Transcriber name Murari

Immunology

Prof. Sudip Kumar Ghosh

Department of Biotechnology

Indian Institute of Technology – Kharagpur

Lecture-4

Basic Concepts in Immunology (Contd.,)

Welcome welcome back to immunology course today we are going to start again the basic concepts in immunology. Today is lecture 4. Okay, In last class we ended up with the dendritic cell is the bridge between innate and adaptive immunity. Today what we are going to see that how that innate immunity and adaptive immunity are reached together and what is happening and how it is going ok.

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So, the first slide the first slide we are talking about circulating lymphocytes encounter and design in peripheral lymphoid tissue. If you see the picture carefully see this is the place in the leg in the foot actually the infected peripheral tissue so there are some infection here. So, what happened in infection if you remember in infection the first thing happen is in it part of the immunity.

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And this is the inflammatory response in inflammatory response we already discussed. So, all these macrophages dendritic cells they pick up the tissue may pick up the infected organism in infectious organism and then it bring to the nearest lymph node. So, from the site of infection the antigen presenting cells then mostly the dendritic cells are taking them to the nearest lymph node and we already know that lymph node is spreaded all over the body.

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And wherever the infection here in this case we so that the feet is the foot is the in site of infection it can happen any part so that from innate, as a result of innate immunity the infectious organism is processed and bring to; having brought to the nearest lymph node region. In this case it is here so in this lymph node it will go and we will discuss what is going

to happen in the lymph and then it will go to the circulatory system goes to heart and from that heart it is circulated all over the body if the site of infection is only one place it will take care there and if it is all over the body then it will take care by the blood.

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So, like after inflammation and the dendritic cells bring them to the nearest lymph node.

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So, how the lymph nodes look like this is a cross-section of lymphoid the schematic diagram. So, if this is the lymph node and here there are two channel one it is called efferent lymphatic vessels where it is coming from outside entering into the lymph node and other is going out after the immune reaction happened this is called efferent lymphatic vessels. In this lymph node cross-section if you see there are different parts this part the pink color part it is the medullary part of the ah lymph node and this region is cortical region.

If you remember the color code that we always so that B-cell is yellow in color and T-cell is blue in color. So, here this blue and yellow are meaning the same part like blue region means this region is packed with T-cells and this color I mean this pink region is when you record macrophage and plasma cells are there. What is plasma cells? We will discuss later. But we already told actually like B-cell is converted to plasma cell and then only it can secrete or it.

The plasma cell is ac actually producing the antibody molecule and secretly. So, here this yellow circle this is called germinal Center. So, what happened in previous slide we have seen that the dendritic cells are bringing the pathogen here and then it is going come in entering inside then in the blue region there are lots of T-cells and these T-cells this is already discussed this like this T-cells there are many the specific T-cells specific or particularly interacting T-cells which interact with that pathogen will find it and attach to it.

After attachment they get the signal and they proliferate, proliferate means they increase their number. These activated T-cells then help the B cells to produce antibody and B cell also after getting the signal it multiply converted to plasma cells and plasma cells produce antibody which is secreted to the system and peripheral system that goes to heart and then gradually distributed all over the body. So, wherever the infection will find the antibody is going to do its own job.

So not only lymph node there are two types of lymphatic organ one is called primary and there is secondary.

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So, another important lymphatic organ is spleen, so spleen also if you see the cross-section of spleen here also you will find two different zone one is blue zone another is yellow zone. So, blue zone is full of T cells and yellow zone is full of B cells. So, there are different part so the germinal center is also here. So, it depend where infection happened which is the nearest lymph node or lymphatic organs.

Say for example if you go here so if there is any infection in teeth or mouth or in throat we are very much acquainted with that what happened we heard like tonsils swells right tonsil is located here. So, tonsil is taking care of all this region infection in this region instead of mouth cavity, throat. So, any infection happen so that time the macrophages and dendritic cells bring the infection to the tonsils.

So, similarly it is taken care by the nearest lymph node which is I call in the last class or in last one of the last lecture that it is the local thana kind of thing. So it is taking care immediate part. So, lymph node spleen tonsils are there.

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Besides this in case of the mucosal region where there is no lymph node there is no direct connection of blood so what we also have several system or several mechanism to handle the infection in that cases. Like mucosal serface, surface have specialized immune structure which take care of the infection of that region. Similar what we have we have mucosal immune system or mucosal associated lymphoid tissue it is called MALT or got associated lymphoid tissue GALT which includes tonsils, adenoids, appendix, Payer's patches, nasal associated lymphoid tissue and bronchus associated lymphoid tissue. In short we call MALT, GALT, NALT or BALT, Okay.

