Host-Pathogen Interaction (Immunology)
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Lecture – 25
Signatures of Inflammation

Hi, ~~S~~so, in previous session we have discussed about the inflammation, we have looked at various causes of inflammation. We have looked at the signatures of inflammation now we will continue further about the inflammation. So, you have seen there are several factors but eventually all these factors result to the inflammation and what are the inflammatory mediators which cause the inflammation?

Basically, I am going to talk about, some cytokine~~sis~~ which is playing important role in inflammation.

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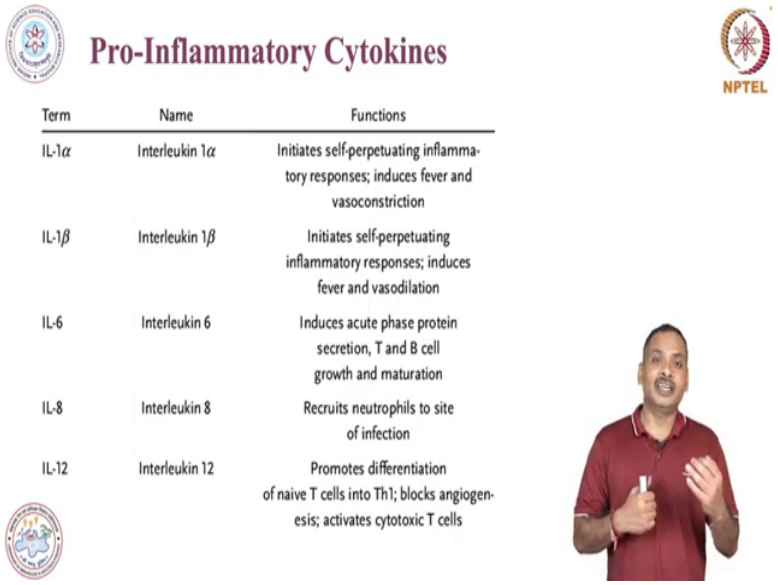

Term	Name	Functions
IL-1α	Interleukin 1α	Initiates self-perpetuating inflammatory responses; induces fever and vasoconstriction
IL-1β	Interleukin 1β	Initiates self-perpetuating inflammatory responses; induces fever and vasodilation
IL-6	Interleukin 6	Induces acute phase protein secretion, T and B cell growth and maturation
IL-8	Interleukin 8	Recruits neutrophils to site of infection
IL-12	Interleukin 12	Promotes differentiation of naive T cells into Th1; blocks angiogenesis; activates cytotoxic T cells

So, here you can see there is a list of cytokine, for example, IL-1 alpha. Basically, it ~~initiate~~initiates self-perpetuating inflammatory responses and that will also induce fever vasoconstriction, constriction of blood vessels. IL-1 beta, it is also causing fever and vasodilation. So, here I would like to say that some of these inflammatory mediators, for example, IL-1 beta, this is very tightly regulated.

Their production in the cell or their functional form in the cell or production of these functional form is very, very tightly regulated. It has a some additional handle means they are very much potent if it is release, it will cause a quite complicated situation therefore they are tightly regulated. Some additional mechanism are existing over there for production of IL-1 beta.

Here, in short, I will just tell that this IL-1 beta, besides all those transcriptional level, translational level, in translational level there is a some additional regulation is there. Basically, this IL-1 beta is produced in inactive form, zymogen~~enzymes and~~ form. Like if you have studied in class 10th or 12th standard or maybe in graduation, some of those enzymes which is secreted in our gastric juice, they are produced in inactive form like pepsinogen.

It is an inactive form and when there will be a cleavage of this protein then this pepsinogen is converted into the active pepsin. So, similarly, for IL-1 beta and the IL-1 beta is produced in pro form in inactive form. And then there will be a need of some additional signalling which will convert this pro form of IL-1 beta into active form of IL-1 beta. So, I am just telling that the nature made it very, very complicated. It is not so, easy.

The production, for example, this production of this inflammatory cytokine because this is a very potent if it is present in very small amount that will cause a major effect in physiology. Let us move on to the IL-6 interleukin-6, basically, this induces the acute phase protein, so, there is a various acute phase protein which is synthesized in the liver. So, during inflammation this acute phase protein is increased.

So, you may look at the one test which is basically a doctor recommend to go for this test if the doctor suspect some kind of inflammation in the individual. So, they asked for go for the check for this CRP level, C reactive protein levels, so, this is a one very good signature. And this is also kind of acute phase protein, so, this CRP level will be increase if there is a some chronic inflammation will be there.

