Immunology
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Lecture No -39
B - Cell Activation and Differentiation

So welcome back and we will keep continue our discussion about the B cell activation and differentiation inside the lymph node and in the germinal centers of the lymph node so what are the events in the germinal center of the lymph node happening.

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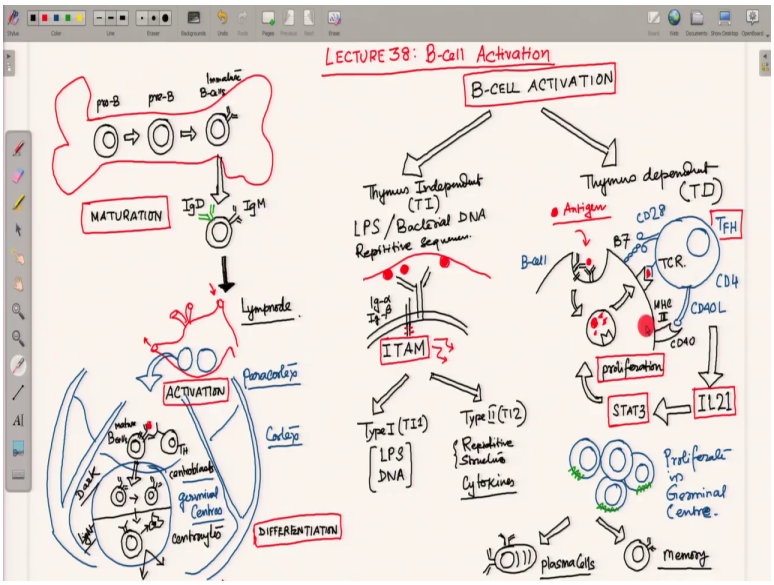

So as we discussed in our last class if you look into the picture from our last class we have discussed about the activation of the B cell primarily the thymus dependent activation we have discussed much more in details. So when there is a thymus dependent activation and this process is primarily meant for example the protein antigens the proteins the protein antigens that are processed antigens. So these protein antigens they actually elicit this kind of a response there's a thymus dependent response.

And a thymus dependent activation as we have seen that it leads to proliferation of the B cell now the B cell we call it the activated B cell so here after this B cell here. This B cell here is an now it is an activated B cell because it has got signals from the T follicular helper cell the

follicular helper T cell it has received the signals force for its activation and it is now kind of ready to develop into a specific B cell producing a specific antibody type against the antigen that it has captured.

So it has captured the antigen presented it by the MHC class 2 to r T helper cell and the T helper cell helps it to activate and now it this B cell starts to proliferate. Now it starts to increase in population. So now it proliferates we're in the germinal center now this what happens in the germinal center. Let us look quickly in the next part.

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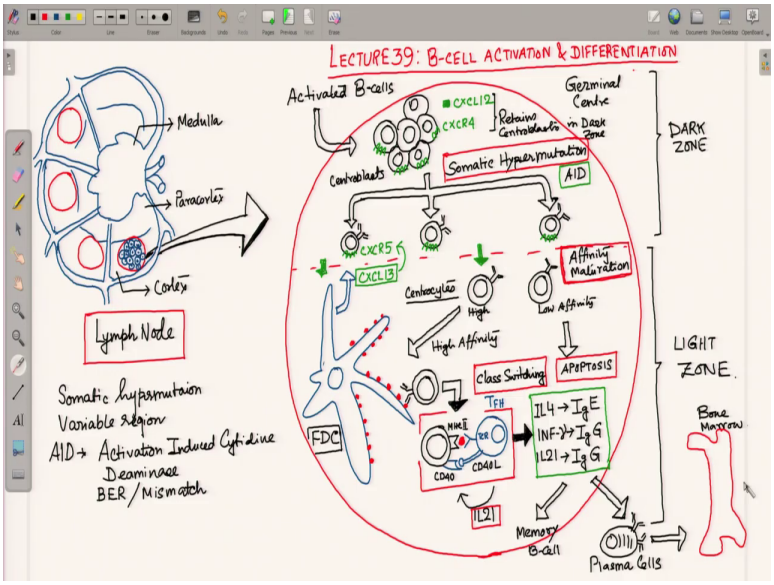

So now this is the lymph node this is the lymph node let us say so the lymph node I told you previously as well so the lymph node has some specific regions the medulla, the para cortex and the cortex. So there are at least three specific regions in the lymph node the medulla the para cortex and the cortex and within the cortex you have this kind of follicular structures these are the germinal centers.