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So, they are taking care by a specialized cell called M cells okay, so this is a specific example of the spare spats but pair special covered by epithelial layer you can see the epithelial layer are there which contain a specialized cell called M cells which have the characteristic of the membrane ruffles. So, this ruffles are there so here also we can see there are packed of T cell region the blue region we have germinal center, dendritic cells are migrating in between, okay.

So there they take care of the infection if there is any in the mucosal region. All the GALT, MALT everywhere they have this kind of structure.

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So, what happened I am revising back or repeating the same thing what happened in the site of infection, immediately the innate immunity take cares. Inflammation happened that inflammation as a result of that inflammation the pathogenic organism brought to nearest lymph node where it interacts with T cells. T cells get activated it helps B cell these are also activated both way by directly by the antigen or and at the same time by helper T cells then they converted to plasma cell produce antibody. Okay

In many times it happened like if you go to doctor what happened doctor first like there is a pain or there is wound something happened muscle pain doctor check whether the gland is swelled or not because inflammation will make the gland will swell there is a good amount of infection and there will be pain in the lymph node also on lymph node region. So, from that pain, if pain is there as well as in as well as there are some wound we can say inflammation happened.

So that means infection is there if there is no swelling just pain happen by some hit to the muscle or by some overwork that time information is not going to happen. So, from there doctors can understand infection is there and according to their prediction and other symptoms they decided what should be there for the treatment whether antibiotic is required or antibiotic is not required they will decide.

So this is the starting of adaptive immune response. So, if we consider at the beginning just the B-cell part or antibody production part what happened so it is not like innate immunity within hours we already see that it takes days to week. What happened so first antigen will come to lymph node B cells, there are many B cells they will see specific B-cell with their receptor will recognize the antigen same way specific T cell receptor will recognize between there will be a cross talk between B-cell and T-cell as well as with the antigen that will activate the B cell which is going to convert it to plasma cell.

And the B cell receptor will be produced in a different form because there will be no transmembrane domain so it will be now secretory. So, the B cell receptor in the form of antibody same molecule same specificity will secrete to the peripheral system. So, here we are showing a graph in this picture this is a very important. Important in that sense this is the response how it goes and this particular graph is also going to I am going to tell you that

this is the major principle or on this principle of this phenomena what we are going to explain now are the base of immunization or the basis of immunization.

So I am trying to explain this crap. What is happening say for antigen A suppose we are considering antigen A and assume for the time being we will discuss later how assume for the time being in blood serum we can measure how much specific antibody is there. So, antibody against antigen A we can measure. There are several techniques, so suppose one of the techniques is used to measure the specific antibody concentration in blood against antigen A.

So what happened suppose antigen A is injected this is day zero and every day if you try to measure or if you measure the specific antibody presence of specific antibody in serum what we will see up to almost 7 days there is no increase in antibody against antigen A. And after that it gradually goes up and it reached a plateau that means antibody is going to increase anymore.

We injected antigen A once at day zero so up to certain day it will increase and then will not increase anymore and if we keep on continuing the measurement of antibody what we will see it is gradually going down going down at this moment suppose here we are injecting antigen A again, listen carefully we first injected antigen A then we measure the antigen A specific antibody in serum and we see the pattern of this graph.

So first 7 days almost there is no increment the antigen is increasing then reach maximum stay for some days and then going down gradually. When it is going down at this moment if we inject the antigen A again what is happening you see this is the nature of graph nature of graph means this is the nature of antibody concentration in in that particular individual. So, what is happening if you see in the beginning it took almost 7 days, okay.

Next time if I inject same antigen within very short maybe one or two days it start increasing not only it takes less time to produce antibody it produce much more and if you see it stay for a long time. This is called secondary response. So, first one when our bodies see any antigen or any pathogen first time this is the first reaction this is the first reaction but second times if it sees the same antigen again the reaction is much quicker and the amount of antibody production is very high.

So two differences so if I now ask you a question what is the difference between primary response and even secondary immune response? There are two points right one the lag phase that means first point where it goes up the lag phase is more it is about 7 days here is

much less, 2 to 3 days this is number one. Number two, the amount of antibody production in the primary immune response is much less than the secondary response the amount is very high.

