Immunology
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Lecture No -38
B - Cell Activation

So welcome back and welcome back to our lectures on even ology and we keep continuing talking about the B-cell developments. So for the last two lectures we were discussing mostly about the maturation of the B-cells. So how the B-cells they become from the Pro B-cells there is a progenitor B cells that become the pre be sales as a precursors and then finally they become immature B-cells. In our last lecture we have discussed the the genetic events that are occurring particularly the the DJ recombination that is occurring in the different steps or in the different stages of the B cell maturation within the bone marrow.

So all these stages they occur in the bone marrow but as we know or we have already discussed in our previous lectures that the B cell activation occurs in the lymphoid organ for in the lymph node. For example and the activation and its differentiation so then it differentiates and then it class which is the antibody class switching occurs all these things these events actually occur in the which falls under the whole humoral response.

So this whole humoral response which involves the activation and the differentiation proliferation and differentiation of the B cells this entire thing occurs in the lymph node.

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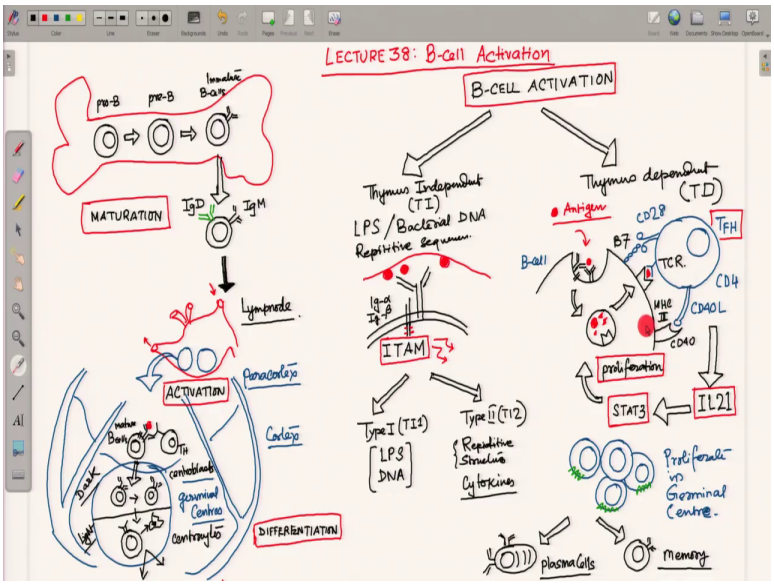

So now what happens what is the fate of a mature B cell as we discussed in the last lecture that the immature cells once they leave the bone marrow they have that their main fate their fate is determined by their interaction with the different self antigens. That means they interact with the antigens of the own system the cell surface antigens and other soluble antigens and then they undergo different fates. So only a very small percentage of this be cells that are actually produced from the bone marrow are selected for the later stages.

So they they pass the initial screening and they are allowed to go to the lymph node and the periphery and then they go to the lymph node and then they are allowed to interact with the antigens and then initiate the humoral response. Now the thing is what exactly happens because these cells which enter the lymph node they are called the resting B-cells. So they are in the resting situation in the g0 phase let us say.

So what happens inside the lymph node so we know that these cells they enters the lymph node. So they will enter the lymph node by the afferent vessels and go out by the efferent vessels in inside the lymph node as I probably already told in one of my initial lectures we have this kind of germinal centers. And these germinal centers are primarily they are located in the cortex region of the lymph node.

So the lymph node if you have a kind of a closer look the structure is some little bit like this and inside you have you have the medulla you have the para cortex which is the primary the para cortex is a primary region for the development of the T lymphocytes with the T activation and differentiation of the T cells or the T lymphocytes. And the cortex region is mainly meant for the B-cells. And inside you have this kind of centers which we call the germinal centers.

And these germinal centers are actually the centres of the development the proliferation and the differentiation of the B-cells. So these B-cells which enters into the cortex region they undergo activation. So now these cells they are expressing on their surface the B-cell receptor with the IgM and they with the help of some antigen with the help of the antigen and the TH cells or the T helper cells so there are T helper cells in the para cortex region which actually interacts with their T-cell receptors and they send some signaling this match.you these are mature B cells.

So these are mature B cells which are actually in resting state and these mature B cells then they get activated. So they are activated by this kind of T helper cells they get activated and they enter into the germinal Center and the germinal Center has two regions one we call it the dark zone and the other one we call the light zone. So these B cells the mature activated B-cells then enters into the germinal Center into the dark zone.

And inside the dark zone they undergo proliferation they start to proliferate and then there are somatic hypermutation and then these cells enter into the light zone. I am giving a very very brief overview we will discuss all these events in much more details as we proceed with our lecture. So these these are called the central blasts in the dark zone and when they enter into the light zone they are the central sites.