Now this germinal centers contains this B cells this proliferating B cells. So once the B cell is activated so what we what we got from our last lecture this activated B cells they will now enter into this terminal center and then starts to proliferate here in the germinal Center. So they now increasing number undergo mitosis and they will start to proliferates increasing numbers.

And at this stage I told you they will start expressing certain chemokine receptors and these are the CXCR4 receptors and these receptors can recognize a specific chemokine which is the CXCL 12 which is secreted from the stromal cells. And this helps this interaction of this chemokine to the chemokine receptor helps to retain the; retains this interaction here is primarily required for retention of these central blasts retains the central blasts in the dark zone.

So this is the dark zone this part of the germinal center we call it the dark zone. And this part where the final differentiation occurs we call it the light zone. Now what happens in this dark zone this cell which has started proliferating these are called the central blasts. Now these central blasts they will undergo a specific process known as the somatic hypermutations. So they will undergo somatic hypermutations and they will produce different central blasts with different affinities.

Affinities for what so does the B cell they will develop different B cell receptors or the antibodies on the surface which has different affinities for the antigen. So these central blasts have this kind of they express these antibodies on the surface which will now have different affinities for the antigen. So they have been activated by an antigen that we have seen in our previous lecture in the previous case. So now they are activated these B cells are activated and these Centro blasts what we call the central blasts now will undergo what is called somatic hypermutation it is called somatic hyper somatic hypermutation.

That is the somatic hypermutation and in during this process of somatic hypermutation they start to develop mutations. So there are mutations in the variable region in this somatic hypermutation process. So the somatic hypermutation process they will start to develop mutations in the variable region mutations occurs in the variable region. So there are point mutations in the variable region and these point mutations are primarily carried out by an enzyme called the AID.

So AID is basically activation induced Cytedine Deaminase it is the activation induced cytedine deaminase. So this activation induced cytedine deaminase that is lead that leads to deamination and then there is a kind of DNA repair processes like base excision repair or mismatch repair there are different processes of DNA repair processes that are being activated after this AID. So

we have the AID now these central blasts here they will start expression of this AID they will express this AID enzyme.

So this activation induced cytedine deaminase is being expressed in the central blasts. Now this central PLAs they will start expressing AID and will acquire mutations in the valuable region of the heavy and the light chains. So how they will have mutations in the variable regions and they will have this each of these central blasts will now express B cell receptors on the surface which have different affinities for different for the same antigen.

So they have different affinities for the same antigen so some of them will now carry high mutation high affinity or low affinity. So this hyper mutation is primarily to increase the affinity of the antibodies towards the antigen. So now these central blasts which are now prepared to enter the light zone so these central blasts are now kind of prepared to enter the light zone they will now start to express on their surface and the class of chemokine receptors which is the CXCR 5.

Now what is the role of the CXCR 5 let us see. So now what happens now this these these central blasts in the dark zone they have proliferated under and somatic hypermutation point mutations being introduced in their in the variable regions of their heavy and light chains. So now they have differentiated into now they're different yet they are not same. So each of the central blasters may be some central blast for example this one let us say here this has very high affinity for the antigen.

The receptor has a very high affinity for the antigen and; let us say this one does not have a high affinity so its affinity has reduced towards the antigen. So they have either a good mutation or a bad mutation. So if it is a bad mutation that means a low affinity mutation it is the receptors affinity towards the antigen is reduced if it has a good mutation then its affinity towards the antigen has increased or improved affinity.

