Essentials in Immunology
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Module No. # 08
Lecture No. # 14
Hypersensitivity type I

Today's lecture is going to be on the subject of hypersensitivity.

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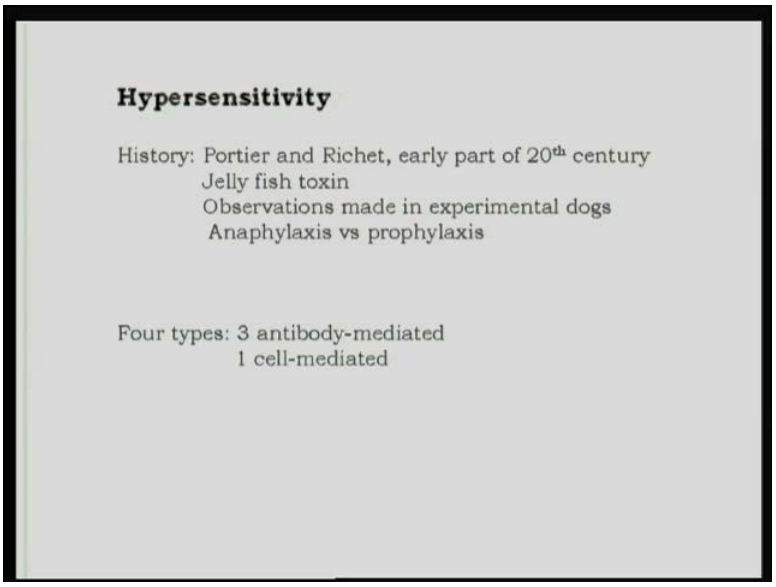

Just a little history about hypersensitivity – now, this was recognized in the early part of the 20th century by two scientists Portier and Richet. It was found… they realized this condition because of swimmers who swimmed in the sea, and were repeatedly being stung by jelly fishes. Now, that is what they realized later, that these individuals reacted to the jelly fish toxin in different ways. Sometimes, these, this hypersensitivity due to toxin also cause death. So, when they started looking for what could be there in the sting of the jelly fish, they found that it was a toxin; so, purified the toxin and started injecting in experimental dogs.

Now, this was where an important finding was made; an important observation was made that after a couple of injections in the dogs by the jelly fish toxin, it was found that these animals did not respond by way of synthesizing antibodies, the way normally other

antigens do, but soon after, a few minutes after the injection with the toxin, the dogs wend into a state of vomiting, diarrhea and a shock like syndrome.

So, they realized that in some cases, antigens which now we know as allergens bring a shock like state and which brings an increased reaction which they called anaphylaxis as oppose to prophylaxis. Prophylaxis is the treatment which is going to decrease the symptoms, whereas anaphylaxis actually brought about a heightened response which was not normal and which was unwanted.

So, what is hypersensitivity?

This is better known as allergy, in common man's language. So, hypersensitivity would mean that a heightened immune response. But though the name suggests that, we know that hypersensitivity is actually unwanted immune response, inappropriate immune response to a particular molecule. Normally, an immune response generated to any pathogen - be it cell mediated or humeral, causes a localized inflammation such that, that particular pathogen is deleted from the system. Now, this causes some tissue damage to the host, but it is minimal and it is corrected very fast. However, in case of hypersensitivity, the same immune response goes berserk and there are reactions which may delete the organism, but all protein, but causes extensive tissue damage. And like I said, in case of the jelly fish toxin, in which they found an allergen or hypersensitivity inducing molecule, this can also be fatal.

So, let us look at hypersensitivity and the types of hypersensitivity, and look at the reactions that what actually causes.

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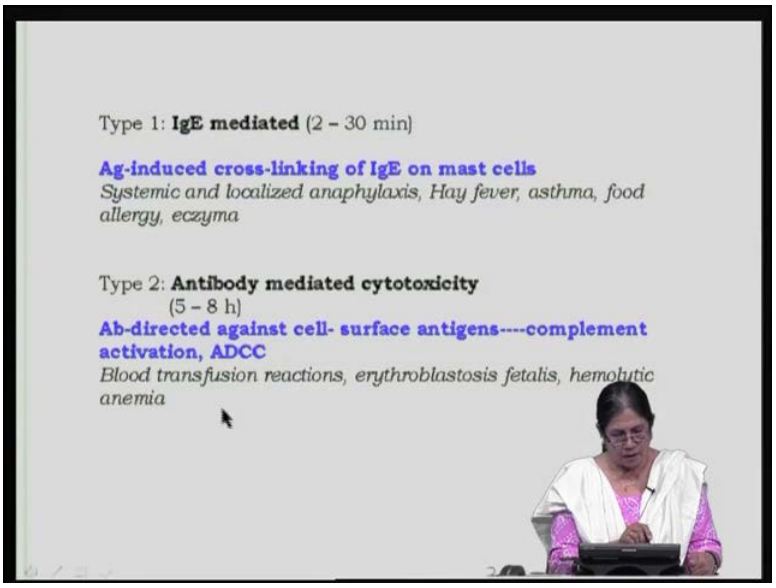

Now, hypersensitivity can be understood in as being classified under four distinct types: three of these four are antibody mediated and one is cell mediated, where T cells are involved. Let us just go through very fast on the that four types and what mediates them, and then will go to details of this.

Type 1 is IgE mediated and the reactions can be seen anyway between 2 to 30 minutes after exposure to that allergen or that molecule. This is caused by antigen induced cross linking of IgE on mast cells or basophils. Now, we will come to that in a little while in detail and in fact my talk today is going to be around hypersensitivity type 1.

Now, the symptoms are systemic and localized anaphylaxis can cause hay fever, asthma, food allergy, eczyma - all these come under type 1 allergies which are mediated by IgE, which would mean that these molecules elicit a class switching from IgM to IgE.

Type 2, on the other hand, which is also antibody mediated, it is because of cytotoxicity which is caused by the antibody. This includes blood transfusion reactions, erythroblastosis fetalis and hemolytic anemia. This is because of antibodies that are directed against cell surface antigens and because these antigen antibody interactions triggers complement activation, as you might remember from their previous class, this brings about antibody dependence cellular cytotoxicity. If there is too much of that, that might be deleterious to the host tissue.

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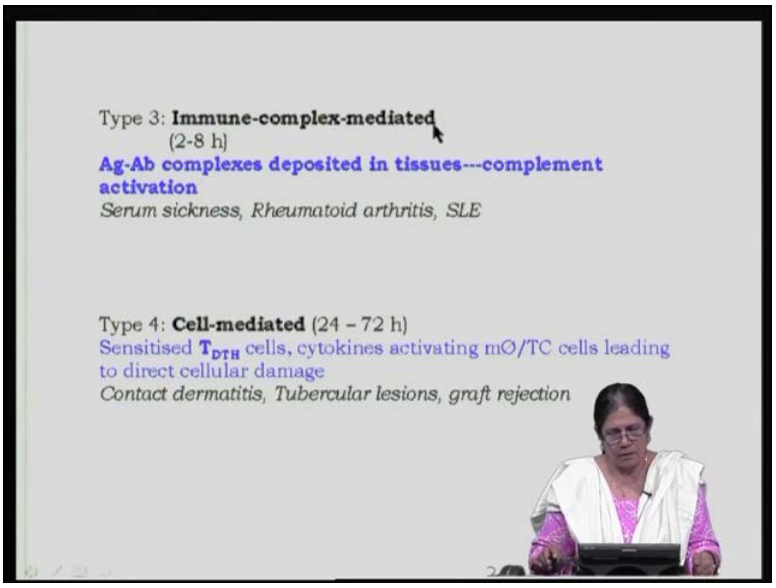

The third type is because of immune complexes. Now, this is immune complex mediated. Now, what happens when there are antibodies in circulation and then there is an antigen which enters? If it is in small amounts, then there is a complex that is found; antigen and antibody form complexes which can be small to particulate, but this is very efficiently deleted from the system by macrophages.

However, in case the antigen is foreign exist and the complexes are too small cannot be efficiently deleted from the system by macrophages, through phagocytosis. These complexes can get deposited in tissues and though they are small complexes, they are able to activate the complement.