And this central sites they are then selected for affinity mutation so after thus because there is somatic hypermutation in the dark zone then there will be selected for affinity maturation. So there will the high affinity cells will survive what do you mean by high affinity cells. So the high affinity cells primarily means those cells which has higher affinity for the antigen. So the the the antibodies expressed on the surface they undergo mutations and these mutations render them either less reactive or more reactive towards an antigen.

So that means their affinity either decreases or increases so if the affinity decreases those cells will undergo apoptosis. So those cells will be killed they will die and those cells which survive that means those cells which has higher affinity towards the antigen those B cells whose B-cell receptors they have higher affinity for the antigens they will survive. And now they will undergo a specific process called class switching.

So, now they will switch classes and so an antibody class switching and once they undergo this antibody class switching they will now differentiate into different the plasma cells and the memory B-cells. These plasma cells are mainly the secretroy of the antibody so this secrete the antibody and memory B-cells they will have the IgG molecule and they will have the immunological memory.

So then there differentiates into the ayah the memory cells and the plasma cells. S,o there will differentiate into memory and the plasma. So let us see what are the; so this in this whole flowchart word what I am showing here so there is there are two distinct processes one one part I am showing this in this part we call this the activation. This is the activation part and this part is the differentiation. So this part is the differentiation part of the B-cells in this part here.

We call it the maturation to be cell maturation which we have already discussed. So we can see here in this in this flowchart that the B cell undergoes at least three distinct processes. One is the maturation then the activation and finally the differentiation into the different antibody producing B cells. So now we have discussed about the maturation in our last lectures in the last two lectures we have discussed how the B cells they maturate or develop in the bone marrow.

And they leave the bone marrow then they go to the peripheral organs. Now goes to the lymph node for example and there they will start to get activated so the lymph node. So now look and let us look into the process of the B cell activation in a bit more. So what happens or what are the signals that are actually responsible for activation of the B cells. So before we start there the first thing we need to mention is that a B cell can be activated by two distinct processes.

One is a thymus dependent process another is a thymus independent process now what is the thymus dependent thymus independent process. So basically thymus dependent process is a process in which the B cell gets activated by a direct interaction with a T cell or a T helper cell. So with a physical interaction of the T helper cell whereas in case of a thymus independent activation it does not require a direct contact with our T helper cell.

It does not require any physical involvement or any physical contact with the T-helper cell there is no physical contact with the T-helper cells. So that is a thymus independent activation, so if we classify the two different pathways the thymus or the two different ways of activation then of course we come across thymus independent or the TI we also call it sometimes the TI process and a thymus dependent.

So it is a thymus dependent process which is also called the TD process. Now what we will discuss about the thymus dependent and the thymus independent processes separately as we can understand the thymus dependent process relies on its interaction with the with the T helper cells mostly. So, the thymus independent process is primarily initiated or it is actually works in case of certain kinds of antigens for example small antigens like the lipopolysaccharides LPS or in case of bacterial DNA or as well as in case of some repetitive sequences.

Like some change some polysaccharides some polysaccharide chains present on the surface cell on the cell surfaces. So these are basically activated directly they are direct activators so they can directly activate the B cells. Now this activation process occurs usually through the B cell receptor and what does the B cell receptor look like? So the B cell receptor usually comprised of the IgM molecule linked to the two Ig alpha Ig beta, Ig alpha and Ig beta which are the signal transducing parts.

And so if there is an small antigen like this binding small antigen like a leap of lipopolysaccharide or a bacterial DNA for example they can bind to this B cell receptor and for example present on the surface of a bacteria if this is a bacterial surface and you have this kind of small antigens which can activate the B cell. They can activate the B cell directly via or using

these receptors. So these signal transduction parts of the receptor which is the Ig alpha and the Ig beta they are responsible for this kind of signal transduction.

And they transduce the signal by a specialized domain in the cytosolic part of this Ig alpha an Ig beta which are known as the immuno receptor tyrosine the immuno receptor tyrosine based activation motives or the items. So these items are present in these regions which basically transduce the signal and leads to activation proliferation of the B cells which then produce the antibodies against these antigens.

Now this process can again this Primus independent process can again be divided into two types of timers independent processes. So one is the type 1 thymus independent process the other is the type 2 thymus independent process. So this are basically so this is also called the TI 1 and there is a type 2 process which is the TI 2. So and basically these two types are classified on the basis of the type of antigen the B cell meets width.

And type 1 antigens are usually the small antigens like the LPS for example the lipopolysaccharides the bacterial DNA for example these are actually the small antigens that fall under the type 1 thymus independent activation of the B cell. And type 2 are mostly these are the repetitive structures this includes the repetitive structures and another major difference is that in case of type 2 there is no requirement of any help from any T cells.

