Immunology
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Lecture No -36
B - Cell Maturation - I

Welcome back to the immunology lectures and so you have got introduced already to some bit of the T cell development as well as the antibody structure the gene the gene rearrangement for the antibody heavy chain and the light chain production. So, VDJ recombination and all these things; so; you have got a fair idea about all these things and so we will be starting in this section of the lecture series.

We will be starting with the B cell development. So the B cells which are the primary components of the humeral branch of the immunity. The B cells they develop in the bone marrow the main place where they develop is the bone marrow. And as we I also told in my previous lectures that the B cell the humeral branch of the immunity so that that is activated and in the uh the the lymphoid organs like the lymph node.

For example where it meets the antigen and then there is activation then there is all this class switching the somatic hypermutation the class switching of the antibodies all these things occur and then finally they start producing they they start to differentiate there. So there is the differentiation and it differentiates to produce the plasma cells and the memory B cells. So the memory cells in the plasma cells are produced and then the plasma cells are the they they have the secretory antibodies.

So they start secreting the antibodies and then these antibodies can function in different ways so they can either lead to neutralization they can lead to optionalization and many other functions so where does these B cells come from and you have also learnt about the T cells. So the T cells the the cell mediated part of the immunity so the adaptive immunity we can grossly divide into the humeral branch and the cell mediated branch.

And the humeral branch is mainly the B cell mediated branch the antibody mediated and the T cell mediated the cell mediated where you have the T cells and the T cells they develop in the thymus. So they they they come as the thymocytes and then they develop in the thymus with the help of the thymic epithelial cells. So all these cells they originate from a common progenitor so they originate from this hematopoietic stem cells.

And then they have a common multipotent progenitor from where they finally become either a B cell or a T cell. So at this stage when it is still like lymphoid progenitor cells at this stage it is still not committed to become a B cell or a thymocyte. Then there are certain signalings that occurs that would commit it that is a population of a part of this population will go for B cells and a part of this population will develop into thymocytes and they will move to the thymus where they will develop.

So and how does this B cells they develop into specifically B cells. So B cells means they will produce the antibodies and that means they would require the the recombination process which allows the rearrangement of the VD and the J gene fragments. So this rearrangement process has to occur in the B cells. So all these processes occurs primarILy the site of action is the bone marrow. So now if we look into the lineage of the cells where they start from in the bone marrow.

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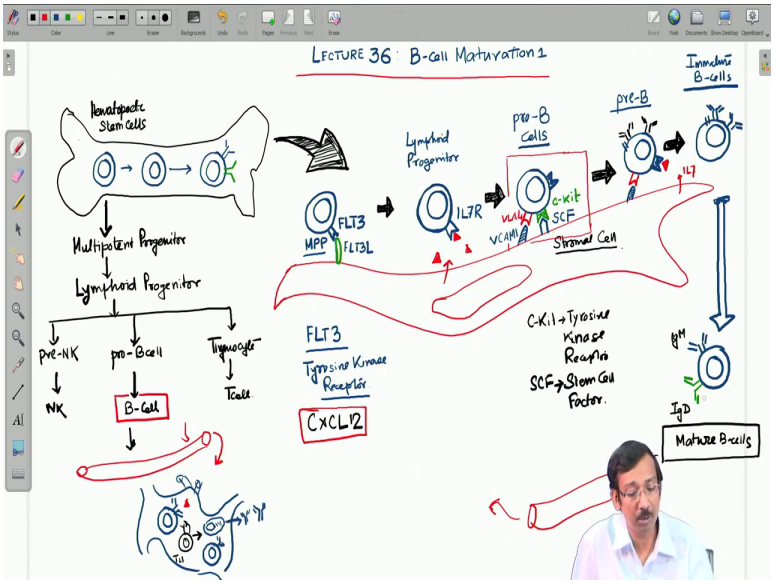

So they basically start from the common hematopoietic stem cells we call them the hematopoietic stem cells. So the hematopoietic stem cells and these hematopoietic stem cells they then develop into the multi potent progenitor cell. The multi protein progenitor then develops into a lymphoid progenitor and still it is not actually committed to become a B cell or a T cell.

