Immunology
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Lecture No -37
B - Cell Maturation – II

So welcome back to the immunology lectures and we will be continuing our discussion on the B cell maturation. So in the last class or in the last lecture we started with the B cell maturation and we had talked about how the B cell undergoes different stages of development starting from the multipotent progenitor cells and then it develops into the progenitor B cell and then to the pre B cell and then finally develops into an immature B cell.

And then finally the match would be self so this whole development process as I already told in the last lecture as well that this whole development process has a certain significant or important signaling molecules which are essential for the occurrence of the gene rearrangement of the VDJ gene rearrangement heavy chain locus. So if the rearranges the heavy chain locus and then it rearranges the light chains and then finally it comes up with the expression of the IgM along with the fully matured IgM with the heavy and the light chains along with the Ig alpha and the Ig beta subunits.

And this subunits are essential for signaling. So these are the signaling subunits so what we have if we go back into our last lecture quickly.

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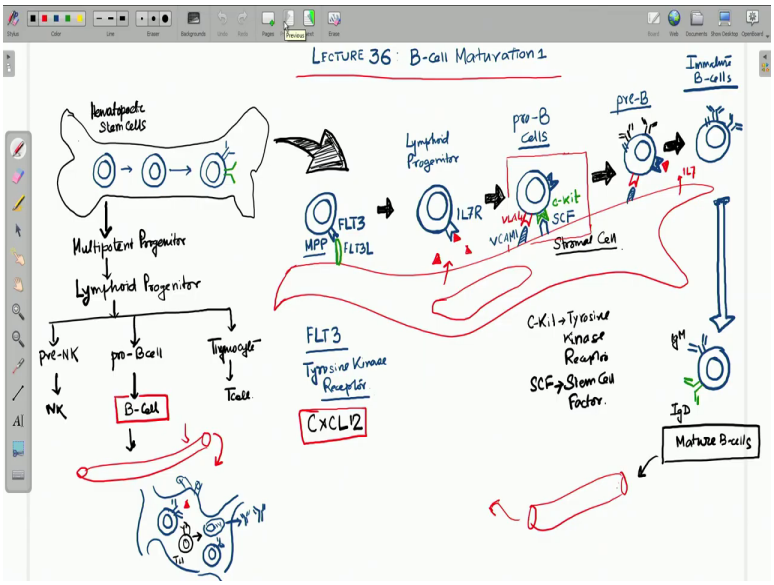

And if you see what we have where we left in the last lecture is that this MPP or the multipotent progenitor cells they first develop into this lymphoid progenitor cells and as I told this after this stage it becomes committed to become a B cell. So basically the rearragement of the VDJ it starts occurring immediately after this stage and from the pro B cell to the pre B cell it is the heavy chain mostly the heavy chain rearrangement.

And at the end of the pro B cells when it is a pro B cell at the end before it becomes a pre B cell the heavy chains are rearranged. So you have already gone through the lectures where professor Ghosh has introduced you to the VDJ recombination process the rag proteins and everything. So I will not go into the details of those processes in these lectures the only thing I will keep talking about VDJ recombination of the there is rearrangements with an understanding that you know the processes already.

So this the VDJ recombination or the rearrangement starts with after this lymphoid progenitor cell becomes committed to become a pro B cell or a progenitor B cell and from this progenitor B cell so this progenitor B cell again has an early phase and an late phase early progenitor B cell. And a late progenitor B cell and that is where the entire process of the heavy chain rearrangement starts occurring and then it occur and then it finishes the heavy chain rearrangement.

And when it is when when the from the in the late progenitor B cell stage that is in the late Pro B cell stage this this this Pro B cells there is an early and late phase. So there is an early and a late phase so in the early phase in the beginning it starts with the VDJ recombination or the rearrangement and at the late stage this rearrangement of the heavy chainc conflict and it starts the rearrangement of the light chains.