So, in many cases in this doctor recommend to test for the CRP. So, here I was explaining the acute phase protein, IL-6 also help in growth and maturation of adaptive immune cell, like T cells and B cells IL-8 is there which is playing a very important role in recruitment of

neutrophils at the site of inflammation. So, you can imagine if the lot of neutrophils are there at the site of infection.

It is a very severe battle between pathogen and the neutrophils you know that neutrophils are extremely dangerous to the pathogen and too much activation of neutrophil is also dangerous to the host also. So, neutrophils will be recruited if there is a IL-8 over there. IL-12 basically promote differentiation of ~~knife~~naive ~~of~~ T cells and basically it plays an important role in activation of cytotoxic T cells as well.

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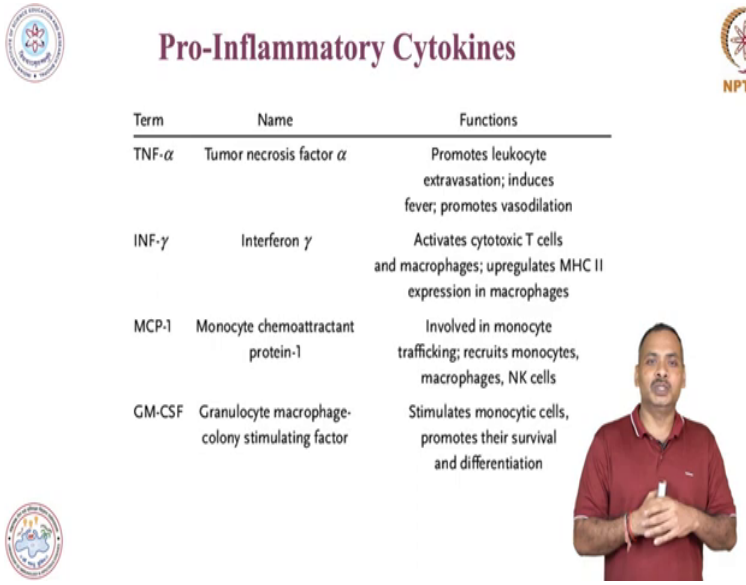

TNF tumor necrosis factor this promotes a leukocyte movement across the blood vessel. We call it as an extravasation, it induces a fever and promote vasodilation. There is the interferon gamma basically interferon gamma is basically activate various cells, including macrophages and cytotoxic T cells and it also basically upregulate the expression of major histocompatibility protein along with the antigen.

And it also induces the expression of adhesion molecules which is needed for appropriate activation of T cells. Another is a MCP-1 this is a basically a monocyte chemo attractant protein one and this is involved when, as the name suggests, this will attract the monocytes. And recruit the monocyte macrophages, as well as natural killer cells. So, when this will be secrete, all these guys will come at the site of infection or whatever there is an inflammation.

And another is a granulocyte macrophage colony stimulating factor. If you remember this cytokine we used for making dendritic cells. If you remember from bone marrow cells, or

bone marrow stem cells, or hematopoetic stem cell. So, if you put this GM-CSF, this will differentiate into the dendritic cells. So, this is also playing a very important role in inflammation. So, they stimulate the monocytic cells, promote their survival and differentiation.

So, all these cytokine, we collectively call it as a pro-inflammatory cytokine. So, you might be thinking that when there is a pro-inflammatory cytokines means which activate the inflammation, there must be some anti-inflammatory cytokine. Yes, we do have anti-inflammatory cytokine and one of the major anti-inflammatory cytokine is IL-10. So, basically these are IL-10 damp all~~solve~~ this inflammatory or fight kind of thing in our system.

And they play a very important role in recovery phases but if there is too much anti-inflammatory cytokine then that will also result to the immunopathology. For example, this cancerous cell or some of pathogen they try to induce these and anti-inflammatory cytokine in order to establish the infection or establish the cancer in the host. So, it is the balance is very important the balance between pro-inflammatory and anti-inflammatory cytokines.