So there can be two situations it has bad or low affinity or it has good or improved affinity. Now these cells for getting selected for their now this cells has to be selected because they have to be

selected for their affinity. So which one has higher affinity which one has more affinity so that has to be selected only those cells will be selected. And those cells which out of this somatic hypermutation we just developed lower affinity whose affinities has reduced will now be rejected.

Now this cells has to come into the light zone, so what is there in the light zone? In the light zone we find specialized cells like the follicular dendritic cells they have this kind of the structure and this dendritic cells. They are the primary producers of a class of cytokines that is the chemokines basically chemokines there is the CXCL 13. Now this CXCL 13 is a ligand for this CXCR 5 receptor. So this CXCL 5 binds to this CX ER 5 binds to the CXCL 13 and they are attracted towards the they are kind of attracted towards the light zone.

So now they start moving into the light zone in this these central blasts they start moving to the lights zone now. Now once they come to the light zone they are the central sites we call them the central sites and these central sites they as I told they can have a high affinity mutation or they can have a low affinity mutation and as for that mutation they will have different fates. So now they can have two different rates let us say this one has a high affinity mutation and this one has a low affinity mutation.

So what will happen now this one which has a lower affinity mutation that means it now it has less affinity towards the antigen will undergo apoptosis. And there are specialized macrophages in this region of the light zone in this in the germinal center there are a specialized group of macrophages who will engulf them this apoptosis cells will be engulfed by a specialized class of macrophages and they will die.

So they will not exist they will be excluded from the system this low affinity mutation cells the cells which has low affinity mutations on their B cell receptors. Those with the high affinity receptors will now be helped by these follicular dendritic cells. Now what does this follicular dendritic cells do? So these follicular dendritic cells they kind of adheres these antigens on their surface. So they now display these antigens on their surface these antigens are present on this on these follicles on the surface of this dendritic cells this is that this is the antigen.

So now these B cells these P cells of the central sites these are the central sites this central site which has a high affinity. Now since it has a high affinity it will try to capture one of these antigens by the B cell receptor. So a B cell will now interact by this B cell receptor with this antigen which is being adherent to the surface of the follicular dendritic cell. So this is the follicular dendritic cell we also call them the FDC or the follicular dendritic cell.

This follicular dendritic cell is present inside the germinal Center inside the light zone of the terminal Center and they carry this antigen. So they carry the antigens on the surface and this cell these B cells the activated B cells will has already a very high affinity mutation that means. They have hardened they now have developed higher affinity for the antigens they will interact with the antigens that are captured by the sketcher on the surface of the follicular dendritic cells.

So now they will immediately get hold of this anti antigen by these B cell receptors and again there is another interaction what is that interaction. So now they will interact with the they will now interact with the T helper cells and which class of T helper cells they will interact with the T follicular helper cells again. So there are follicular helper cells that are present so this is a B cell now again these B cells which has interacted with which has the high affinity and has interacted with an antigen with a very high affinity they will now again internalized.

So they will now again internalize the antigen process it and again present it on the surface by MHC class 2. So then again there is an MHC class 2 interaction so they will now present the antigen on the surface by MHC class 2 and again there are follicular helper T helper TFH cells that are present here the T follicular helper cells the TFH or the T follicular helper cells which are present in the light zone of the germinal Center they will interact by the T cell receptors.

So with the TCR, so there will be an interaction and again there will be interaction of the CD40 ligand to the CD4 T so again our CD40 to CD40 L interaction the CD40L ligand which is expressed on the TFH cell will again interact with the CD40 and this interaction here is very essential. So this interaction here is very essential for the next step that is the class switching. So let us let us look at this part again our quickly.

So there is somatic hypermutation leading to increase or decreases in the affinity of the B cell receptors expressed on the surface towards the antigen remember. Then this D cells the central blasts they will start expressing CXCR 5 is has a high affinity towards CXCL7 this is a chemokine. A chemokine called the CXCL 7 is produced from the follicular dendritic cells the FTC's and that will pull kind of that will bring the due to the attraction they will this these central blasts will now move to the light zone and now they are called the central sites.