And then there is certain intermediate IgA molecules produced which are expressed on the surface. So the Muchin the MU heavy chains are being produced and are expressed on the surface and along with that there are some intermediate peptides which forms the light chain and finally it develops into a complete IgM after there is the light chain rearrangement also occurring. And then it becomes a fully matured B cell with a complete antibody receptor.

So this whole process occurs at the genetic level and this process is actually mediated by several transcription factors and which are basically the downstream of these signaling processes. So there are several transcription factors which are involved in this whole process up and up regulation of certain genes and certain gene products. And we will see we will very briefly see an overview how these cells they undergo this what are the stages of this region rearrangement process.

And finally what are the stages of selection so I also told that after an immature B cell is formed it has to undergo a selection. That means it has to undergo a quality check it has to undergo a quality control check whether it can interact with the self antigens or not. If it can interact with the self antigen it will be rejected and it will die die out of apoptosis either it will die or it will remain as an unresponsive cell so it will not respond to any antibodies.

So there are there are many ways the B cells they can circulate or they can remain we will discuss more.

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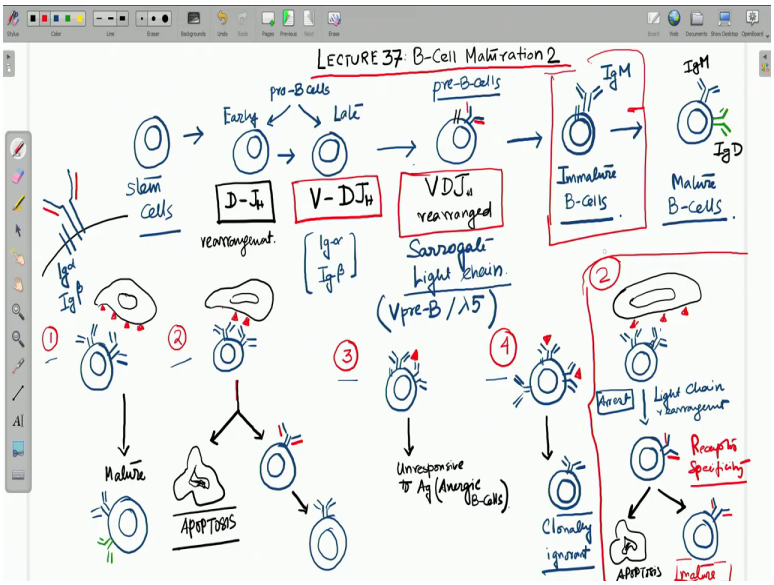

So let us see what what exactly happens in this in this case so as we have seen from starting from the stem cells. If we start from the stem cells again where we so from the stem cells we have the pro B cells and as I told the pro B cells the pro B cells the pro B cells can be of an early pro B cell we call it the early in the late pro B cell. So it can either it first develops into an early and then it develops into a late pro B cell.

So what happens in this early pro B cell is initially there is a defragment to the J heavy chain rearrangement so this D to J rearrangement starts to occur here in this early stage. The first we are the gene rearrangement in the VDJ rearrangement process. So these cells in the early stage they start with the D to J rearrangement and then once this D to J rearrangement has taken place there is a V to DJ H rearrangement.

So this is also a heavy chain rearrangement and the first is our D to J rearrangement and then a V to DJ rearrangement. So now this rearrangement starts to occur in the pro B cells and once this rearrangement is complete then we call these cells the VDJ rearranged cells. So now they have completed the VDJ rearrangement of the recombination process and this are the pre B cells. So now this is the pre B cells and these pre B cells they have already they start to express the IgM or the surface IgM also sometimes called the membrane IgM or the surface IgM the S IgM.

They start to express on the surface although the light chain rearrangement has not started occurring in this stage. So the light chain rearrangement starts occurring at the pre B cell stage and initially what happens is there is a surrogate light chain. So you have you get a surrogate light chain and this surrogate light chain basically comprises of two small polypeptides which is one is the V pre B and is the lambda 5.