So its still the lymphoid progenitor and this lymphoid progenitor can actually develop into either pre NK cell a natural killer cell. So this will finally develop into an NK cell or a natural killer cell. It can also develop into a pro B cell that is a progenitor B cell in also a thymocyte. Now this thymocyte will finally go into the thymus and then it will develop into a T cell. And this progenitor B cell will finally develop into a mature B cell and this maturation process.

So it will finally become a mature B cell and this maturation process actually occurs within the bone marrow. So this is very important how these B cells they develop? Now this B cell has three steps in the development. So the first step is the maturation or the development development stage. So they match your into a matured B cell what is a mature B cell. So a matured B cell is a B cell which will be producing a fully formed receptor on its surface a B cell receptor that will be comprising of the immunoglobulin as well as a signaling subunit.

So it will develop into a complete mature B cell which can recognize foreign antigens, antigens it will start developing the antigens specificity and then it will leave the bone marrow. So then it will go out of the bone marrow and then it will encounter the antigens and then it will go go from the bone marrow and then it will go to the periphery and then it will finally move to the lymphoid organs. And where they will start meeting antigen and then they will get activated.

So then that process is the activation. So the first process is the maturation then it is the activation and then it will start to differentiate. So I have a little bit probably I have discussed in the initial classes in the initial lectures how the B cells they when meet the antigens and with the help of the T helper cells after they get activated they differentiates and then there is class switching and they become different they start producing different types of antibodies and they then produce the plasma cells and the memory B cells.

So this B cell development this what we have seen here so it starts in this bone marrow here and then this B cell then leaves and it goes into the circulation it has to go into the circulation and then it goes to a peripheral lymphoid organ. So it has to go to a lymphoid organ for example a lymph node. And inside the lymph node this mature B cell which now expresses on its surface the B cell receptor in presence of an antigen.

There has to be an antigen present in presence of the antigen and with the helper of the T helper cells so along with the TH cells the T helper cells they will now develop into either a plasma cell or a memory B cell with the IGG molecules and then this plasma cell will start secreting the specific antibodies. So this is the whole kind of the whole story about the B cell. Now what exactly happens that how this this these progenitor cells or the multipotent progenitor cells they become the lymphoid progenitor cells and once from there this lymphoid progenitor cells after that they start getting committed to become a B cell.

So who are the who are the key players in this whole process of the development. So, one of the key players in this whole process or the helpers in this whole process is the bone marrow stromal cells. So it requires the help of the stromal cells so these B cells these these immature or the lymphoid progenitor cells they adhere on the stromal cells by some cell adhesion molecules. So the cell adhesion molecules we have discussed very briefly in the in our earlier classes like the the the immunoglobulin famILy of adhesion molecules binding to the integrins.

The mucine molecules so these are all the cell addition molecules. Now these cell adhesion molecules are expressed by different cell types of the immune system including the B cells. So this B cells this lymphoid progenitor cells they will start to also express this kind of cell adhesion molecules. So how does this whole thing start? So what happens is inside this bone marrow let us see what happens inside a bone marrow.

And how it develops into a complete, so what happens inside is the initial stage as I told is the the multipotent progenitor cell or we also call it the MPP. So now this this kind of cells they are not committed and they do not express any receptor on the surface like the B cell receptors on

the surface they do not have the B cell receptors on the surface. What they express on the surface is a protein tyrosine kinase receptor which is also known as the FLT3.

FLT3 now this FLT3 receptor can bind to the FLT3 ligand which is present on the stromal cell. So let us say this is the stromal cell and on the surface of the stromal cell there is this FLT 3 ligand. So, FLT 3 ligand that is present or the ligand that is present on the surface of this trommel cells. Now once this binding occurs the cells because this FLT3 is basically this FLT3 is basically a tyrosine kinase receptor.

So it is basically a tyrosine kinase receptor and it starts signaling that out it starts downstream signaling and there are many changes that occurs in these cells. So one of the major changes that occurs in these cells is that they start to express a class of cytokine receptors on the surface and then these cells become the; so these cells are the MPP or the multipotent progenitors and then they become the lymphoid progenitor cells.

