Immunology
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Lecture-9
Adaptive Immunity (Humoral)

So, welcome to the immunology lectures. So, today we will try to understand the we will continue with adaptive immunity that we started in the last lecture. So, in the last lecture we started with the cell mediated part of the adaptive immunity. So, as I described that the adaptive immunity or the adaptive immune system can be classified or has two branches. So, the cell mediated part which is primarily mediated by the T cells activation of the T cells and and there is the humoral part of the humoral response which is the antibody mediated response and that is mainly carried out by the B-cells.

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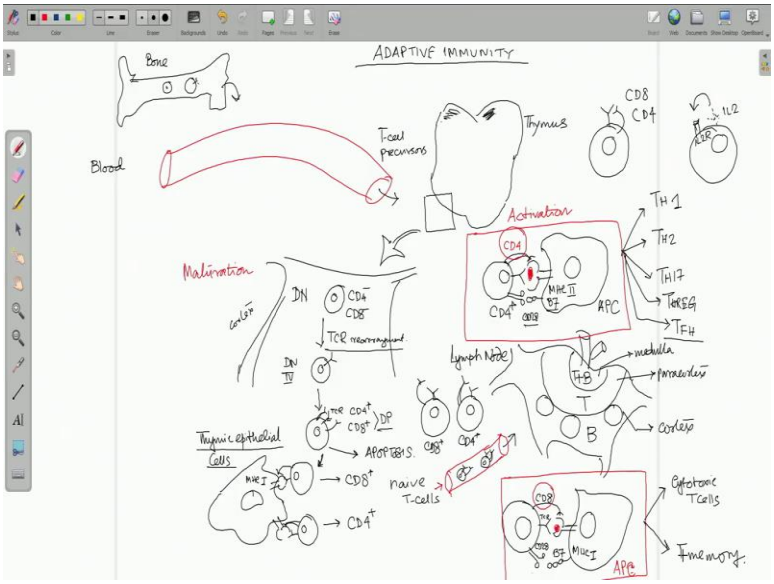

So, if we look into the picture from the last class or the last lecture we described the cell mediated immunity that is a T-cell mediated immunity and we left where in the primarily in this lymph node. We discussed how these T cells they get activated in the para cortex and then differentiates into different types of T cells among which a very important class is the T helper cells convert the CD4 plus T cells which differentiates into the T helper cells.

And then these T helper cells they help in the activation and the differentiation of the B cells which will now be producing the antibodies. So, let us see how this B cell actually gets activated and then it starts producing antibodies and it does many other functions like it also forms the memory the memory B cells. So, let us see what happens in the humoral branch community we try to get an overview of the humeral branch of immunity.

How it works and how things are connected so this whole the whole system of this immunes the whole immune system is kind of connected it is like a connection so between the adaptive and the innate system and again within the innate system within the adaptive system there is connection between the humoral and the cell mediated parts. So, it is all connected we cannot think of individual compartments in in immunology.

So we have to get our overall gross picture of whatever is happening. So, to get a gross picture starting from where we left in the last class; that is in the lymph node the events that are occurring in the lymph node. So, we discussed the events in the para in the para cortex where the T-cell activation occurs primarily.

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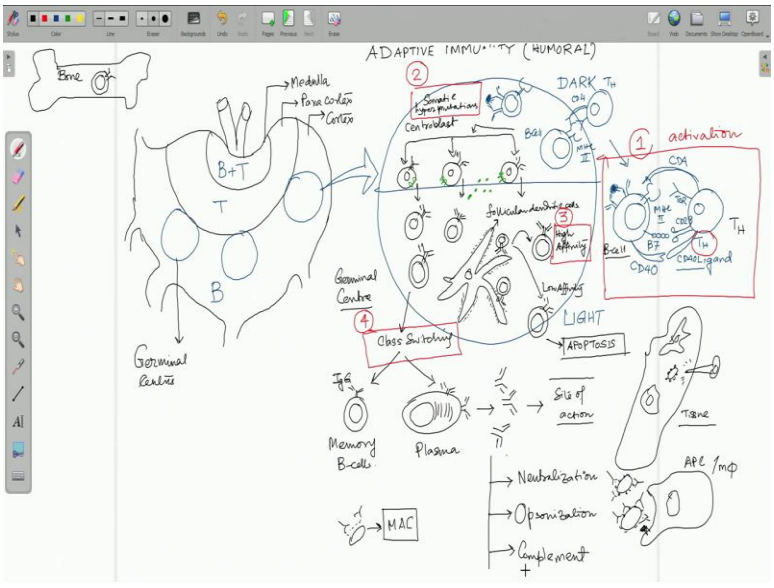