In case of type 2 it is it requires so type 1 does not require any help or any indirect help from any T cells or any other cells of the immune system. In case of type 2 it requires help from other T cells as well as to some extent from the dendritic cells in a way they do not interact physically with the T cells but they require certain cytokines. So there is requirement of cytokines so they require cytokines to be present in the vicinity for the activation process.

So these two activation processes type 1 and type 2 activation processes these two processes basically the TI 1 and TI 2 falls under the thymus independent. And this primarily depends on the type of the antigens. So there are two types of the antigens are classified and from there they

are called the type 1 thymus independent process or the type 2 TI independent process and they primarily depends on the type of antigen that is interacting with the B cell receptors.

Now we come to the thymus dependent process this is a much more elaborate process and this involves interaction of a mature B cell with the T helper cells. And the specific type of T helper cells that are required for this thymus dependent process are the t follicular helper cells. If you remember about the T T helper cell subsets we had discussed previously then I will remember we have the effector cells the TH1 TH2 TH17.

So these are the effector T cells and also we have a specific class of helper cells that we discussed about or we told about are the t follicular helper cells and these follicular helper cells are present in the germinal center. So they are present in the germinal center in and they help in the in the cortex in the germinal center they are present everywhere and they are actually required for activation as well as differentiation of the B cell.

So we will look into the process of the activation what exactly happens during the activation of the B cells. So let us say this is our B cell this is a diesel end this is a T-cell so this is a T follicular helper cell T F H and this is the B cell a mature B cell. So as we know that a mature B cell expresses the IgM molecule IgM the receptor on the surface and with the help of this IgM molecules on the surface it can bind to the antigen.

And this antigen binding can lead to receptor cross-linking so this normal if the B cell is in the resting stage the receptors are also in the resting stage. Once there is an antigen coming in so this is let us say this is the antigen once it meets an antigen what happens it binds to the B cell receptor. Now and as well as this I this I G alpha and the Ig beta subunits are also involved you have the IgM which can bind to this and this leads to the internalization.

So now this antigen is internalized you know that these cells can be cells can also phagocytose they can also internalize antigens. So they will now internalize the antigens. So the antigen is internalized inside and is degraded and this antigen is now presented by the B cell on the surface

of the pizzelle it is presented by the class 2 MHC, the MHC 2 MHC class 2 it presents the antigen on the surface by the class 2 MHC.

And this is recognized by the by the T-cell receptors. So the MHC class ii after in tonight after internalization of this antigen by the B cell that is internalized and then presented on the surface by class two MHC molecules. Once it is presented on the surface where the class two MHC molecules the T cells the T cell the T follicular helper cells which are basically the CD4 cells having the city for Co receptors they can now recognize by their T cell receptors they bind to the MHC class 2 molecule.

And then there are additional interactions what are the original interactions we know a little bit because we have learned about it earlier as well. So they express this T helper cells they express on their surface the CD28 and the B cells they have on their surface the B7 so there is B7 to CD28 interaction as well as there is CD40 ligand which is expressed on the surface of the T cells so we have the CD40 ligand.

And that binds to the CD4 T which is expressed on the surface so this is the CD4 T binding to the CD40 ligand or the CD4 TL so the CD40 ligand is the CD40 L is expressed on the surface of the t follicular helper cells. So that CD40L binds to the CD40 so now once these interactions are complete that is when this MHC class 2 molecule expressing this antigen presenting this antigen on the surface with the class 2 MHC molecules on the surface of the B cells that interacts with our TCR with a T-cell receptor then there are more interactions more supporting interactions like the B cell, B7 2 CD28 interaction CD28 present on the T cells.

So this is the TF8 cell remember this is the T follicular help ourselves which on their surface has the CD28 and that interacts with the b7 which has a CD40 ligand that interacts with the CD4 TS the CD40 is present on the surface of the B cell and that leads to once these interactions are complete there is signaling which leads to the release of cytokine specialized cytokine which is the interleukin 21 we will discuss about the cytokines later on.

I told you in one of my previous lectures that cytokines are one of the very very important effector molecules they are one of the very very important effector molecules of the immune system that actually mediates all types of functions. So IL 21 is one of the; such molecules and this IL 21 has many many roles in the B cell activation and differentiation. So, one of the primary roles of this Syal 20 is that it activates the transcription factor stat 3.

So there is activation of the transcription factor the stat 3 you probably have learned about the stat transcription factors that is a Jak-Stat pathway where you have the Jak Kinase and the stat we will also discuss about the Jak Stat pathway more in details when we will be talking about the cytokines particularly. So the stat 3 is then activated so there is activation of the transcription factor stag 3 by apprent induction of the interleukin 21.