So, let us say that these complexes are deposited on membranes. Then, that is where, there will be complement trigger which will lead to mac formation that is membrane attack complex formation and this would lead to tissue damage. Immune complex mediated hypersensitivity includes serum sickness, importantly rheumatoid arthritis and systemic lupus erythematosus. Now, both rheumatoid arthritis and SLE are ortho immune diseases, and we will come later, to why and how immune complexes can be formed in these conditions which can lead to activating the complement cascade. So, this comes under type 3.

Now, like I told you before, type 1 and 2, 3 are mediated through antibodies; either IgE as if case in the first type or IgG and IgM type 2 and type 3. Type 4 is caused because it

is cell mediated; it comes under cell mediated immunity, and therefore, are involved T cells. This condition includes contact dermatitis tubercular lesions and graft rejection. Now, the reaction is because of sensitized T DTH cells. T DTH cells, you may have already discussed this in earlier lectures; T DTH stands for T delay type hypersensitive cells. Now, these are cells that release cytokines that activate macrophages and cytotoxicity T cells. This leads to direct cellular damage at the site of where the sensitized T DTH cells arrive.

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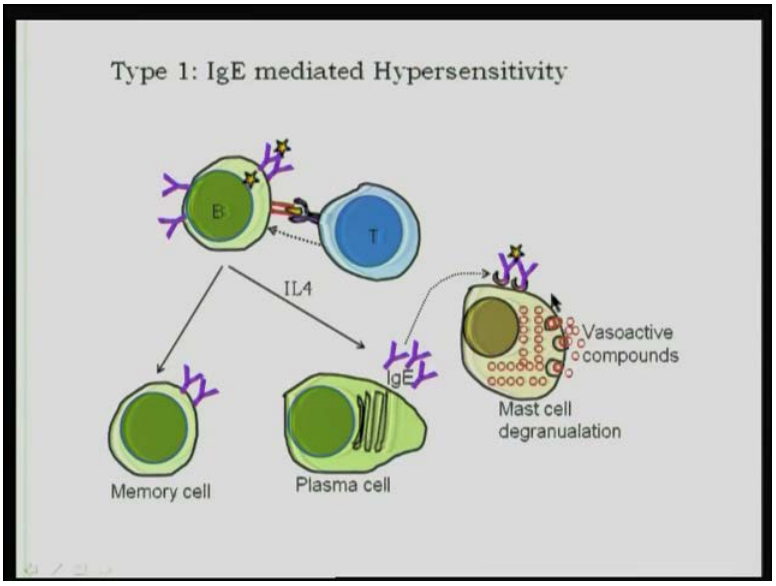

Let us get on with the type 1 which is IgE mediated hypersensitivity and look at the molecular mechanisms.

Now, IgE secretion - if you might remember, should be the B cells should undergo the same set of steps in activation proliferation and differentiation like any other T cell dependent B cell. Allergens are recognized by those B cells which require T cell help. Therefore, always the first time the allergen is exposed to the B cell which has a specific receptor in the form of immunoglobulin with the idiotope corresponding to the allergen. This would lead to activation of the B cell, as would happen internalization of the antigen and the receptor complex; Proteolytic degradation of the allergen into peptides which are then presented to T hyper cells in the context of class 2 molecules.

The T cells would get activated, produce cytokines which are beneficiary for the B cells interleukin 4 and interleukin 5; interleukin 4 which would now allow proliferation of the

B cell, clonal proliferation, which would now further lead to generation of memory cells and plasma cells, now has not been shown here, but you might remember from the previous lectures that the memory cell before becomes the memory cell after the first immunization or exposure to the allergen. One would The B cell would be making IgM type of antibodies which now switches to making IgE type of antibodies, let us say, when this memory cell is exposed to the same allergen.

Now, this is a plasma cell which would be in the secondary immune response; that means second time the cell is exposed to the antigen were now the plasma cell, again this differentiation well again proliferation and differentiation of the memory cell to plasma cell producing IgE. If you might remember, the IgE in circulation is very low concentration, but because even if there are large number of plasma cell which are secreting good amount of IgE, the IgE is sequestered very specifically to the surface of mast cells and basophils because of the presence of a receptor, specific for IgE and that too for the FC region CH 2 and CH 3.

Now, here is the depicted mast cell (Refer Slide Time: 12:40) which has large number of granules present in the cytoplasm. Mast cells also have specific receptors which are talked about, which are known as FC receptor for IgE type 1.

Now, we will come to the types of receptors which can now anchor, specifically these IgE molecules. So, all the IgE that is produced or more than 90 percent gets in a non-specific manner; non-specific with respect to the antigen. Non-specific manner gets sequester to the FC receptors of mast cells and the basophils. Remember, the specificity here, lies in the FC region which binds to the FC receptor, but it is non-specific with respect to the allergen because the plasma cell would be specific with respect to its antigen recognition. Therefore, the antibodies that the plasma cell would be made to one particular molecule, but the mast cell can bind to IgE of different specificities because all IgE molecules would have the same CH2, CH3, CH4 domains.

Now, the mast cell has like I said large number of granules which are preformed and these membrane coated granules are present and waiting to be secreted out of the cell, which happens due to signaling caused by cross linking of the IgE via the allergen. So, what is released now, would be immediate almost within minutes after cross linking takes place and these are a large number of molecules; they are called vasoactive

compounds what I mean what is present in the mast cells. So, mast cell degranulation takes place.

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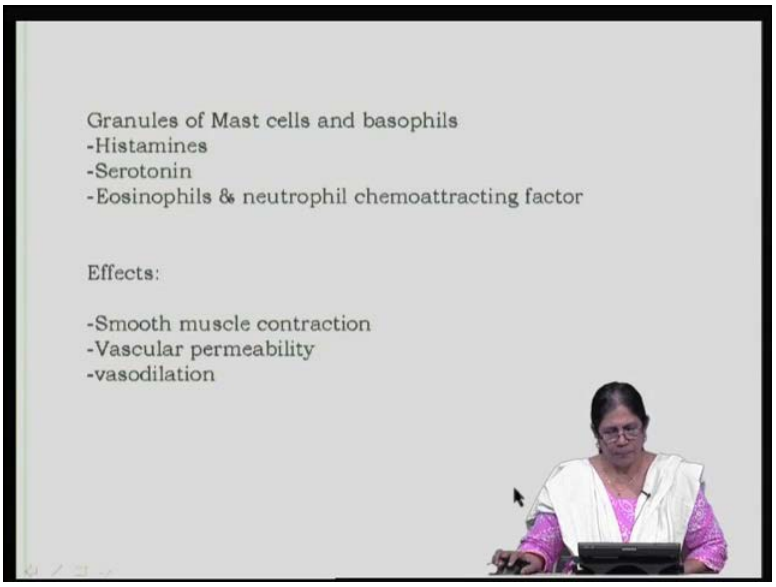

Let us see, what are the granules of the mast cell and basophils. They consist of histamines, serotonin, and eosinophil and neutrophil chemo attracting factors. What do these granules or what are these pharmacologically active vasoactive compounds do? They bring about smooth muscle contraction vascular permeability and vasodilation.

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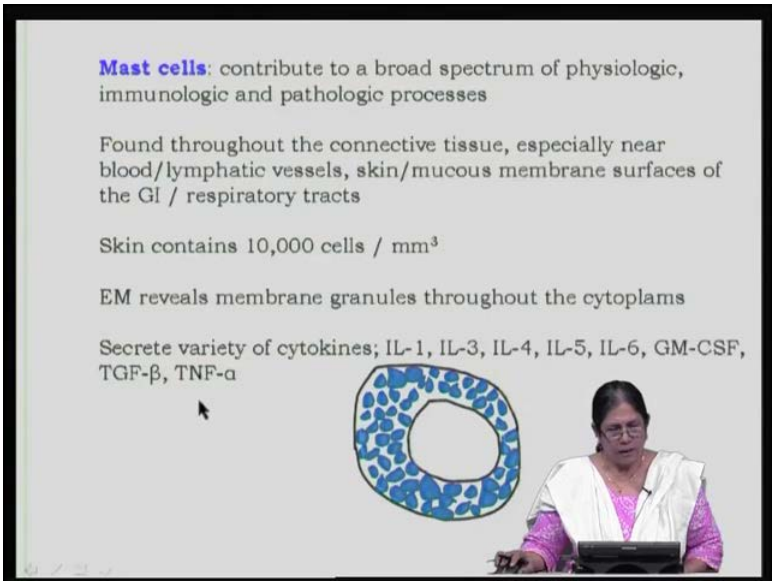

Let us look at mast cells. You have been introduced to mast cells so far and you know that mast cells are found not in circulation, but in the connective tissue. Mast cells contribute to a broad spectrum of physiological, immunological and pathological processes. They are found throughout the connective tissue, especially near blood and lymphatic vessels. They are present in the skin and the mucus membrane surfaces of the gastrointestinal or the GI tract as well as respiratory tracts.