Now we move on to the lymph node again we look into the lymph node the cortex part. Now in the cortex part we described in our last class or I told in the last lecture that we have specialized centers which are known as the germinal centers. And these germinal centers are the sites of B

cell activation and differentiation well what happens in this germinal Center? And how the B cell a mature B cell how it starts to get activated and then produces different types of immunoglobulins and develops into a plasma cell or a memory cell memory B cell what happens there let us see into those events very quickly.

So as we know all that these B cells they mature in the bone marrow and then they come to this lymph node and where they encounter with the antigens. But only an encounter with the antigens will not lead to the activation of the B cells. There are other events that are required so again some co-stimulatory effects or events would occur that will lead to the activation of the B cell and many other events leading to finally differentiation of these B cells into the different producing different classes of antibodies or immunoglobulins.

Now what happens in these germinal centers? So now this Maxell b-cells they come to this lymph node and as I told that there are three distinct sections of the lymph node that is the medulla the para cortexs and the cortex. So, this medulla is primarily the site of the P and the T cells. so, it hosts both the B cells as well as the T cells. We can find the T cells only in the mostly in the para cortex and the B cells in the cortex region.

Now this B cells the main feature of these B cells is that the B cells are also antigen presenting cells. So, they can also bind to antigen they can also express MHC molecules on their surface and that is required for their activation. So, now antigens which are being presented by the antigen presenting cells or the antigens that are reaching this lymph node that has reached this lymph node they will confront with those B cells.

And these B cells which are mature B cells they on their surface are already producing are already expressing on their surface the IGM's. So, now they can bind these antigens but this binding is not sufficient for activation of the B cells. There are some other events which are required and co-stimulatory events that are required for activation of these B cells. Now what happens in this germinal center?

Let us magnify and have a closer look of the germinal center. So, let us say this is the germinal center. This germinal center can again have two zones we call them the dark zone and the light zone so this is the dark zone in the light zone. Inside the dark zone this B-cells this mature B cells expressing on this surface the immunoglobulins already the IGM. They interact with the antigens. Now this leads to cross-linking of this immunoglobulins and there is some signaling that occurs leading to the expression of class 2 MHC molecules on their surface.

Now they start expressing MHC's on their surface class 2 MHC is on their surface. And as soon as they can express the class 2 MHC molecules on their surface they can interact with the helper T cells the TH or the T helper cells. So, the T helper cells interacts with the T cell receptor and of course with the CD4 they interact with the B cell which expresses the MHC. The MHC class 2 on their surface and this CD4 interaction this is a T helper cell and this is a B cell. Let us look into this interaction more carefully because this interaction is very vital. This interaction is it is not just an image see to the T cell receptor interaction there are certern other other co stimulatory interactions that are also required.

One of them is, so let us see what exactly happens so let us say this is a B-cell expressing immunoglobulin bound to the antigen leading to the expression of the MHC class 2. And then you have a helper T cell the TH cell. Now this TH cell expresses that TCR or the T cell receptor the CD4 co-receptor. And of course we have seen in our last lecture that they also Express this CD28 and that can again interact with the B7 which is expressed on the mature B cells.

So, this B7 to CD28 interaction is also vital and then there is another interaction between that we call the CD40 L that is expressed on the surface of the T helper cells or the TH cells the CD40 L, L denotes for the ligand. So, it is the L is the ligand the CD40 ligand and the CD40 which is expressed on the surface of these B cells. So, you have at least 4 types of interactions which needs to be completed before a B-cell can be activated.

So then once these interactions are complete once these interactions are complete then there is activation of the B cells. So, what are the interactions let us just revise them. So, you have receptor this IGM binding to the antegen MHC class 2 expressed on the surface of the B cell

leading to its interaction with the T cell via the T cell receptor and the CD4 co-receptor. Along with CD28 to b7 interaction and CD4 T to CD40 ligand interaction so now this is our T helper cell and this is a B-cell.

So a B cell to a TH cell interaction is kind of established here. Now this once this interaction is completed then this B cell which is in still in the dark zone starts proliferating and what we get are basically the centro blasts we call them the centro blasts they are still expressing the on their surface the immunoglobulin molecules on their surface. So, these are the centro blasts what occurs immediately after this interactions?