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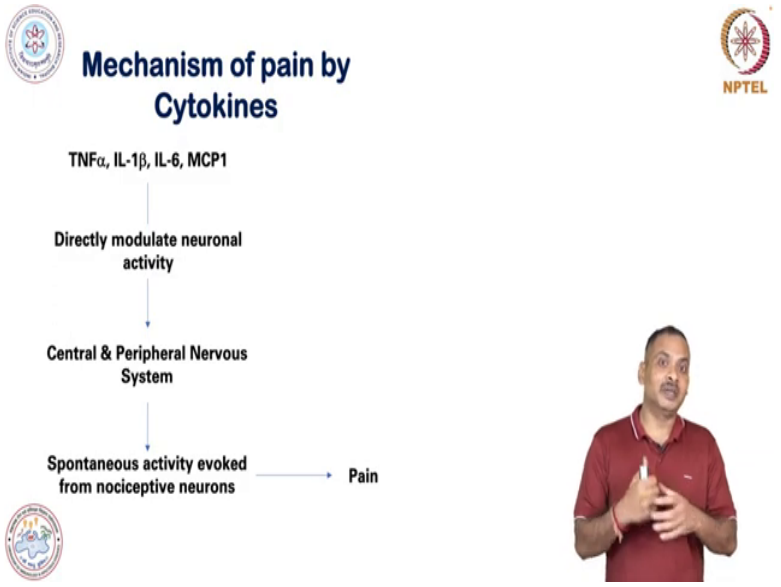

Now, let us look at how this inflammatory pro-inflammatory cytokine basically cause the pain. What is the mechanism? Although, I am presenting you here in a very broad way it is a quite complex still it is under the investigation. So, these cytokines are produced and these cytokines basically directly modulate the neuronal activity. This cytokines can activate these neurons and basically, they activate the neurons in central or peripheral nervous system.

And basically, this is spontaneously activate or evoke the a group of neuron which we call it as a basically nociceptive neurons, and basically that result to the pain. So, this basically sends and give the signal to the brain and then there will be a pain. So, this is a very simple mechanism I do not know the neurology in a great detail, so, I cannot tell more than this. So, maybe, if you take some neurologic course over there, you will learn how this pain is sensed?

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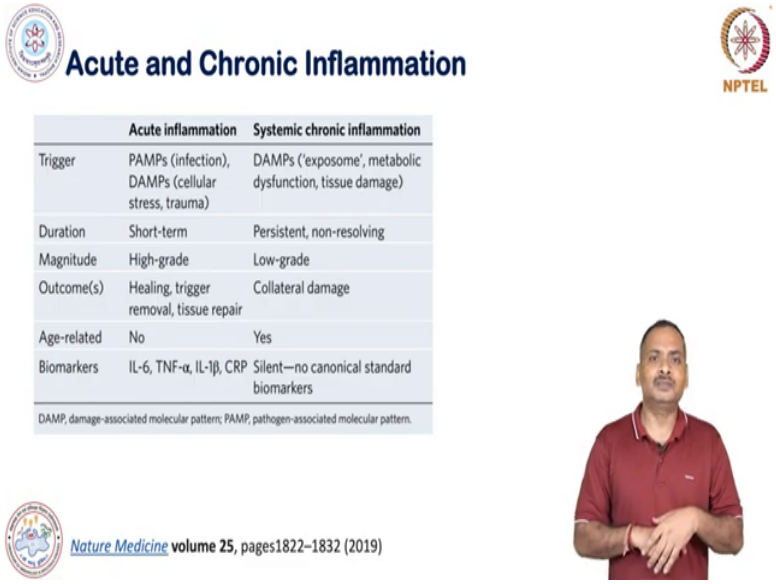

Now, i will talk about the another very important aspect of inflammation that is acute inflammation. What is acute? And what is chronic inflammation? Or I have explained you the meaning of acute and chronic word in previous session probably you remember here, I will repeat it again acute means there will be a very high intensity but for shorter duration. And chronic will be the intensity will be less but it is for long time persistent it is a chronic thing.

So, there is a acute and chronic inflammation, so, acute inflammation is basically triggered by PAMPs, DAMPs and this PAMPs and DAMPs are nothing. It is a pathogen associated molecular pattern PAMPs stand for pathogen associated molecular pattern and these are the signature molecules on the pathogen. For example, if you take the gram-positive bacteria or gram-negative bacteria, the PAMP will be like in gram-negative bacteria it will be LPS lipopolysaccharide.

And in case of gram-positive bacteria one of the PAMP will be the peptidoglycan, the cell wall, the covering of the bacteria. So, there are so many PAMPs in the bacteria, both gram, positive and negative, so, these PAMPs can induce the acute inflammation. For example,

there is an infection immediately this bacteria will replicate in more number and that will cause the acute inflammation.