Now these central sites either can have a high affinity or a low affinity now then there it needs a selection. So then there is a affinity maturation or an affinity selection process and this process is called affinity maturation or affinity selection. So now depending on its affinity towards the antigen it will be selected. So, either if it has a low affinity that affinity or a low affinity it will undergoes apoptosis. If it has a high affinity it will be exposed to the antigens that are presented by or that are captured by the follicular dendritic cells that are present here.

Now these follicular dendritic cells which has captured antigen on the surface will present this antigen to this central site or the B cell or the high affinity receptor producing B cell and this high affinity receptors can now bind with very high affinity to this antigen. And this binding ensures that the pre cell is now this central site is now selected for a high affinity. So this process is known as affinity maturation or affinity selection.

So now the high affinity B cells or the B cells having very high affinity towards the antigen will be selected out of the whole population. It is a very small population it is not a very big population. So many of the cells they die by apoptosis and once they die these apoptotic cells are also phagocytosed by a class of Macrophages that are present here. So they will be killed basically they will be rejected those that population of the P cell is rejected.

Every so in this whole process of this immune system there are very careful checkpoints everywhere so it is not like it is the processes are very random. So there are very well-designed checkpoints where it is being kind of checked or it is there. There are quality control checks so there is a mutation there will be a quality control check at the B cell receptor with the high

affinity will pass through with the low affinity will not pass through there will be dying they will be rejected and that population will not continue to exist.

So the high affinity population will be selected and by a process called affinity maturation with the help of the follicular dendritic cells. And of course the T follicle will help ourselves the TFH cells which are also present in this region. Now the TFH cells as we remember from our last lecture the TF itself one of the major components that is being secreted by these TFH cells are interleukin 21 remember the IL21.

So now this TFH cells will start to produce IL 21 as well interleukin IL 21 specialized interleukin or specialized cytokine that is been produced from this TFH cells the follicular helper cells. So this IL 21 will be produced and that IL 21 is primarily required for the survival and the proliferation of the B cells the mature B cells are activated B cells as well as they will start to produce a whole subset of cytokines.

There will be production of a whole set of cytokines and that will actually govern the process called the class switching. So now these antibodies will start to class switch. So they will pray induced glass switch to different, different isotopes. So now this antibodies so far we were still having this IgM's on the surface then the main B cell receptors are comprised of these IgM molecules. Now they will start to switch so there will be isotype switching there will class switching.

And then they will start to produce different types of antibodies now they will start producing different types of antibodies like IgG, IgE, so for example and this is being governed by the types of different cytokines that are being produced from them. So for example they will produce interleukin 4 you will you will get a more detailed idea about this. So different cytokines they will prefer preferentially they will induce the switching to different types of eyes so isotypes for example you will have IL4 interleukin 4 when we will study about the cytokines more in details.

We will see the role of the different cytokines the different interleukins. So for the time being we are let us know that this interleukin 4 is mainly responsible for switching to IgE that is

immunoglobulin E which is responsible for mainly the hypersensitivity reactions allergic reactions you will have IgE you can have interferon INF gamma which mainly switches it to IgG you can also have IL 21 which is also responsible for IgG.

So there are many other cytokines to name I am only naming a very few of them I am not naming all of them so this is a very, very small class of names that I have mentioned here we will get to know this when we will learn the cytokines more in details for the timing I am not discussing them in very details. So but at least you know that once there is this kind of an interaction. So once they it is affinity selection process is done affinity maturation process is done that is the B cell or the central site is selected for the high affinity mutation.