So these two small polypeptides they together comprises of this surrogate like chain which is not really the complete rearranged light chain it is in that. So it forms an intermediate receptor along with the signaling subunits so a receptor on the surface of the B chain typically looks like something like this. So you have the sarrogate light chains and you have the Ig alpha and the Ig beta subunit so at this stage so the Ig alpha Ig beta subunits they also start to be expressed in this stage at the stage of the Pro B cells.

In this Ig alpha Ig beta sorry the Ig alpha and the Ig beta they are expressed along with this rearranged heavy chains and they are also up they are also a part of the B cell receptors. So they are the signaling subunits and they are the signaling subunits having a transmembrane domain and like other cell surface receptors. So they have a cytoplasmic tell from where the signals are being transduced. In this Ig alpha a beta subunits of the receptor are particularly important because they send the signal for stopping or halting the heavy chain rearrangement.

So now from the Pro B cell after the VDJ recombination of the VDJ gene rearrangement is completed in the early and the late phase of the Pro B cell it becomes a pre B cell. Now this pre B cell has a completely rearranged heavy chain loci. The heavy chain locus has been rearranged now the light chain rearrangement starts. And the light chain rearrangement is completed when it reaches the next stage that is an immature B cell.

Now this immature B cell will have on its surface are completely rearranged like chain. So it has the it will express on the surface IgM with the Kappa or the lambda chains and it will also contain the Ig alpha in the Ig beta. So this is the immature be cells the immature B cells will have the complete IgM molecule on the surface. Now this will finally when it becomes a mature B cell

this will finally start to have the IgM as well as the it should as well as have the IgD immunoglobulin D.

So it has the IgM and IgD expressed on the surface and this is the mature B cells. So let us look into the whole entire stages of the B cell maturation and starting from the stem cells it develops into a probl a progenitor B cell and first the early progenitor B cell which where the D to J rearrangement D 2 J rearrangement starts and then in the late phase the V to DJ rearrangement starts and the Ig alpha in the Ig beta they starts to express on the surface.

And now after the late pro B cell then the surrogate light change they starts to express and then they form this intermediate immunoglobulin molecule containing the rearranged heavy chains and the surrogate light chains. And this surrogate light chains are primarily comprised of two polypeptides the pre B and the lambda 5. Now it starts to rearrangement the light chains and once the light chains are rearranged then it produces the immature B cells.

Now this immature B cells will finally develop into the mature B cells. Now the question is what exactly helps in development of this immature B cells. So the first thing is that this after the cells the pre B cells they have completed this VDJ rearrangement of this VDJ recombination then you have this Ig alpha and there Ig beta which are required for the signaling. So as I told that they have the Sigma they are the signalling subunits of the B cell receptor.

So they have a as cytoplasmic part assigned to cytoplasmic tail by which they transduce the signal and they are essential for halting or stopping the heavy chain rearrangement and then the light chain rearrangement occurs. So finally this immature B cells are being produced. Now this immature B cells what is the fate of this of these immature B cells? So what is the fate of this inmature B cells. So let us see one immature B cell as I told on its surface will start to express the IgM.

Now if this immature B cell the IgM of the signature B cell. Now will be tested for its ability to react with self antigens. So now if there is a cell nearby so and you have the antigens. So basically the cell surface molecules. So now if if they can interact with the cells of cell surface

molecules if they cannot interact that means there is no reaction no reactivity that means they are unreactive they do not react then they will continue to mature and they will form the mature B cells.

With the IgM as well as the IgD being expressed on the surface but so this is for example this is the first case. Second case is like this where these B cells with the IgM molecules on their surface can actually interact with a cell surface antigen or a self antigen and that can lead to cross-linking of the receptors. So it can interact with or it can recognize the a multivalent ligand or a cell surface cell surface self molecules.

Then this interaction can have two fates what so either either the cells can die by apoptosis or they can undergo a second round of receptor editing they can undergo a second round of receptor editing and they can have different light chains. So now they can have their receptor specificities will change so that they have more light chain rearrangements and their receptors specificities will change and then they can then they might become non reactive to the self antigens.

