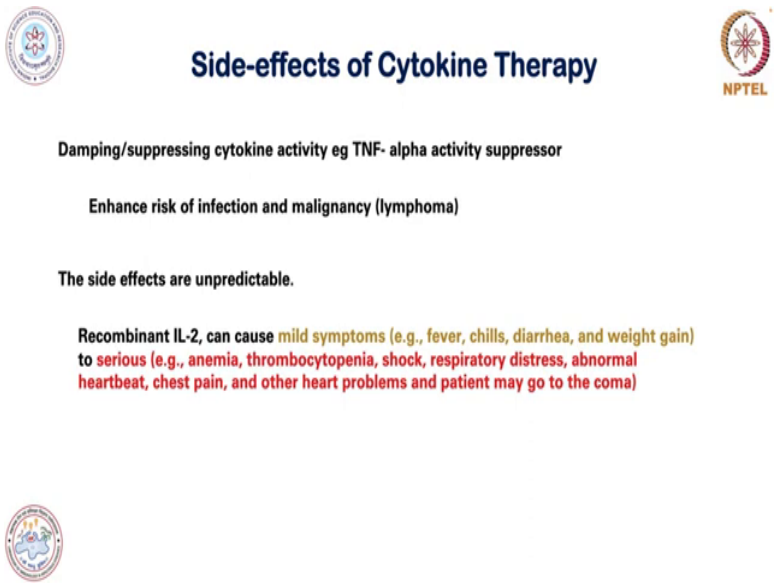

All these things are basically associated with again side effects, try to understand these cytokines or interferon they are extremely potent molecule. And when you give to the individual then there will be a there must be some side effect because you are basically skewing the normal homeostasis. So, like a damping this cytokine activity example TNF-alpha, basically suppresses the TNF-alpha activity and that will enhance the risk of infection.

And when these inflammatory cytokine is quite low then there will be a probability for development of some or other kind of cancer or malignancy or lymphoma. So, this is a one of key side effect in case of inflammatory damping the inflammatory cytokine and side effects are in many scenario it is kind of unpredictable. For example, recombinant IL-2 can cause mild symptom for example fever, chill, diarrhea, weight gain to very serious side effects.

Such as anaemia, thrombocytopenia, shock, respiratory distress, abnormal heartbeat, chest pain other heart problem and patient may go to the coma so, this is quite unpredictable. So, whenever these therapies are administered to the patient then all this therapy is done in hospital setting in order to take care of these worse scenarios.

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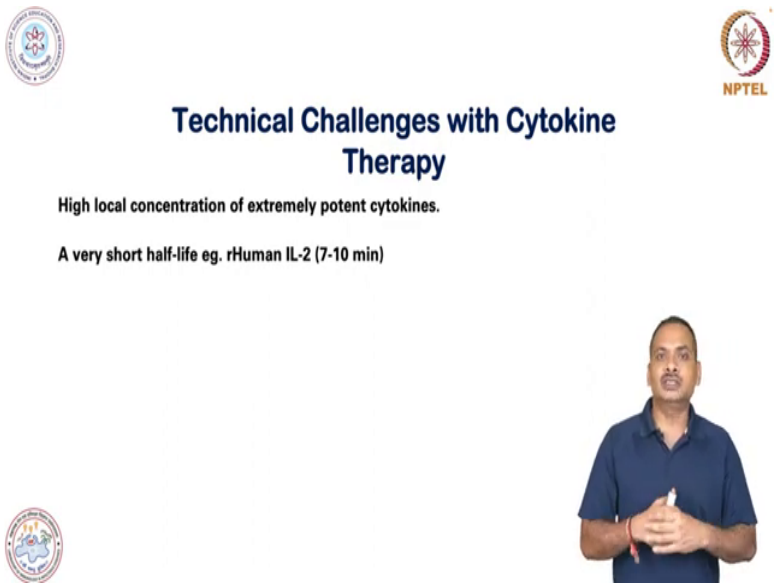

There are some technical challenges with cytokine therapy, the most important challenge is there is a high local concentration of extremely potent cytokine. So, when you give the cytokine there will be a locally very high concentration. Try to understand this is a very potent molecule and they act at very low concentration. So, when you will provide this thing then there will be a very local, very high concentration and that may result to some or other complication.

Another is very short half-life this cytokine some of these cytokine is extremely their half-life is very short as here you can see that recombinant human IL-2 it is half-life is only seven to ten minute. Interferons also have a very short half-life so, over there what they do? They mix with polyethylene glycol. So, this basically stabilizes this interferon and we call it as a PAGylated interferon. So, this is used for the treatment of interferon mediator therapies.

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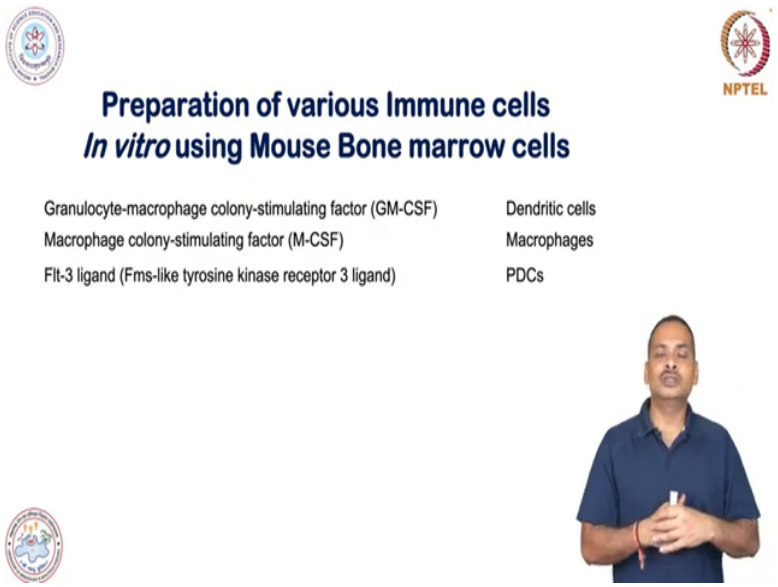

Preparation of now, we will talk about the how this cytokine is used in preparation of various immune cell which I have discussed earlier. But here I will just give you a quick glimpse, we use the GM-CSF if we treat the bone marrow, mouse bone marrow cells with GM-CSF. So, we can differentiate those cells to the dendritic cells. There is a M-CSF this is macrophage colony stimulating factor.

If you treat this bone marrow cells with M-CSF then that will result to the development of macrophages. There is a Flt-3 ligand which is also known as Fms like tyrosine kinase receptor 3 ligand if you treat the bone marrow cells with this cytokine then those cells will differentiate to the plasmacytoid dendritic cells. So, with this I will finish this cytokine and therapy and application in therapy and in research.

In next session, I will start with innate immunity, we will discuss in great length about innate immunity. We will discuss in great length about pattern recognition receptor, various pattern recognition receptor which is expressing on various component of cells for example, cell surface, cytoplasm, endosome and so on so, thank you.