And this is independent of antigen, it is not that antigen A if happen this way it is going to work for antigen B also that is why here what happened along in the second time injection of antigen A antigen B also injected. You see in case of antigen B again it tooks it took 7 days. You start with and again it goes up to certain level. So, for every antigen first administration is the primary response. So, secondary response of antigen A is not doing any effect or not having any effect for antigen B.

And this is the basis of this is a principle of immunization. What we are doing in immunization? We are doing immunization we are giving our body to the exposure of the antigen for primary response. So, in primary response body see it, it takes time make a specific antibody. So, what is going to happen when it is going down it is never going to come down to the basal level. Some of the B cell will convert to memory cell that means that you will remember that who entered in our body.

So that one is that is that population of B cell and the memory B cell and memory T cell are going to stay in in our immune system. So, next time if it comes it will not take much time because they already know it is how it looks what to do with that so immediately they will take care of that and with much less time they goes up and make more production. There are two more important things happen one I will say now another I will come later.

And in the during the discussion of antibody what happened in this secondary immune response it is not only that it is quick and much more aggressive another thing is happening. In the secondary response the quality of antibody or the specificity of the antibody is increased. So, better quality antibody or more specific antibody are going to form. So, in secondary response it is always better it is a always better. So, that is how vaccination or immunization work.

So we prime our body with the primery, with the antigen at the first time and in secondary response it goes high and can take care of our infection much quicker and much specific way or more effective way.

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So, what is the effective mechanism affected mechanisms what will happen? What what this antibody is going to do? Because antibodies produced more antibodies produced, so, how it is going to handle the immune system.

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We already know that there are four type of pathogen right the pathogens are like virus which is intracellular then intracellular bacteria protozoa like Listeria is intercellular micro bacterium Mycobacterium leprae, Mycobacterium tuberculosis their interest several bacteria there are some protozoa, protozoan parasite like *Leishmania donovani* which cause kalazar which grow inside the macrophage. *Plasmodium falciparum* you know it grow inside the RBC.

Similarly which is very common the extracellular bacteria parasites, fungi ok. Any kind of tissue infection is most of the time it is extracellular the Streptococcous, Clostridium, trypanosome is a protozoan parasite, then parasitic worm the big one Schistosoma, Ascaris. And here is the disease I mean disease the viral disease like smallpox, flu, chickenpox. Then leprosy, Leishmaniasis, malaria, toxoplasmosis they are the disease and I mean these are the corresponding pathogens.

So summary; if I say summarize this we don't have to remember all this thing if you it is good like which organism cause which disease but in general we have to remember there are four types one is virus, pathogen that antibody can handle. Pathogen is the virus intracellular bacteria protozoan parasite, extracellular bacteria parasites, fungi and parasitic worms which is also extracellular. So, immune system or the effector function of antibody is going to handle all these 4 all these 4 different kind of organism or pathogen.

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How they are doing if you go back to virus. Virus is going to take care by cytotoxicity of the cell cytotoxicity mostly by NK cells and CD8 T-cells and I will come later but for these slides cytotoxic T cell also called CD8 T cells because cytotoxic T cells express a specific receptor which is CD8 which is present only in cytotoxic T cells. Similarly helper T cell produced another receptor which is specific to helper cells are CD4.

So many times instead of telling helper T cell we also say CD4 cells same way cytotoxic T cell also we call CD8 T-cells CD4 T cells are the helper cells CD4 sorry CD4 T cells are the helper cells CD8 T cells are the cytotoxic cells. So, virus is mostly taken care by NK cells which we already discuss by and cytotoxic T cells or CD8 T cells by cytotoxicity what it is doing elimination of virus infected cell or metabolically stress cells.

Intracellular bacteria or parasite ILC1 innate leukocyte 1 or TH1 cells we will see what is that which eliminate the intercellular pathogen by activating macrophages. Similarly mucosal barrier is taken care by ILC2 and TH2 the effect is the effected function is elimination and expulsion of parasites, recruitment of eosinophils, basophils and mast cells to handle the infection. Extracellular immunity is taken care by ILC3 and TH17 cells.

What they are doing they are eliminating the extracellular bacteria, fungi and recruitment and activation of neutrophils which is taking care the innate immunity part ok.

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So now what antibody is doing all this thing is going to activate B-cell T-cell and B-cell; T cell is going to help B-cell they produce antibody how antibody is going to help us from to get rid of the infection or infection related material because some extracellular bacteria they produce toxins and that toxins create problems like diphtheria toxin, cholera toxin, okay, tetanus toxin, then pertussis, the whooping cup all are not direct bacterial is causing anything.