Can you imagine how many such mast cells are present in the skin? It is an enormous number. It is 10,000 cells per millimeter cube. So, very small area under our skin has large number of these mast cells. You might remember that allergic reactions are tested or the diagnosis is done by now coating the skin on the arm of individuals who come with that complaint, trying to find out to which they are which compound or which molecules they are allergic and the clinic has a large number of antigens which are in fact put on the skin and within a few minutes reaction is observed.

Now, why is this done? Have you ever thought why is this done on the skin? Why is this testing done on skin? This might reveal to you why; that the skin contains mast cells in case of atopic individuals or those individuals we were allergic will have mast cells under their skin with IgE to the allergen to which they are allergic to, and the IgE sitting there when the antigen is put on the skin, the same mast reaches, now, the mast cells which have IgE sequester; the antigen would bring about cross linking and giving rise to that inflammatory reaction which the doctor now reads.

This is specific. They might use in the entire gamut of allergens which would could be 8 to 10. They will be able to find that the person is allergic to one such allergen. So, coming back to mast cells now, electron microscopy reveals that mast cells have membrane granules throughout the cytoplasm and these mast cells can secrete a variety of cytokines interleukin ,1 interleukin 3, interleukin 4, 5; interleukin 4 5 - does it ring a bell? These are the ones that I told you as synthesized by the T cells, but also by the mast cell which can activate, which can induce proliferation in B cells. Interleukin 6 is also made by mast cell, and this cytokine, as you might remember, helps in differentiation of B cells to plasma cells. GM CSF - that is colonist stimulating factor ,TGF beta and TNF alpha - all these cytokines are secreted by mast cells; in fact these granules have these cytokines.

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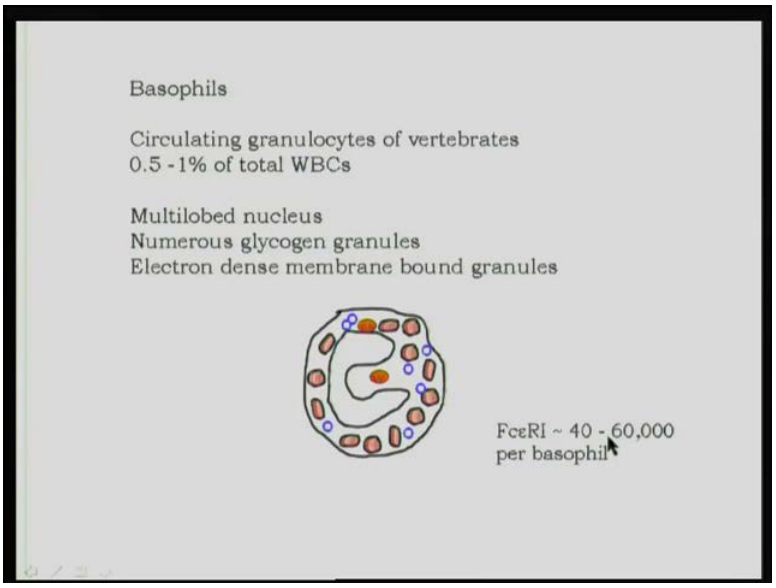

Let us look at the other cells which can also bind to IgE through the FC receptors. These are basophils, and unlike the mast cell, basophils are present in circulation. They are the circulating granulocytes of vertebrates and the percentage is very low; 0.5 to 1 percent of the total white blood cell population. You all might remember from your earlier lectures that basophils have multilobed nuclei and numerous glycogen molecules which are shown in blue here and they also have electron dense membrane bound granules. Each of these basophils has been estimated to have 40 to 60000 of those receptors which I talked about, which can anchor IgE.

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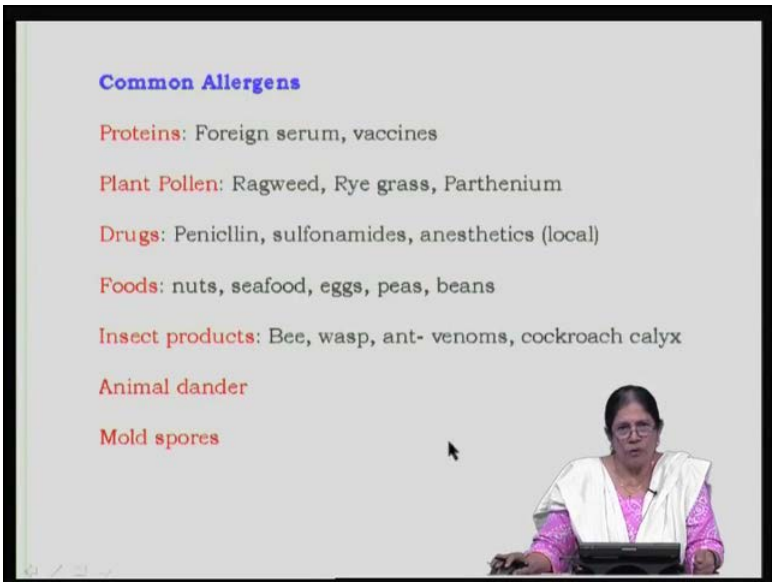

Do you remember which allergens you may have heard of which are common? They can be proteins; they can be plant pollen. Now, proteins of common allergens can be foreign serum, vaccines, plant pollen, ragweed rye grass as well as parthenium. Now, parthenium is what we seem to have imported in from another country and now we have fields of parthenium, and there are quite a few people who are allergic to parthenium grass. Drugs such as penicillin, sulfanomides, even anesthetics; foods such as nuts; this is rather, I mean not very common, but yet yes, one can see many people are allergic to seafood, to egg, albumin, peas, beans.

Insect products - there are quite a few individuals who are allergic to bee and wasp as well as ant venom, also cockroach calyx. Amongst common allergens are also animal dander that is the hair, but one is not allergic to hair, not to the hair protein, but to the epithelium which comes along with the hair. So, this is cat; people are allergic to cats because of the epithelium of the cat skin which is associated with the hair when the hair falls; also mold and spores; there are some individuals who are allergic to rooms; when you enter a room which is which is little humid, that is because there would be spores lining the wall and people are allergic to that.

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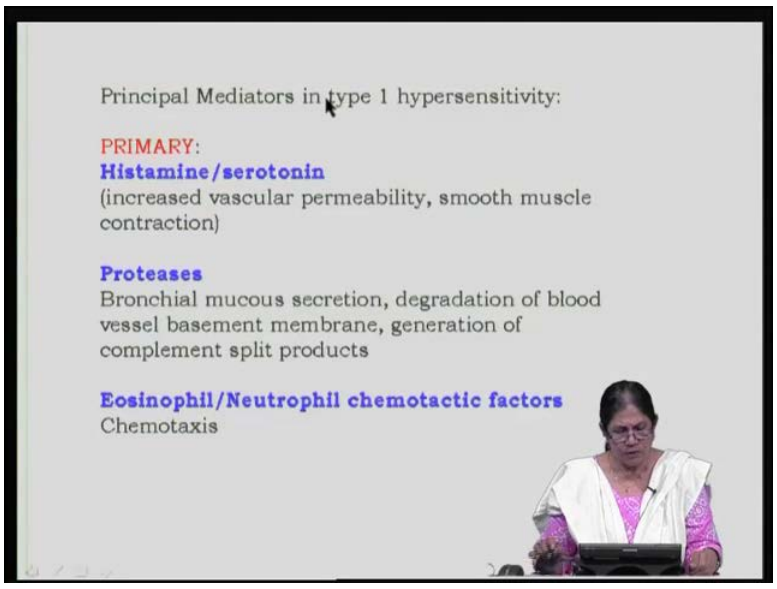

Principal mediators in type 1 hypersensitivity are histamine/serotonin, as I said earlier. They also include… so, what is there in the granules which come out? It also has proteases and eosinophil neutrophil chemotactic factors. Now, histamine/serotonin

increases the vascular permeability and also brings about smooth muscle contraction. Proteases on the other hand, induce bronchial mucus secretion, degradation of blood vessel basement membrane and generation of complement split products.