So interleukin 21 comes when there is activation of this these thymus dependent activation occurs then there is IL 21 and then there is stat3. And what the stats we do is eat now regulates the gene expression. So it now enhances gene expression of those genes that are responsible for enhancing the B cell proliferation so now this will to the enhancement of or controller regulation of the gene expression and that will lead to proliferation proliferation of the B-cells.

So now the B-cells which we're actually in the resting state will undergo proliferation will undergo mitosis so now they will start to proliferate and they will produce many of this B-cells that is the central blasts and we will discuss about the central blasts and the reactions in the dark and the light zone in our later classes how this occurs and what is the role of this. So now they will start to proliferate in the germinal Center. So now they proliferate inside the germinal Center in the dark zone and then they start expressing certain receptors on their surface.

We will discuss in about this receptor so they now start to express certain chemokine receptors on their surface we will discuss about these receptors and their expression and the role of these chemokines in our upcoming lectures. So now they will finally undergo proliferation and then they will have somatic hypermutation affinity selection and finally they will differentiate into the plasma cells and the memory cells.

So the final step is so we are skipping many of the steps in between in between there is a lot of other steps involved here in this in this region after the proliferation these cells will then move to the light zone and then there will be selection based on the affinity. And then there will be class switching and after all these events have occurred there will be finally formation of the plasma cells with the specific antibodies and there will also be formation of the B cells expressing the IgG molecules the memory B-cells the memory and the plasma cells.

So this is so this part in this last part after the proliferation part we have not discussed yet. So we have only discussed about the activation part what is the activation or how the activation of the B cell occurs. So if we quickly look again into the whole thing quickly. So the B cell activation occurs in at least two different ways one is the thymus in independent way where you have which is mostly activated by this leap of polysaccharides the bacterial DNA some repetitive sequences and this occurs via signaling.

From the signaling subunits of the B cell receptor that this is the IgM which can bind to the surface antigens like this the small small antigens and the signaling occurs through this Ig alpha I beta and primarily through this ITAM region which is the immuno receptor tyrosine based activation motifs. This motives they transduce the signal from this IC alpha I beta and that helps in the activation of the B-cells.

Now this activation process the thymus independent activation process can actually occur in two different ways there's a type 1 process in the type to process and primarily it depends on the different types of antigens that are being presented or that have been recognized by the receptors. So the small molecules like the DNA or the Aleppo polysaccharides they fall under the rag under the type 1 and the type 2 are mostly the repetitive structures long large polysaccharides these falls under the tie to and one major difference with the type 1 and type 2.

Is that in the type 1 you do not require any intervention from any T cells or any other cell types whereas the type 2 requires certain interventions from our helps from other cell types like endritic cells mostly from the dendritic cells. The cytokines are being secreted which helps in the

type 2 process then we come to the thymus dependent process now the thymus dependent process occurs or starts by internalization of the antigen.

So the B cells they internalizes the interacts first the antigen interacts with the IgM molecule or the receptors and B cell receptors and then it internalizes the antigen it processes the antigen and then presents it on the surface by the MHC class 2 molecules. And then this t follicular helper cells which are actually CD CD 4 expressing cells the co-receptor city for expressing cells they immediately by their TCR.

So the T cell by the T cell receptor this is the TCR so by the TCR they immediately interacts with this MHC class 2 so MHC class 2 is recognized. And then there are as other certain other co-stimulatory signals as well like the b7 to CD28 interaction the CD4 T to CD40 ligand interaction and all these

interactions leads to the secretion of interleukin 21 aisle 21 and aisle 21 is a very very vital interleukin or a cytokine that is involved in the whole process of B cell activation and proliferation. Now this aisle 21 once it is secreted it helps in activation of the transcription factor stat 3 we will learn in our next lectures. As I told how the cytokines actually work and most of the cytokines they work by activation of this Jak-Stat pathway.

So this aisle 12 on activates our active transcription factor stat 3 which in turn helps in the proliferation of the P cells now the P cell starts to proliferate starts to express on their surface certain chemokine receptors which we will discuss in our next lecture. What is the role of this chemokine receptors. And finally this proliferating this proliferation occurs in the germinal center mark mainly in the in the dark zone.

And then they undergo a somatic hypermutation and then affinity selection and class switching and finally they transform into either they become plasma cells or the memory B cells. So this part we have not really discussed today now after the activation that is the differentiation part the proliferation and differentiation of the B cells; we will be discussing in our next lecture. So this is all from today's lecture. We will be discussing more in details about the differentiation of the

B cells the somatic hypermutation affinity selection all these things we will discuss in our next lecture, thank you.