Immediately after this interaction there are many other events occurring in the base and many signaling going on in the B cell among which one of the very vital events is the somatic hypermutation. You will read about these somatic hypermutation's, you will study about the somatic hypermutation maybe more in details. But what happens is there are there are mutations in the variable region of the heavy or the light chains.

And this that leads to a change in the affinity of this immunoglobulin molecules towards the antigen. So, the antibodies they develop into either high affinity or low affinity antibodies. So, those who having higher affinity for the antigen and some class of antibodies having less affinity for the antigen, so, naturally as we can understand from the logic that only those antibodies which has been which has developed a higher affinity for the antigen by the somatic hypermutation's they will sustain.

And those which have lower or lesser affinity for the antigen they will be destroyed. So, now this central blasts they start to proliferate and in between they have this somatic hypermutation and they start developing this type of antibodies their mutations in the variable variable regions and by that they start to become either high affinity or low affinity they express high affinity or low affinity two bodies. Now these central blasts also express something else they start to express on this surface specialized receptors that can bind to the chemokines.

I have described the chemokines in one of my previous lectures that the chemokines are the chemoattractant. So, they attract the cells from one site to another site. So, it is kind of a magnet to iron interaction. So, the chemicals are secreted from the light zone. So, now these cells which started to express the chemokines chemokine receptors binds to these chemokines and they migrates to the light zone. So, this that is the stimuli which leads to the migration of these cells from the dark zone to the light zone.

And now these are known as the centro sites. So, now these are the centro sites which comes to the light zone. Now they in the light zone we get some specialized cells which helps in the B cell activation and selection of these correct B cells. So, there are in every step in the immune system in every step if you see whether be it the T cell maturation or the T cell maturation the T cell activation in every step we have certain specialized cells and molecules which are helping in a process of selection.

So selecting the correct molecule selecting the correct cell so like for example the thymic epithelial cells which were helping in selection of the CD4 and the CD8 cells, say CD4 and CD8 plus cells. So, similarly there are specialized cells which are waiting in this light zone and are the follicular dendritic cells and the T follicular helper cells. So, now this follicular helper cells and the follicular dendritic cells they are present in the;

So the molecular dendritic cells have this kind of a branched structure and these cells they are waiting inside the light zone and that they have these antibodies bound on this. Now what happens is an affinity selection. So, now these central sites which were the centro blast previously after the somatic hypermutation and expression of the cytokine chemokine receptors on their surface they have migrated to the light zone they are now known as the centro sites.

Now these centro sites they start interacting with these antigens. So, they start to compete for this antigen so there basically is a competition. So, now they this these centro sites there are many of these centro sites. And some of them are having high affinity some of them are having low affinity. So, they will now start to compete the high affinities the high affinity the centro sites

which are expressing high affinity antibodies on their surface they will start competing with the centro sites which has low affinity antibodies.

So now there will be an affinity selection affinity based selection. And so depending on their affinity for their antibodies so high affinity selection occurs and only those B cells which has antibodies expressing antibodies having high affinity for the antigen will be selected. And so these are the high affinity selection and those with low affinity that means those which could not compete with the high affinity cells to bind to the antigens they will be excluded and they will finally die by apoptosis.

So now they are excluded, as I told in all this all over the immune system we get this kind of selection processes where the better or the best is being selected and those which are not good they are rejected. And those cells they die by some process of apoptosis or programmed cell death. So, those which are selected for this high affinity antibodies they will now undergo a phenomenon of class switching. So, now they will start class switching and finally they will either produce the memory B cells or the plasma B-cells.

So these are they will start producing the antibodies they have these plasma B cells are the cells which are finally the effector cells so they will produce the antibodies. Now these antibodies will now go to the site of action that is the site of infection on the site of inflammation and they do their respective jobs. So, now overall what we have seen what happens inside the germinal center. So, this is the germinal center so what happens inside the germinal center at least 3 major events are occurring.

So we have somatic hyper mutations so at least 3 different events are occurring one is the somatic hypermutation okay. So, let us start from this region. So, here the first thing is the interaction of the back the B cells or the B lymphocytes with the T helper cells leading to activation. So, we call this the activation of the B cells. so, now there are at least three different four different classes of interactions including the co stimulatory interactions.