Those high affinity cells will now interact with the T follicular helper cells and this CD40, CD40 ligand interaction will again occur MHC class 2 will present antigen on the surface and will interact with the TCR with the PLT follicular helper cell leading to secretion of different cytokines. These cytokines will basically help in the class switching to different isotypes. Now this that will done now they will class switch and depending on the type of cytokine that is being secreted or the type of cytokine that is available they will switch into different antibody types.

So different isotypes, so now then this process we call it as class switching so this is the class switching. We are not going into the detail mechanism of the class switching at this moment but this cytokines as you know they lead to certain activation of certain transcription factors and that can actually lead to the final effect. So the cytokines mediate their action by mostly by the induction of or activation of certain transcription factors downstream.

We will read about these more in details when we study the cytokines in details. Now after the class switching phenomenon now the last step is finally these cells will finally become either they will become a plasma cell so either they will develop into a plasma cell or into a memory B cell. So it can become a memory B cell or into a plasma cell. So that will produce the antibodies the soluble antibodies. So now these antibodies will now be the mediators actually so this is the plasma cell.

And this is the plasma cells and finally these plasma cells will again they will migrate to the bone marrow. So these plasma cells will now finally again migrate to the bone marrow and from there they will start secreting the antibodies. So if you look into this whole picture actually at least in this part. So we have at least a few distinct steps that are occurring in the whole process of activation and the differentiation.

So after the B cells are being activated these B cells they will enter into the germinal Center into the dark zone in the dark zone this central blast there the centre blasts and this central blasts they will start proliferating. So this is a process of proliferation and in this proliferation process they will start to have they will start expressing a particular mm enzyme known as the activation induced cytosine deaminase which leads to point mutations.

That actually introduces point mutations in the valuable regions and leading to a process called somatic hypermutation this somatic hypermutation. Now this somatic hypermutation introduces point mutations in the variable region leading to an increase or decrease in the affinity towards the antigen. Now this central blasts will then cross the dark zone they will enter into the from the dark zone they will enter into the light zone by the action of a chemokine.

Once they come to this light zone these are the central sites now this central sites will start interacting with the antigens that are captured on the surface of these follicular dendritic cells. Follicular dendritic cells capture these antigens on the surface and present it to the central sites central sites interact with the B cell receptor the high affinity ones will interact with the B cell receptor low affinity ones will be rejected and will undergo apoptosis.

Now once they are selected for the high affinity then this once they can they can recognize the antigens by their high affinity receptors they will internalize again the antigen and will present it on the surface by class 2 MHC molecules class 2 MHC molecules that will interact with our T cell receptors and the T follicular helper cells which are also present in the light zone. Now then there is CD40 CD40 L interaction offering and the TCR interaction and that leads to secretion of certain specialized in the molecules or the specialized cytokines.

This cytokines includes interleukin 21 as we can as we know that that typically interleukin 21 is secreted from the TFH cells and that is required for the survival as well as the proliferation of this of the central sites and as well they will produce certain specialized site cytokines like interleukin 4 INF gamma interleukin 21 which leads to the class switching phenomenon. So switching the class switching to different isotypes and now they will produce different and antibodies will now be produced they will switch to different antibodies like IgE IgG.

And then this central site so these B cells will now differentiate into a memory B cell or into a plasma cell and finally this plasma cell will again migrate back to the bone marrow. So where we started from so it goes back to the bone marrow and it starts secreting the antibodies which mediates all these functions. So we got to know about in this in this lecture we got to know about the B cell activation and differentiation how the B cell activation occurs how it differentiates into different cell types different and finally its class switches into different isotypes produces different types of antibodies.

And you can go through all the details in the book in the books that we have referred to you will be finding more details on the different steps I did not go into the very details of the different steps because that is not really possible in this short period of time. It is very difficult because there are a lot of molecular phenomenon's that are involved in these somatic hypermutations or the class switching phenomenon.

So those they many molecular events that are occurring so it is very difficult to cover in this short span of time but I try to summarize the whole events that are occurring within the germinal Center leading to the activation and the differentiation of the B cells. So that is all from the B cell maturation and development and activation part and I hope you liked it, thank you.