Another is the DAMP, DAMP is basically stand for damage associated molecular patterned. And this damage associated during cell trauma I have explained you if there is some necrosis of the cell then that will cause the release of DAMP which is not seen by the immune system. I have explained you in the previous session. So, this can cause the acute inflammation and the chronic inflammation which may be a systemic, is basically caused by DAMPs.

And this is due to some dysfunction of metabolic pathway and I have told you I gave you the example of arthritis. So, there is a release of some molecules by damage cartilage or damage bone cells that will keep on producing and that will keep on inducing the inflammation. So that will result to the chronic inflammation. So, if you look at the duration, acute is a as I told you, it is a very short term and chronic is a very long term and persisting and not resolving.

Magnitude in case of activity acute it will be a very high grade and in case of chronic it will be a very low grade. So, outcome of this acute inflammation will be maybe the healing of tissue and then there will be a tissue repair but in case of chronic inflammation, the inflammation which is very low grade, persistent for long time that will cause some or other problem and here it is written as a collateral damage. It will cause the collateral damage.

It it will cause a result to some very complex disease. Acute inflammation is basically, it is not dependent on age and but chronic inflammation is a kind of age dependent. In case of acute inflammation there is some signature molecule. If you look at those acute inflammatory sites, you may find out that there will be a more production of say some cytokine, like IL-1 beta, IL-6, TNF and there will be more production of CRP.

I have told you CRP c-reactive proteins but in case of chronic inflammation, you will not see this conventional signatures. There will be some different set of molecules which is still we are not very well, understood. What are those signatures? But that will be a much more complex.

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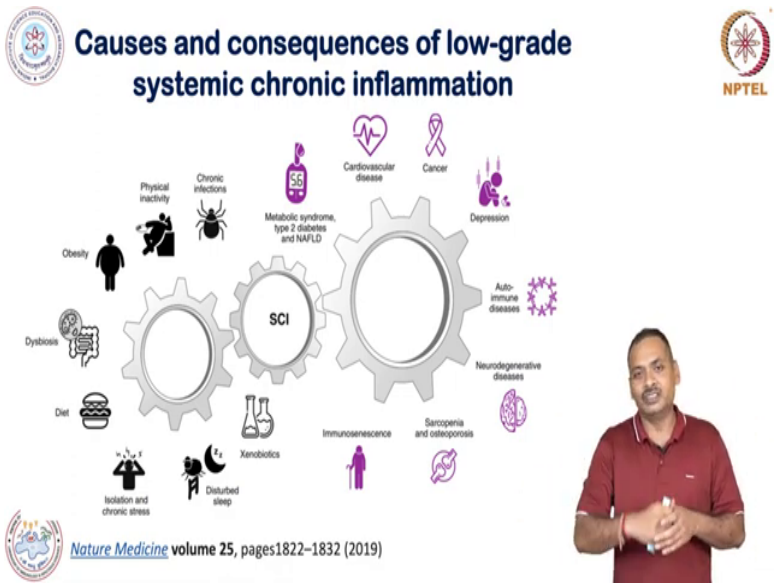

So, what causes and consequences of low grade systemic chronic inflammation? So because there are so many causerves you can see in black color, it is depicted in this slide like a chronic inflammation will cause the this low grade inflammation physical inactivity, obesity. So, if you are not doing exercise, if you are gaining weight, getting lazy that may also cause the chronic inflammation.

And that result to the development of these metabolic disease, cardiac disease and all those things. There is some another factors, such as diet dysbiosis, isolation and chronic stress, isolation and chronic stress probably if you have seen some movies, you have noticed that some of prisoners they were kept in isolation in order to increase their stress. So, this will cause a more severe inflammation disrupted sleep.

Many people you might have seen or if you maybe you are that they work more in night and they do not sleep and they do not eat properly and then they gain weight and all those kind of things. So that is also result to the development of chronic inflammation, taking some drugs and all those things. And there are some of these consequences that result to the variety of metabolic diseases.

Metabolic diseases when I say it is a series of diseases which start with a hypertension and then hypertension and that result to the diabetes that may result to the or maybe both are getting together. And that all these things basically result to the development of cardiovascular diseases that may result to the cancer that may result to the depression that may result to the autoimmune disease which is a very complex.