So they are producing a protein molecule or toxin molecules what they are doing so they release the toxin molecules these red circles the red circles are the toxin. Normally what they are doing this toxin molecules (we) are attached or bound bind to receptor which is already present in ourselves. So, bacteria dimer produced the toxin to kill us we our cell actually have the receptor which can bind this toxin molecules.

So that is a very interesting mechanism those who are interested how these toxins work you can go and read like diphtheria toxins how they go enter and change or attack the elongation factor and stop protein synthesis. Cholera toxin change the sodium potassium channel and a lot of fluid loss is happening and tetanus toxin cause the problem in muscle construction so there are mechanism or molecular mechanism are very interesting .

You can go and read study not for immunology like just for general interest. What happened so these toxin molecules go and bind they internalized by receptor mediated endocytosis and cause the damage or disease. So, if there is any specific antibody which raised against these toxin what is going to happen? This toxin is not going to be free anymore the antibody is going to bind them if you you see this antibody is just captured them.

So what will happen there will be no free toxin to bind to the receptor and this particular toxin is captured by the antibody so upon infection body is going to make specific antibody against this toxin and when antibodies amount is good enough in our body. So, no free toxin will be there to bind to cell receptor and cause the damage. Same way this is called neutralization this method so it is that means the toxin is neutralized by antibody this process is called neutralization.

Same way macrophage we know that they can eat bacteria by different TLRs, okay mannose receptors but sometimes what happened that efficiency is not good. Even after the innate immunity a bacteria grow inside our body and population increase so the disease will continue. So, what happened if it is still continuing for good enough days like seven days or more then antibody against this bacteria will be produced.

So, whatever one just like the toxin molecule and antibody is going to coat the bacteria so the bacteria is big here bacteria is big here and so these bacteria will be quoted by antibody this process is called opsonization clear. So, first one is neutralization second one is opsonization. Another important method, important strategies there in our immune system which is called complement activation. What is this complement activation?

There are proteins which is heat labile but they are a very much part of the innate immunity they do not have specificity. What is going to happen as soon as bacteria is coated by antibody the complement protein which is present in our blood okay, they will go and attack them this is called complement activation. So, antibody is doing three things first neutralization then opsonization then complement activation.

Complement will be taught separately a very interesting mechanism how it works, how our own cells are not affected by this complement. But they are very, very bad proteins, so human complement can kill any other mammals cell. So, they are very specific our own complement is not going to do anything to us similarly others complement system like if it is cow or goat any complement system if you mix with our blood that will kill our own cells.

So they are nonspecific highly nonspecific but individual organism has the protection from their own complement system. So, coming to the previous slide here neutralization optionization and complement activation I will go one by one. So, after neutralization of the toxin molecule what happened macrophage is there. Macrophage I always already told that it is cleaning mace or eating our own thing is there macrophage has if you see this yellow line.

Macrophage has a receptor for antibody so they by this receptor this whole complex will attach to the macrophase surface and they will taken up by phagocytosis or receptor mediated endocytosis. After taking them they will be degraded inside, so there will no toxin molecule anymore and this whole protein is going to be recycled for our own, I mean the macrophage's protein synthesis. Same way opsonise bacteria which is coated with antibody also be endocytosis and phagocytose by macrophage and degraded inside the macrophage.

So no bacteria will survive so that that that is the way the bacteria will be cleared from the system. So, this is opsonization and in product is same both allies product of the antibody and toxic. In complement activation what happened in complement as soon as antibody code this bacteria complement protein come and sit into this bacteria. So, they will make a channel there are proteins which are like this. So, this suppose this is one one proteins one subunit of the protein.

So once I will need then to subunit three subunit and then gradually they make a channel it is just like a pipe. So, if you may take a pipe and put inside the cell what I mean so suppose a ball is full of liquid you put a pipe inside it what will happen all the liquid from out cell will from that ball will come out. Same way so they make a channel inside that so individual protein will sit one by one and how it is happening, how it is happening.

So they will make 1 protein then 2 protein then 3 4 5 6 7 something like that so they will make a channel or hole in it so they will make a hole in it so that hole what is the effect of that hole? So all the cytoplasmic material of the cell will come out so the bacteria dies so these three possible ways are there. So, these three possible ways are there by which this the antibody can take care of microbial infection either the toxin or the whole microbe.

So this is called a vector is that clear so today I mean in this lecture this is end. So, see you in the next class and you just again I am repeating go and study it is very simple and things to remember. Just go and if you remember the image you can remember the whole immunology. Bye for today.