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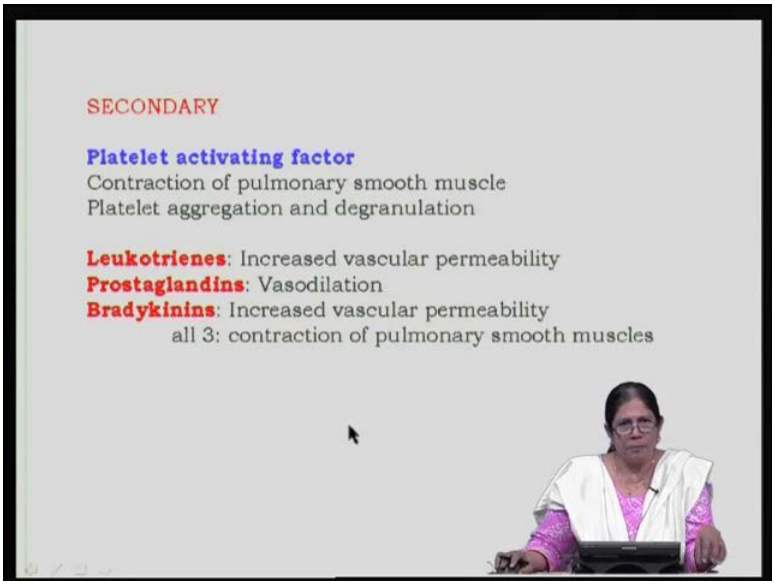

When I say primary, the primary products are those that are already set in as granules in the mast cells and these are immediately secreted out of the cell as soon as cross linking of the receptors takes place.

Secondary, on the other hand, are those that are synthesized in the latest stage of the signaling process. Now, the secondary include platelet activating factor, which brings about contraction of pulmonary smooth muscles, platelet aggregation and degranulation of platelets. Now, there are three very important molecules got leukotrienes, prostaglandins and bradykinins. All three of them induce contraction of pulmonary smooth muscle.

So, immediately, you can think that these are the ones that bring about asthma type of symptoms. Now, even histamine and serotonin can induce that, but these three molecules are at least a 100 to a 1000 fold increased vascular permeability and vasodilation what leukotrienes and prostaglandins induce.

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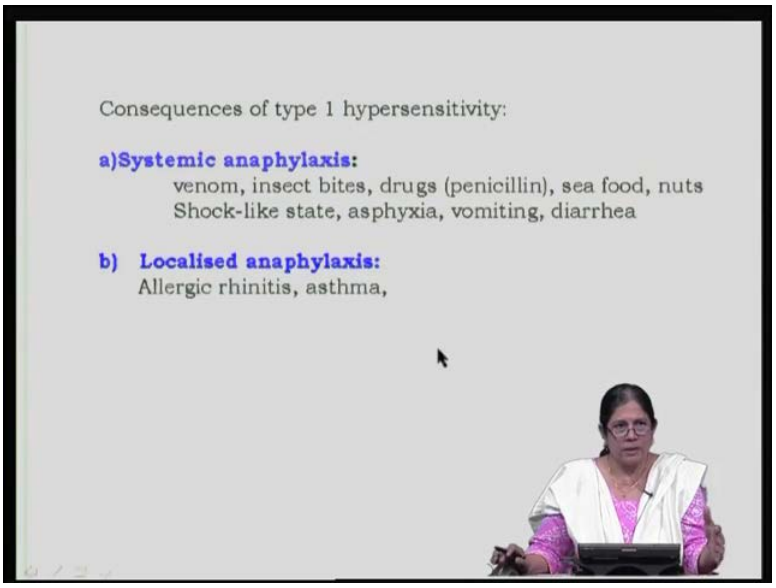

So, what are the consequences of type 1 hypersensitivity? So, let us say, now, we go back to that jelly fish example. People who are stung by the jelly fish, they immediately reacted first to the sting by a shock like state breathlessness that is asphyxia, followed by vomiting and diarrhea. This is if the hypersensitivity is of the systemic type. Now, if the jelly fish is put its toxin into the blood stream, this would be systemic; however, one can have type 1 hypersensitivity is locally localized.

So, localized anaphylaxis allergic rhinitis as well as asthma which is, of course, a most serious condition than allergic rhinitis, but it is still localized in the in the respiratory tract; nevertheless, yes, it can lead to death asthma, but rhinitis, of course, is a much mild form of allergy and it is restricted, of course, to the upper respiratory tract.

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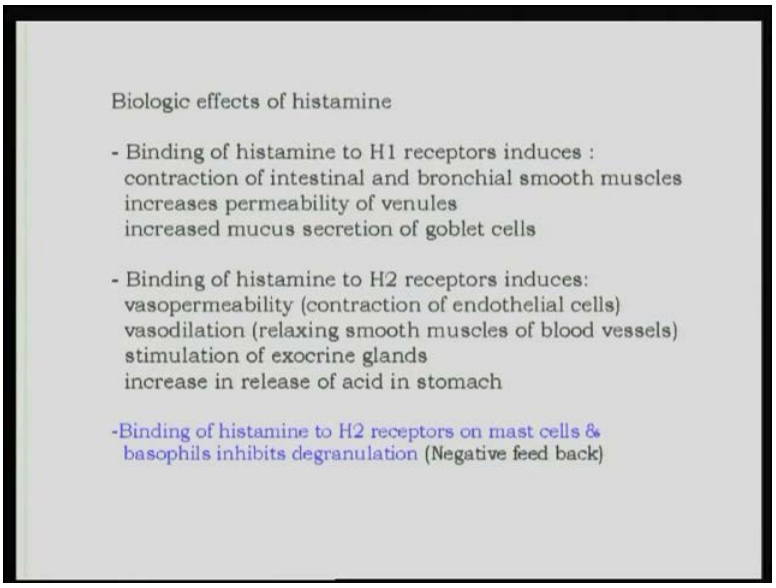

So, biological effects of histamine - what happens to histamine? I am talking about those, the primary mediators of type 1 hypersensitivity; binding of histamine to H 1 receptor induces contraction of intestinal and bronchial smooth muscles. Remember, histamine is much lesser potent than leukotrienes and bradykinins; histamine binding to H 1 receptors increases permeability of venules; also increases mucus secretion of goblet cells mucus.

So, in any of these allergic conditions, there is a lot of coughing and there is a lot of secretion. If it is rhinitis, secretion of mucus; now there are also there are in fact four types of receptors. It is the first receptor which brings about… it binds to it brings about contraction of intestinal bronchial smooth muscles in case of binding of histamine to H2 receptors. This causes vasopermeability, vasodilation stimulation of exocrine glands, increase in release of acid in stomach.

Now, what is this when histamine binds to the receptors on target, is not the mast cells H 1 and H2 binding to those receptors which are present on muscles. All these contraction of the smooth muscle, relaxation of the smooth muscles or the blood vessels and stimulation of exocrine glands takes place, but interestingly binding of histamine to the H2 receptors on mast cells. Mast cells themselves have H2 receptors as well as basophils have H2 receptors and binding of histamine; it inhibits degranulation.