It is very difficult to treat the autoimmune diseases that may also result to the neurodegenerative diseases, loss of memory and all those things that will also result to some structural problem, there will be a loss of muscles that is, we call it as a sarcopenia. And there will be osteoporosis which is more pronounced in females and overall that will cause the immunosenescence the decline of immunity.

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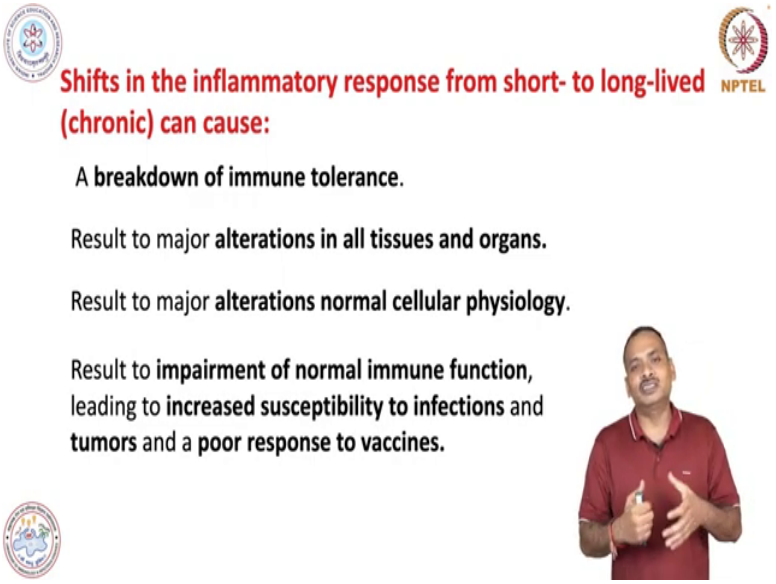

So, this shift in the inflammatory response from short to long lived or chronic inflammation can cause overall variety of things. I am giving you some bullet points this will give a breakdown of immune tolerance. Immune tolerance is very important always immune response is not good, immune tolerance is also needed. For example, the food which you are eating ideally, your immune system do not react.

But if this persistent inflammation will be there that may cause the breakdown of tolerance. Alteration in all tissues and organ there will be a restructuring of tissue and organs will be there. Restructuring means the molecular level or cellular level if you look at. That will also when there will be alteration and tissues and organ then that will of course disturb the normal cellular physiology.

And that may result to the impairment of immune function this is more severe. And that will cause more, the individual will be much more susceptible to the infection. And tumor because I have told you that immunity play a very important role in controlling the transformed cell.

If there is a transform cell, this will be cleared by immunity. So, the individual may be prone to the tumor. And there will be a very poor response to the vaccines.

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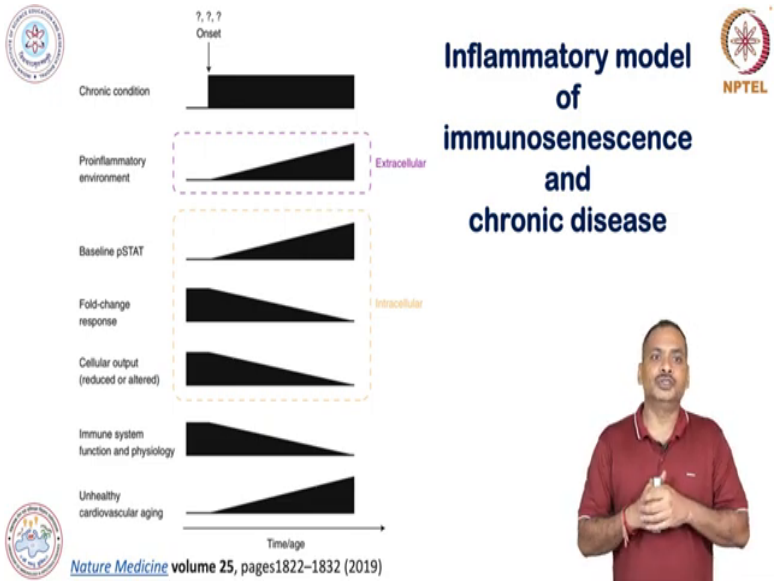

So, these are the very important points here. There is a one, a scheme which I am just want to quickly show that so, the chronic inflammation onset of chronic inflammation then when it happens then there will be a persistent increase in pro-inflammatory environment in the body. There will be a production of more pro-inflammatory, cytokine and other mediators and this is investigated.