The lymphoid progenitor now this lymphoid progenitors they express on their surface they start to express on their surface one of the major important cytokine receptors that is the interleukin-7 receptors the IL-7r. And interleukin-7 is one of the very important key players in the whole process of this B-cell maturation and interleukin 7 is actually being produced from this stromal cells. So this is a stromal cell.

So interleukin 7 is produced from this stromal cell and they can bind to this interleukin 7 receptors and this interleukin 7 has a very big role in the maturation and the development of the B cells. So now once these cells they start to express so the first stage is expression of the FLT 3 tyrosine kinase receptors and binding of the FL 3 to the FLT 3 ligand which is expressed on the surface of the stomal cells.

And then you have the interleukin three sorry interleukin 7 bring being expressed the receptor being expressed on the surface of this lymphoid progenitors. So now these cells which express this IL-7 receptor they are kind of committed to become the B cells. So they are kind of

committed to that B cell lineage so they will now produce the progenitor B cells they will now form the progenitor B cells.

And there is a third component that is the CXCL 12. So the CXCL 12 is basically a chemo kind that is also being produced by the stromal cells and they helps to retain this lymphoid progenitor cells or the and the MPP to remain on the stromal cells. So because this; chemokines are basically the chemoattractants. So they helps in cell migration and cell attraction cell to cell attraction.

So CXCL 12 has a role to play here which attracts the cell and retains the cell on the stromal cell surface and then there is the interleukin-7 receptor expression and then kind of these cells which starts expressing the IL-7 receptor they start to become kind of committed to become the B cell lineage to have the B cell lineage. So now the next is once they become the have this IL 7 receptors start to express the IL7 receptor on the surface then these cells they these cells will then adhere.

Now these cells they will now adhere to the stromal cells. So now they will start expressing this these cams which are the cell addition molecules. For example they will start expressing an integrin like molecule the VLA 4 which is expressed on the surface of this progenitor B cells and that can interact with another chem or a cell adhesion molecule which is known as VCAM 1. So cam is the cell adhesion molecule.

So this is the VCAM 1 so this VLA 4 can interact with this VCAM 1 and by that it adheres to the surface of the stromal cell. So then in this stage the primary thing that occurs in the stage of the probe cells when it develops into the pro B cells or the progenitor B cells we also call them the progenitor B cells. This they start to express these VLA 4 integral molecules on the surface which can then bind to this VCAM 1 or a class of cell addition molecules which is also expressed from the stromal cell on the surface of the stromal cell.

Now once this VCAM VLA interaction starts occurring there is a second interaction that occurs is the the interaction of a factor which is also known as the stem cell factor or the SCF that is

expressed on the surface of the stromal cell and that can interact with another tyrosine kinase family of receptor tyrosine kinase which is also known as the c kit. The c kit which is expressed on the surface of this probe cells or the progenitor B cells.

Now once this interaction is very vital once this interaction occurs here this interaction occurs on the stromal cell here then there is a signaling that leads to the maturation and the development of the pro B cells to pre B cells. So now this pro B they become the pre B cells now this pre B cells. So mainly the signaling occurs through this SCF to seek it interaction. So this c kit which is also our tyrosine kinase receptor it interacts with the SCF and SCF is the stem cell factor.

So this interaction basically there is interaction between these two molecules on the surface. So the surface expressing molecules that leads to downstream signaling in that downstream signaling leads to the development of this probe cells or the progenitor B cells into the pre B cells. So the main characteristics of the pre B cells is that now the pre B cells they will start to express or have the antibodies or the immunoglobulins on the surface.

So we will come to the developmental stages and how how what what exactly happens inside what kind of genetic rearrangement occurs inside we get to know about that in more details in our next class but for the time being we just say that the pro B cells after this interaction the VLA 4 VCAM 1 interaction and the secret to SCF interaction they develops into the pre B cells there is still some existence of this VLA 4 interaction of this VLA 4 to the VCAM in this stage.