So you have the class 2 MHC interacting with the T cells the T cell receptor the CD4 plus cells. So, CD4 co-receptor and the T cell receptor with the class 2 MHC and on with that you have the V7 - CD28 interaction you have CD40 to CD40 L ligand interaction. When these interactions are completed the B cell is activated. So, there are some signaling inside the cell and leading to proliferation of the cells of the centro blasts and in the meantime there is somatic hypermutation.

So this is the second stage, the third stage is then they start to migrate. So, its migration of these cells to the light zone from the dark zone this cell starts to migrate to the light zone where you have the follicular dendritic cells. So, we call them follicular dendritic cells. So, you have the follicular dendritic cells this follicular dendritic cells then helps in affinity selection. So, only the high affinity antibody producing cells will be selected.

So the B-cells are selected for the high affinity antibodies and those after this affinity selection by these follicular dendritic cells and the TFH cells. Then you have the fourth and the final event that is the class switching. So, this is number 3, so if you look into this whole event from starting from here the one is activation this deep T helper cell mediated activation in the dark zone then you have the somatic hypermutation's that is also occurring in the dark zone.

Then the B-cell starts to proliferate and strong starts to express on their surface the chemokine receptors then they are attracted towards the light zone. They move to the light zone there is migration inside the light zone you have this follicular dendritic cells waiting for the T cells to come or the central sites to come. So, now they are the centro sites and this centro sites then which express the high affinity antibodies they are selected by the follicular dendritic cells.

Now those which are selected for the high affinity antibodies they will now undergo class switching and then they will produce either the memory B-cells which primarily have IgG expressing IgG and then you have the plasma cells which are producing different types of immunoglobulins and they will secrete the antibodies. And these antibodies will now be secreted and they will go to the site of action.

So now begin if you recall from our one of our initial classes then we again go back to that tissue portion where there was a tissue invasion and there were pathogens getting in and different types of cells. So, if we again go back to this tissue. So, now these antibodies which have been produced from the plasma cell they will go to the site of action or the site of inflammation and they usually mediates three different functions.

What are the functions these antibodies do? So, they can either do neutralization that means they can directly interact with the antigens on the surface of the pathogen. So, they can neutralize the pathogen directly. They can also perform opsonization so that means assist the antigen presenting cells in engulfing. For example the macrophages they can assist the antigen-presenting cell or the macrophages for example to engulf or phagocytose the pathogen or they can do a third thing that is complement activation.

So they can also lead to complement activation and that can lead to so binding to the surface of the pathogen and leading to the complement activation and kill the cells by formation of what is called a membrane attack complex what we call a membrane attack complex leading to holes on the surface of the pathogen and leading to membrane attack complex and killing the cells, so, these antibodies. So, if we look into the entire picture again very quickly so in the lymph node we have these three regions the medulla the para cortex and the cortex.

The cortex portion primarily has this germinal center. The germinal center if we look into the germinal center is the center for the map for the activation and differentiation of the B-cells. The B-cells they primarily interacts with the T helper cells the TH cells. We discussed about how the TH cells are produced or activation of the T cells in our last lecture. So, now this T helper cells by virtue of these interactions and some co stimulatory interactions it leads to activation of the B cells.

So this is the first step the activation of the B cells which occurs in the dark zone assisted by the T helper cell then it leads to somatic hypermutation’s' in the B cell leading to then leading to the proliferation of the B cell. So, you have different centro blasts this B cells then will enter into the

light zone migrates into the light zone where it is selected for the high affinity antibodies the B cells that are producing the high affinity antibodies.

And then there is high affinity the B cells producing high affinity antibodies will be selected those B cells which produce low affinity antibodies will be rejected. High affinity antibody producing B cells will then undergo class switching. And finally it will produce either the memory B-cells or the plasma B-cells. Plasma B cells are ultimately the secretory cells of this, secrets the antibodies. And these antibodies can then perform several functions at the site of action or they go to the site of inflammation of the site of action.

And they perform several functions like neutralization, opsonization or complement activation. Neutralization directly neutralizing the pathogen binding to the pathogen apsonization they assist the macrophages or the antigen presenting cells to engulf the pathogen and also they can activate the complement system. So, they can activate the complement system leading to a cascade of events we will study about the complement system more in details in our upcoming lectures.

So that is all for today with the adaptive immune system the primarily with the humoral immunity we will continue with our discussion in our next class. So, thank you very much and that is all for today.