So, people found out that in those individuals there will be a much more higher level of some signalling molecule here it is depicted as a pSTAT. So, this pSTAT is a one of signalling molecule which get phosphorylated and ideally it is not present in phosphorylated form but when there will be inflammation this the amount of this phosphorylated, STATa ~~stacked~~ protein will be more in the individual.

And here you can see that the immune system function and physiology is going bad and bad and eventually unhealthy cardiovascular aging will be there in these individuals.

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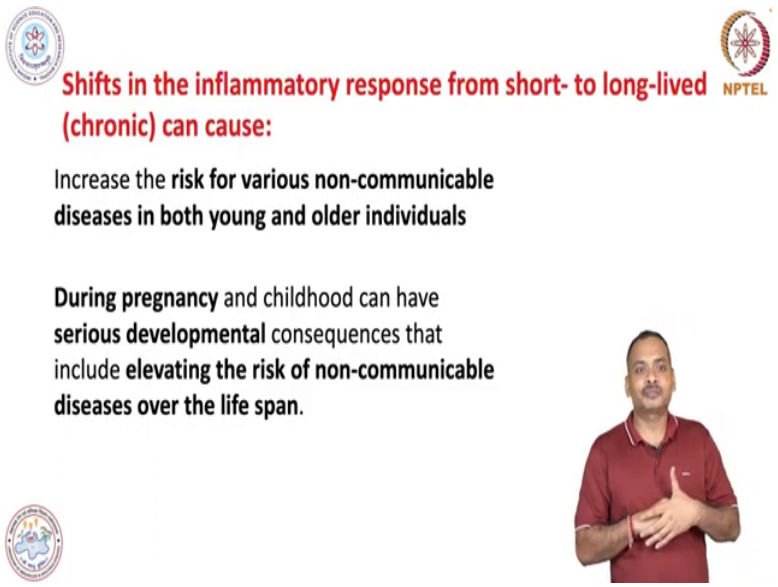

So, they will also increase the risk for various non-communicable diseases. I have already explained the individual will be prone to the autoimmune diseases, cancer, and all those things. And this is not limited to the any age this and this can affect any old as well as young people. So, do not be in any confusion that you are young, so, you will be not developing these diseases.

These non-communicable diseases that is cardiovascular diseases, diabetic, hypertension. So, young people are equally susceptible to these kind of problem if there is a chronic inflammation. So, during pregnancy, if the woman or the parents are in this situation, so that may result to the very serious developmental error in developing fetus. And this will elevate the risk of non-communicable diseases.

So, once the baby will born the baby will be at risk for variety of non-communicable diseases and throughout their life span. So, it is very important to not have a stress and all those things.

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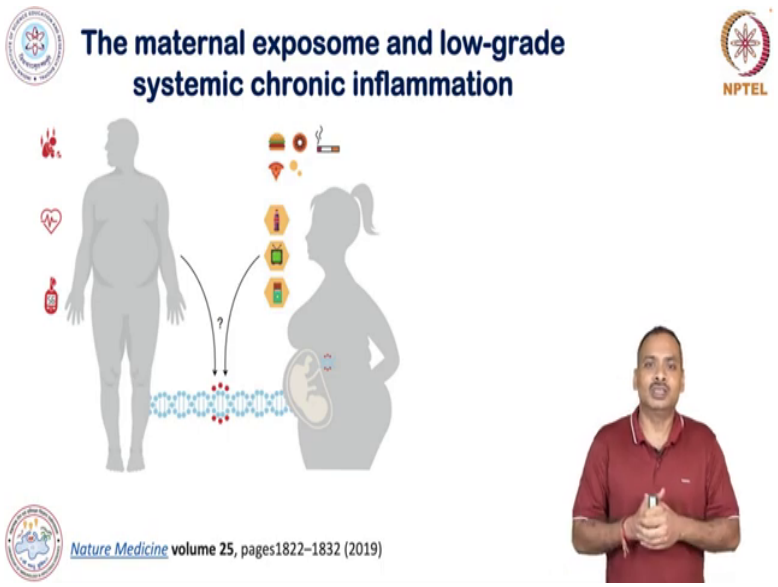

So, here this is the last slide of my talk and this here I am just depicting, how it is this chronic inflammation result to the development of fetus? And that fetus will may develop some chronic diseases throughout their life. So, with this I will stop here and in next session I will talk about some therapeutic application of cytokinesis and so on so forth. Thank you. Thank you very much.