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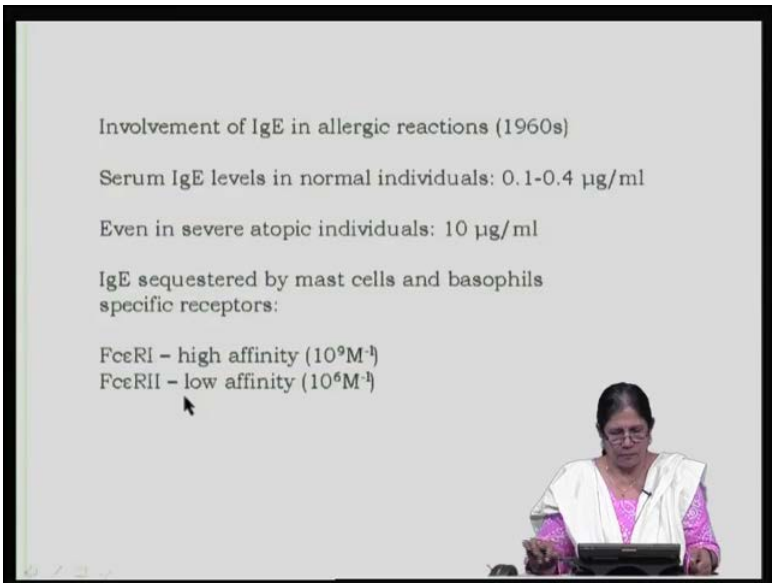

So, therefore, there is a small feedback loop. Now, too much of histamine release tells the mast cells and the basophils to stop any more degranulation. Involvement of IgE in allergic reactions that people knew that there is some kind of an allergic reaction; way back like I said in the early part of the 20th century, but that is the IgE which is involved in this allergic reaction and it is a type of antibody that came to be known only in the 1960s. That late if you might remember from my previous lectures, serum IgE levels in normal individuals in only 0.1 to 0.4 micrograms per ml and if you are thinking in comparison to immunoglobulin g, then it is which is around 10 milligrams per ml. You can see milligram verses 0.1 to 0.4 micrograms, even in severe atopic individuals that the individuals were experiencing allergic reactions. The concentration of IgE in circulation never exists 10 microgram per ml.

That is because, as I said little while ago, that IgE is sequestered by mast cells and basophils because of the presence of very high affinity receptors called FC eta RI. There are two types of receptors that can bind specifically to IgE in the FC region; high affinity receptors which bind with affinity of 10 to the power 9 moles per litre, whereas FC eta RII which is low affinity and it is about 1000 times lower affinity than FC eta R 1.

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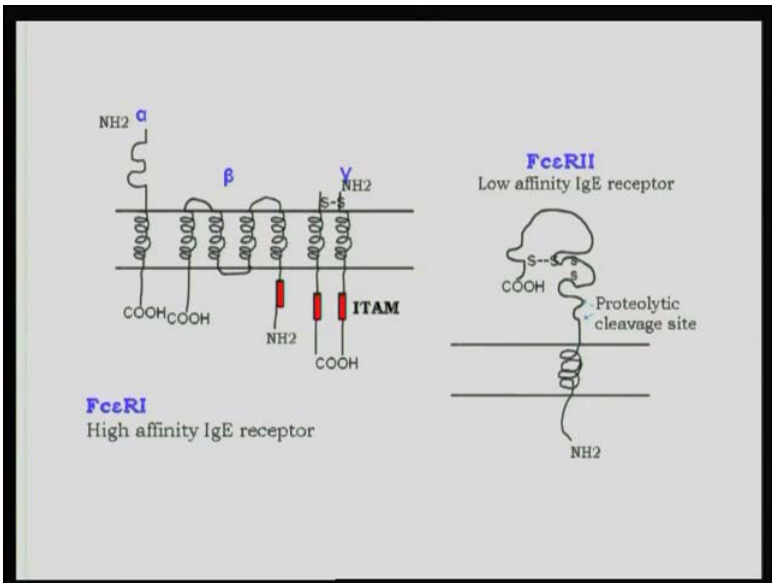

Let us look at the structures of these receptors FC eta RI and FC eta RII; both of these as represented on mast cell and basophils. The exact involvement or the association of FC eta RII with IgE is not very well known sorry not IgE with respect to allergy is not very well known. In fact there are contradictory results saying that FC eta RII enhances IgE secretion, whereas in others, it is supposed to inhibit.

So, this is still a question mark; nevertheless it is known that this receptor which is made up of a single polypeptide and which has low affinity for binding to IgE. It has been seen that this molecule can be present as a soluble form or membrane anchored as I shown here and there are proteolytic cleavage site, and like I said, that this contradictory with respect to the allergic reaction.

So, let us say it was not participated in that. What really induces the allergic reaction is the high affinity FC eta RI to get the structure. Here, it is made up of, in fact, four polypeptide chains, one of which like in case of the immunoglobulin receptor, antigen receptor itself has one molecule which recognizes the FC region of IgE and it is there are two immunoglobulin like domains and the alpha chain which binds to the IgE, one of which only stabilizes; the second loop stabilizes the binding where the first binding contact is made by the first immunoglobulin like domain.

Now, this particular polypeptide does not have signaling molecules. It is the gamma and the beta which has ITAMs. Do you remember, what is ITAM? Immuno receptor tyrosine

based activation motive. Now, the B chain is traverses the membrane; other is the membrane; it traverses the mast cell membrane four times and there are then two polypeptides, both of which belong to the same gamma and these also have these ITAMs.

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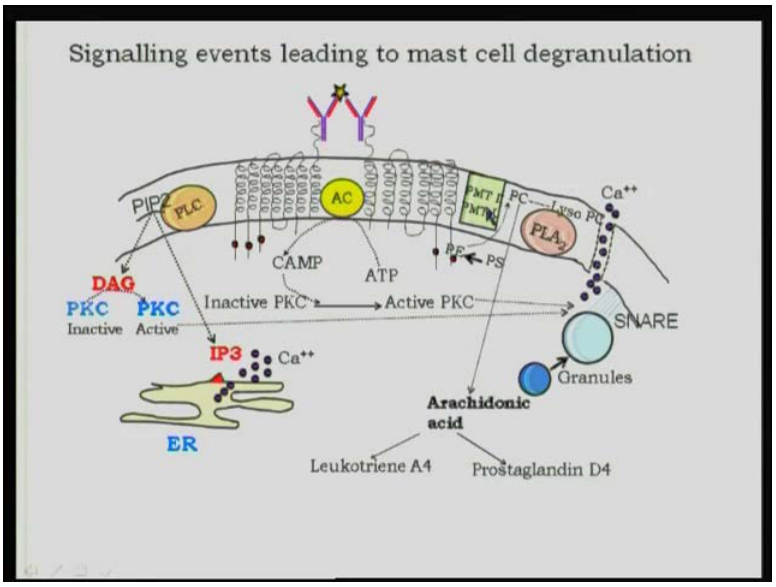

And let us look at the signaling events that lead to mast cell degranulation. What did I say so far? That a B cell which is making IgM soon after its activation by the allergen, which has the cognate, it has the idiotype idiotope for the cognate antigen present on the allergen binds get activated, now starts proliferating. When it gets adequate amount of interlukein 4 and 5 starts dividing to become memory cell or plasma cells. Now, when the memory cell in this particular lineage gets exposed to the allergen again, that is there is class switching and from IgM the cell starts to make IgE. As soon as the IgE is made, it is sequestered; it gets into circulation where it is sequestered very fast by FC eta RI receptors present on mast cells and basophils. And this if you might remember, as present on the FC IgE has a very long life; it can be stable up to 3 weeks or more; in circulation, the same IgE will get degraded within 3 to 4 days.

Now, once cross linking of the IgE takes place because of binding to allergen, there would be cross linking which is experienced by the FC receptor which now sends a large number of signals. What will the ITAMs do? As name suggests, immuno receptor tyrosine based activation motive which should mean that there would be intense

phosphorylation. They are different type of kinases. There are kinases which phosphorylate a large number of molecules; the one being adenylated cyclase, phospholipase C and phospholipase A 2. Activation phosphorylation of these three membrane bound molecules now bring about signaling in different on different molecules. Now, let us look at the phospholipase C.

So, what is not shown here? because we have already discussed in details the kinases which are activated after B cells, now the signaling may be slightly different here, but the ITAMs could mediate the same kind of phosphorylation as happens in B cells. Therefore, those are not depicted here; suffice here to say that phospholipase C which is in its inactive form upon getting activated by the kinases, which are phosphorylated by these ITAMs present on the FC receptor now get activates phosphorylates PLC which gets activated.

Activated PLC, the substrate for which is PIP2 now hydrolyses PIP2 to diacylglycerol and IP3. The diacylglycerol now converts and inactive phosphor kinase to an active form. IP3 on the other hand if you might remember has I mean binds to specific receptors present on the endoplasmic reticulum which now activates the release of stores of calcium from the endoplasmic reticulum to the cytosol.