But the cells they start to express on the surface the pB cells they start to express on their surface the IgM molecule and the B cell receptor. So it is basically it forms the B cell receptor along with the Ig alpha Ig beta sub units so these are the Ig alpha Ig beta are the signaling sub units of the B cell receptor along with that they are present along with the IgA molecules the all together they forms the B cell receptors and they start developing the B cells and of course they also have the interleukin 7 receptor being expressed on the surface.

In all these stages they still have the IL7 receptor on their surface. Now IL-7 has a very important role to play at this stage as well in the final maturation stage. So now these cells will

then finally develop into the immature B cells they will finally develop into immature B cells they are still not mature B cells why we will discuss later. So they will now start losing the adherence. So now since they were adhered to this surface of the stroma cells.

Now the expression of this VLA 4 and VCAM one goes down and this down regulation of the VLA 4 actually occurs due to the binding of the interleukin 7. So the IL 7 which is secreted from the stromal cells IL 7 actually binds to the IL 7 receptors to the ILR and this IL 7 IL IL 7 r interaction actually leads to the down regulation of this of these cell addition molecules and that would lead to the detachment of the cell from the stomal cell.

So detachment of the pre B cells from the stomal cells and now these cells will be known as the immature B cells. So these are the immature B cells now these immature B cells are characterized by expression of IgM on this surface along with the Ig alpha Ig beta which are the components of the receptor the B cell receptor and then finally this a mature these immature B cells they will finally develop into mature B cells which will be expressing on their surface both IgM and IgD immunoglobulin M and immunoglobulin D on their surface.

So, now these are the mature B cells so these are the mature or the final mature B cells which then enters into the; so now it leaves the bone marrow enters into the circulation and then goes to the peripheral organs and then it can get activated by an antigen and then it can produce the memory B cells as well as the plasma cells. Now a very, very important step in this whole process is this after the formation of this match your B cells there is another very, very important step which is that these B cells will undergo a quality control check.

So basically they will undergo a check whether this IgM that is being expressed on the surface of the B cell as a part of the B cell receptor whether this B cell receptors they can actually interact with self antigens or not. So that means in all these steps of the B cell development starting from the lymphoid progenitor to the probe cell to the pre B cell in finally to the mature B cell there are stages of development of the heavy and the light chain.

So arrangement of the heavy and the light chains of the antibodies and this heavy chain and light chain rearrangement is completed at the stage of immature B cells. Now there has to be a check there has to be a check point because there are many, many chances there are at least 45% of chances that there is a fault, there is a there is something wrong in this re in this rearrangement process. And if there is something goes wrong in this process of rearrangement then the B cell receptors.

They can develop affinity for the self antigens that is the cell surface antigens of the same system the self system or they can also get affinities they can also develop some affinities towards some soluble antigens. And they can become they which can activate them basically so and that that can actually be dangerous. So they can if they develop an affinity for the self antigens so that can actually be dangerous.

So in that way these B cells these immature B cells before they leave the before they leave the bone marrow they need at least one round of quality check that is whether these anti these antibodies or these receptors they are self reactive or not. So now if they are self reactive then they will be excluded if they are not self reactive at all then they will pass the quality control check and then they will go out and they will go to the peripheral organs and then where they will finally get activated and differentiate into the final memory cells and the plasmas.

That is the overview what I try to give today is the how these hematopoietic stem cells that develop into this multipotent progenitor cells from where they develop into lymphoid progenitors and from there they become pro B cells and pre B cells and then immature B cells. And on all this process the major major roles that the major roles are played by the cell adhesion molecules which try to adhere these cells on the surface of the stomal cells and then we have interleukins interleukin 7.

For example which helps in this process of development we will see in our next lecture how or what exactly happens inside the cell that actually leads to the development of the B cells or the maturation of the B cells and development of the immature B cells which expresses the B cell receptor on the surface and the IgM molecule on the surface being expressed in the surface of the

cells. So, we end this lecture today and we will be continuing to talk about the B cell maturation in our next lecture, thank you.