Now, let us look at what the adenylate cyclase does. AC is the enzyme adenylate cyclase after its gets activated which is because of phosphorylation. The adenylate cyclase converts ATP to cyclic amp adenylate cyclase. So, it makes cyclic AMP which is also a signaling molecule. Adenylate cyclase activation is a little bit transient and we will understand that as we go along; I will come to that later. Now, within few seconds after the cross linking of these receptors, there are molecules in the membrane that get activated, which bring about hydrolysis of the lipids in the membrane. Formation of phosphatidylcholine, which now gets hydrolyse to arachidonic acid which in turn breaks down to leukotriene and prostaglandin.

Now, when there is change in the membrane because of hydrolyses of the lipids in the membrane, calcium channels are formed and extra cellular calcium now gains entry inside the cell. This increases calcium levels to a very high concentration. All of these signaling mechanisms are important because there are inhibitors of almost each step which can stop the cell from degranulation. What is the role of the cyclic AMP? It now

activates a protein kinase to become now associated or brings about movement of cytoskeleton, such that these granules which are small start to move to the membrane where there are proteins called snare proteins in the inside of the membrane and the same proteins are also present on the outside of the granule, fuse and the granule is then thrown out. Phospholipase A 2 which hydrolyses which gets activated in hydrolyses lipids to the PC and lyso PC and phosphatidyl ethanol from phosphatidylserine to phosphatidyl ethanol amine.

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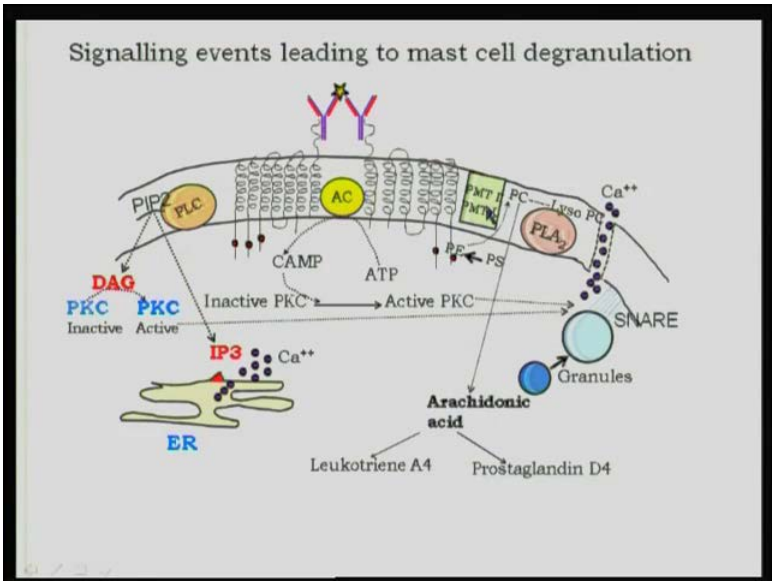

Now, PLA2 is also responsible for phosphorylating membrane proteins of the granules which now allows a changes of permeability of the granules, so that now they can swell up allows entry of water, so that these granules can swell up so that snare proteins can get accessible and the small granules become larger granules. And only then can they fuse with accessibility of the snare proteins and then these fusing with the snare proteins of the membrane, now, brings about exocytosis of these granules.

Now, you look at the signaling here. If one can inhibit let us say calcium from entering and increasing the interested cellular stores to a much higher level then one would not allow exocytosis. If I told you adenylate cyclase activation is transient and it has been seen that cyclic AMP level have to come down before for the exocytosis of these granules to take place.

So, suppose now cyclic one can inhibit the cyclic AMP levels from going down; that means your cyclic AMP gets hydrolysed by a phosphodiesterase and if you can have now inhibitors of phosphodiesterase, that cyclic AMP levels remain high. And if the cyclic AMP levels remain high, then exocytosis does not take place. So, you can have inhibitor for the phosphodiesterase. So, cyclic AMP levels are not decreased. You can have inhibitors of end formation of these calcium channels not allowing calcium to come down; thereby, now you can decrease the degranulation of mast cells. Now, I am telling you all these because there are molecules that can inhibit these and are used as medication.

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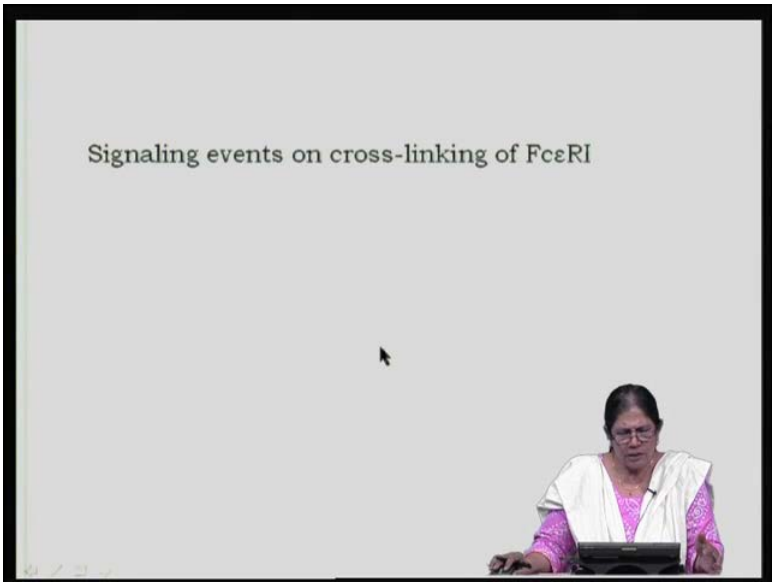

So, just let us look at the signaling events once more.

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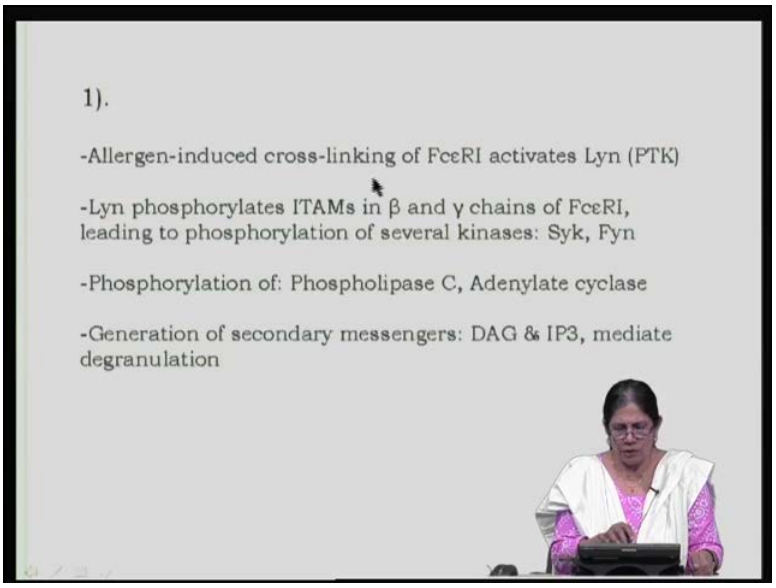

Allergen induced cross linking of FC eta RI activates a kinase called Lyn. Lyn phosphorylates the ITAMs in the beta and gamma chains of FC eta RI, leading to phosphorylation of several kinases. Now, this is what not something that I did not have in the picture those are Syk and Fyn the Syk and Fyn in turn phosphorylate phospholipase C and adenylate cyclase. And now, there is generation of secondary messengers - diacylgycerol as well as IP3 and these are what mediate degranulation.

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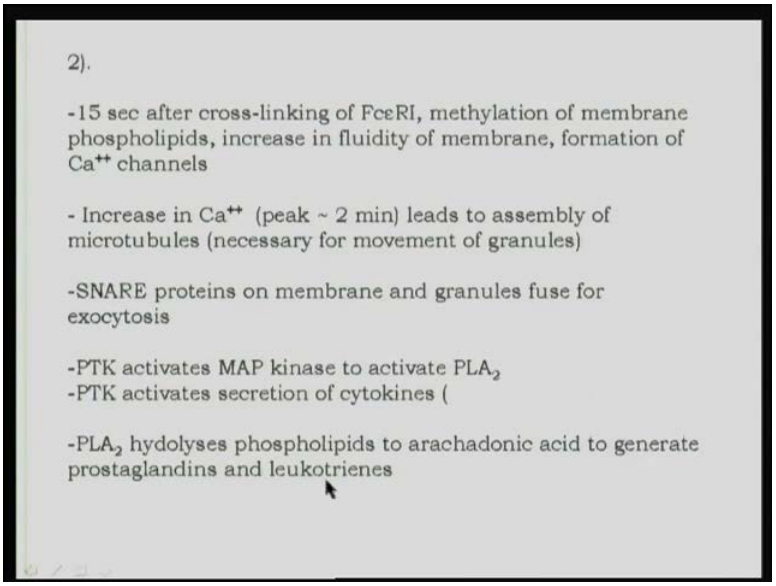

Now, let us come to the methylation, the cross linking of FC eta RI. What it does to phospholipids? There is methylation of membrane phospholipids and this brings about increase in fluidity of membrane and formation of calcium channels. Increase in the calcium through this channel and not only by the release of intracellular calcium deposits of the endoplasmic reticulum. This leads to assembly of microtubules and I told you this microtubules they are necessary this organization of the microtubules is necessary for movement of the granules.

Now, snare proteins on the membrane and granules fuse for exocytosis. So, the granules which by the way are present as small granules, there the membrane proteins on the surface of these granules get phosphorylated, which now the granule membranes become permeable to water so that there is swelling of these granules. So, snare proteins on the granules now can bind to the snare proteins of the membrane. The cell membrane is used and exocytosis is exocytosis of the granules happens. Phosphotyrosine kinase activates map kinases to activate PLA2, the same Syk and Syk kinases, and then this activates secretion of cytokines phospholipase A2 also hydrolyses hydrolyses phospholipids to arachadonic acid and to generate prostaglandins and leukotrienes the second secondary molecules.

Now, primary are serotonin and histamine; the secondary are leukotrienes prostaglandins and bradykinins. These three, the last three are products of the arachadonic acid which is because of membrane lipids; hydrolysis of membrane lipids.

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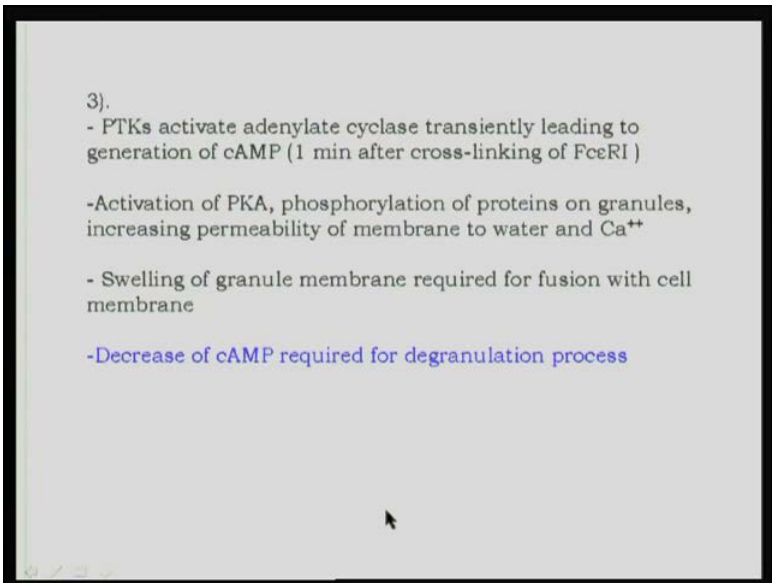

Phosphor tyrosine kinases which are because of the phosphorylation of ITAMs and other molecules - now these activate adenylate cyclase transiently, remember, leading to the generation of cyclic AMP and this can be seen one minute after cross linking. Activation of PKA that is protein kinase which is dependent on cyclic AMP, brings about phosphorylation of proteins and granules, which I said just a little while ago, increasing permeability of membrane to water and calcium, swelling of the granules which is required for fusion. Decrease in cyclic AMP. This is an important thing; decrease of cyclic AMP required is required for degranulation process. So, if we can keep the cyclic AMP at elevated levels, this will inhibit degranulation of mast cells and thereby decrease the symptoms of hypersensitivity.

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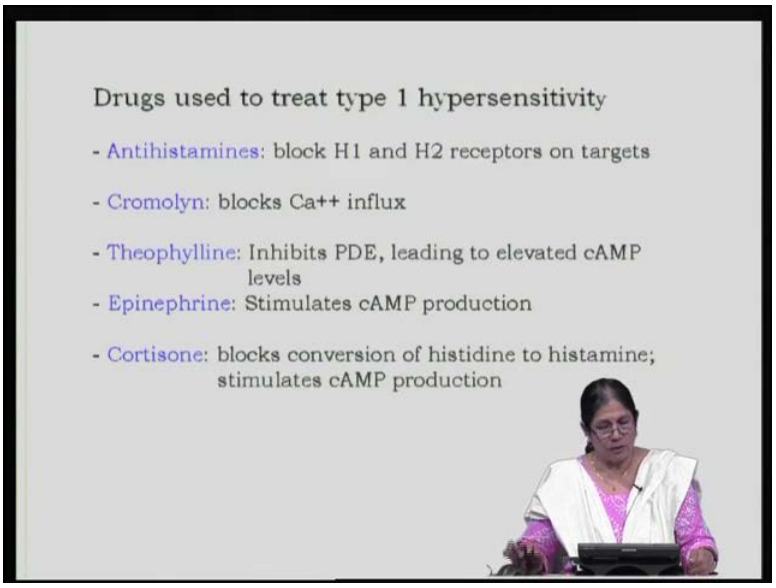

So, soon after signaling, I will like to touch upon the drugs that are used to treat hypersensitivity. Like I said, it is the signaling mechanism which was unfurled, which gave well doctors and immunologist a hand to use certain drugs which can block. For example, antihistamines - this blocks H 1 and H2 receptors on targets. So, if binding of histamine to the receptor does not take place and you will not have smooth muscle contraction vasodilation etcetera. Cromolyn - this blocks calcium influx; thereby it will inhibit the generation of the secondary mediators and those are much more important than the primary theophylline.

This molecule inhibits phosphodiesterase PDE; this inhibition of PDE would mean that cyclic AMP has not broken down, and therefore, there are still elevated levels of cyclic AMP. This will again inhibit degranulation. Epinephrine is another drug that is used because it stimulates cyclic AMP production. So, well, in a sense theophylline and epinephrine, both of them do the same job though in different ways. They both bring about elevated cyclic AMP levels, and like I told you before, decrease in cyclic AMP levels is a must for the actual degranulation process to take place.

Lastly, Cortisone - this is this molecule blocks the conversion of histidine to histamine and also stimulates cyclic AMP production.

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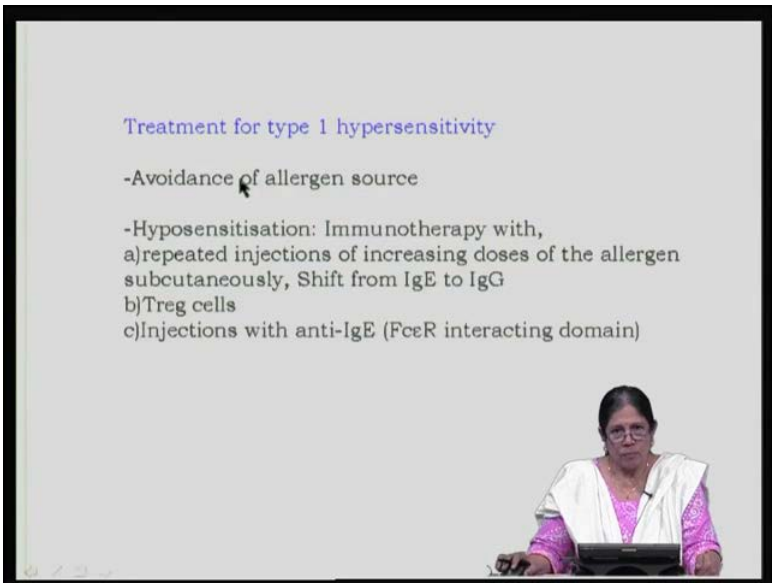

What is the treatment for type 1 hypersensitivity? Other than the drugs that I discussed a little while ago, now the best would be to avoid the allergen source. Now, for example, now you cannot always avoid.

Let us say that you are allergic to cat dander; so, you see that you do not have cat as a pet. Of course, you do not visit people who have cats as pets; so, avoidance. People who are allergic to pollen or ragweed or parthenium should see that when they are going out, they always… they should not inhale these because allergic reactions to these grass because of inhalation. So, one can use a mask when you go to areas were they put these. So, avoidance would be the best. But of course, if it is not possible for that matter, if you do not know what you are allergic to, it is a big problem, but if you do know what you are allergic to, there are clinics were a method of hyposensitisation is initiated. It is a regimen of immunotherapy, where repeated injections of increasing doses of the allergen are given subcutaneously, so that there is a shift from IgE to IgG.

Now, how will this happen? It has been shown that the way the route of immunization also matters with respect to what type of antibody, what class of antibody is generated. And it has been seen that if subcutaneous injections are given with increasing dosage as compared to, let us say, exposure by way of the through the nose or the mucus membrane may give raise to or often does give raise to IgG verses IgE.

So, people who are allergic to let us say pollen, if they are given repeated injections subcutaneously of the pollen extract, then they have a shift from IgE to IgG and definitely now if you have more of IgG, the IgG will sequester away. The IgE, before cross linking can takes place. T regulatory cells also are in the pipeline now. To try treatment to for treatment of hypersensitivity type 1 and also there is a possibility one can give injections with anti IgE such that the FC eta receptor interacting domain actually sequesters the IgE away. This is important because the antibody itself should not induce cross linking.

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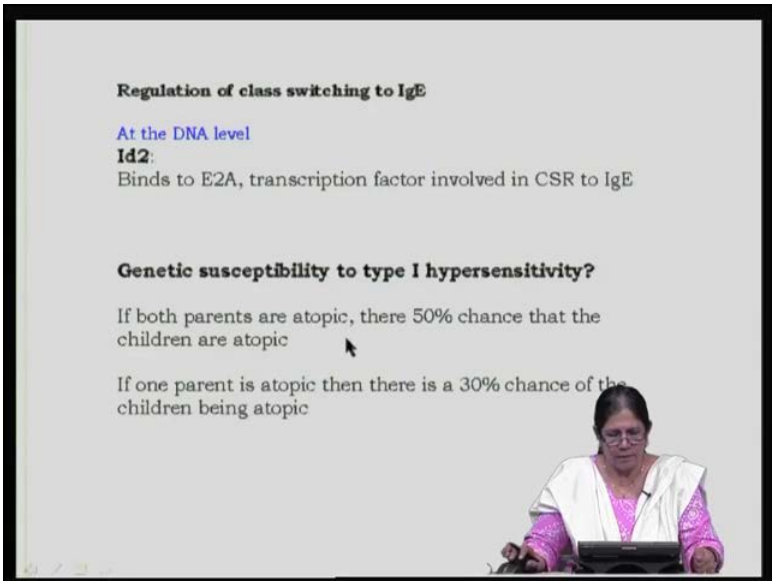

Regulation of class switching to IgE - I would just like to remind you that when we talk, when I discuss the regulation of immunoglobulin expression, I did mention that at the DNA level Id2, a factor Id2 binds to a transcription factor E2A which is involved in class switch recombination to IgE. Therefore, one can imagine that if it is at the DNA level, then there would be genetic susceptibility to type1 hypersensitivity that, that was a question mark. And now it is well known that if both parents of a child are atopic, there is fifty percent chance that the child is also atopic; that means the capacity to generate more IgE.

There are, of course, certain molecules which will generate IgE in the normal course of in immune response. We do know that the type of antigen, the type of immunogen

actually regulates the class switching, so that it is beneficial to the host to reject or obliterate that type of molecule.

Now, in allergic individuals IgE is being made towards even other molecules, where normal people would be making IgG. Therefore, if fifty percent chance for the child whose parents are both atopic and allergic to certain molecules, but if only one parent is atopic, then there is thirty percent chance of the child being atopic or the capacity to generate IgE in an inappropriate way.

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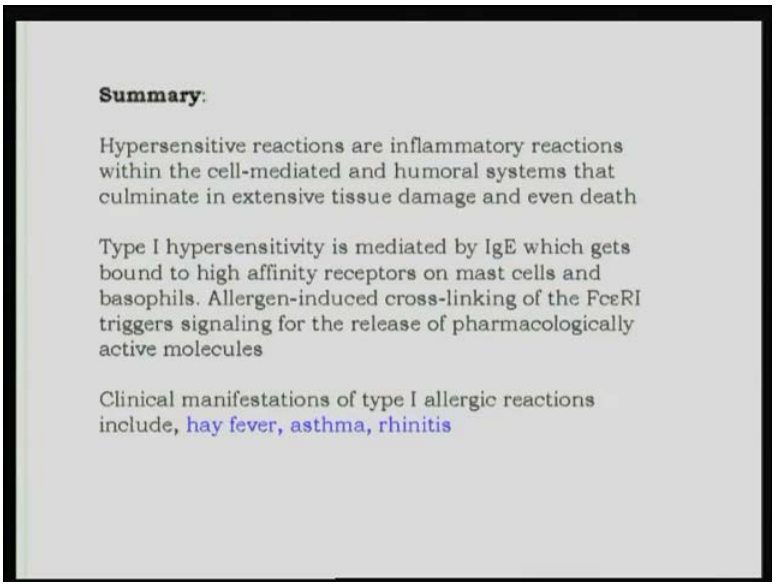

So, therefore, now, let us look at this hypersensitive type 1 reaction. So far, what I have said is hypersensitive reactions are inflammatory reaction. Now, this is within the cell mediated and humoral system, but why they are called hypersensitive because these culminate in extensive tissue damage and this can also lead to death.

Let us now classify these. If you have type 1 hypersensitivity of the systemic type as happens in case of allergy to bee venom, or well again let us go back to allergy to the jelly fish toxin or allergies to penicillin. Now, this is something which I did not deal with; penicillin is a very small molecule. We discussed about immunogens that is small molecules such as penicillin or sulphonamides. Now, these on their own are not immunogenic, but when they react with skin proteins or proteins in the body, they become immunogenic because they use the skin proteins are well systemic than any proteins, as they carry a protein.

Many people are known to be allergic to penicillin. So, you do know that doctors always test whether you are allergic or not, before prescribing penicillin or sulphonamides for that matter. But, in case this has not happened and an individual has been injected with penicillin to take care of an infection, then now there already IgE antibody that are synthesized by this individual to penicillin and these IgE anti-penicillin IgE would be sitting in on all almost all the mast cells. Now, mast cells and basophils, now mast cells because they are present in the connective tissue allover.

Therefore, now you will have IgE and you have now the allergen also, that gets sequestered in circulation through circulation to all the connective tissue which has mast cells. And you can imagine that there would be an intense reaction. Once cross linking of this mast cell FC eta receptor takes place, this becomes systemic if you have, now, a systemic reaction. And one thing, there is a cascade of reaction that starts taking place and then this can, of course, lead to death because inflammation on skin is localized, but inflammation in the system is not localized. And what would have started of as an allergen, and specific IgE interaction now culminates in extenuative extensive tissue damage because of the recruitment of these mast cells and basophils, which are throughout the body; this can cause death.

And we do know penicillin of other matter, eating sea foods a eating sea food Why is this not localized is because that whatever is the allergen of the sea food is now in the elementary canal. Through the elementary canal, it is absorbed into the intestine and you do know that you do have immune cells in the intestine. You do have mast cells through the intestine. Of course, through the blood, this allergen is spread systemically.

So, therefore, even sea food allergy is because food can also become systemic. Type 1 hypersensitivity is mediated by IgE which gets bound to high affinity receptors on mast cells and basophils, and then allergen induced cross linking of the FC eta RI triggers the signaling which, as I discussed in detail for the release of pharmacologically active molecules. Now, clinical manifestation of type 1 allergy reaction includes hay fever, asthma and rhinitis. Now, just imagine the signaling in the mast cell is so very intensive.

You have so many molecules that kept which participate in the signaling, all of which finally culminate in exocytosis of the principle primary mediators which are present in granules in the mast cell, but the secondary molecules are generated after the

phospholipids in the membrane now get hydrolyzed and very potent molecules like bradykinins, leukotriene and prostaglandins are synthesized. All of these go to inducing vascular permeability as well as smooth muscle contraction, which can lead to respiratory problems, can lead to vomiting because the gastrointestinal tract is also affected and which can actually bring a shock like syndrome.

Thank you.