And then if they are non reactive to the self antigens then they will finally mature into a mature P cell, this is the second case. A third case is when there is any mature B cell expressing IgM on the surface and they can interact with some soluble antigens not the cell surface antigen some soluble proteins or some soluble peptides. Some soluble antigens but self antigens that can lead to receptor cross-linking. So if there is receptor cross-linking that means there there is a higher high affinity for this self antigen.

So the affinity is high so it binds to that antigen the soluble antigen with quite high affinity then what happens then basically there is this these cells they become unresponsive to the antigens. They becomes unresponsive they are rendered unresponsive to antigens also there sometimes they are called the annergic cells, annergic B cells and they hardly respond to any ligand or any antigen and they cannot be activated by any antigen or any ligand.

So there will be a kind of remain unresponsive to the antigens and they will not so once they go to the peripheral system they will not basically respond to the antigens and they become the annergic cells. So and then they can not be activated and differentiated so this is a third class. And a fourth situation or a fourth case would be that a B cell which expresses the B cell receptor it can still bind to or soluble antigen similar to case three it can still bind to a soluble antigen but not with a very high affinity.

So in this case we have seen at least in this case we have seen it binds with it with a very high affinity but in this case it does not bind to it with a very high affinity. So the affinity is low or with a low affinity with the self and antigen, so there is no receptor cross-linking. And if that happens it will keep maturing normally these cells will not be destroyed like what we have seen in case of the other cells those which can interact with high affinity.

This cell since they do not interact with the antigens with very high affinity they will still keep maturing. So they will become mature B cells of course but the they will become kind of clonally ignorant population. So they cannot actually be because they have very low affinity for this self-antigens they can mature but since they still have the ability to bind to the soluble antigens they will remain as clonally ignorant.

And these they they will not be able to bind to ligands that can activate them because they can till bind to the self-antigens if that is present in very high concentrations. So if that soluble antigen is present in a very high concentration it can still may be able to bind to it or active gate activated but normally they remain as clonally ignorant and they are not they do not interact with the ligand.

So they there are at least four different situations we can come across during the selection or the quality control check of these B cells what the immature B cells so the first case is that they do not react they are unreactive they do not react with any anti self antigens. So then they will normally mature and they will interact and finally they will move out of the bone marrow and then they will go to the periphery and then they will interact with the foreign antigens and will get activated and they will differentiate and produce the antibodies.

A second case is where they can interact with the cell surface antigens or the self antigens and multivalent ligands which can lead to receptor cross-linking that means they have very high affinity for these ligands. In that case those B cells can have two fates those immature B cells can have two fates either they can die because of apoptosis or programmed cell death or they can have a second round of receptor a second round of cross-linked in the second round of the rearrangement of the receptors.

So that would then lead to the development of the mature B cells. So overall what we see that at least there are four different situations that can arise when a b cell and immature b cell develops into a mature b cell and then it leaves out of the bone marrow. So the first in the in the quality control check the first situation is that it does not interact so there is no interaction with any cell surface antigens and the the B cell will mature normally.

A second situation is that it interacts very avidly or very tightly with a cell's surface self antigen and that can lead to two different situations one they can die by apoptosis or programmed cell death in a second case they can still undergo reediting of the receptors. So there is another round of reediting of the receptors and there is another round of light chain rearrangement that would lead to the development of the B cells.

A third case is that the B cells they mature B cells the receptors can bind to some soluble antigens like some soluble proteins or some soluble peptides that can lead to cross-linking of the receptors. Remember the situation 3 and the situation four are a bit different. So in case of situation 3 the binding of the soluble antigen to the B cell receptor is strong that can lead to cross-linking of the receptors.

And if that happens then that can lead to unresponsiveness and lead to the annergic B cells and in case of situation for if these antigens are so the B cell receptors can still react with a soluble antigen but the interaction is not that strong. So it is a low affinity interaction. So in in case number 3 it is a high affinity interaction in case number 4 it is a low affinity interaction and in that case the these cells will they will mature normally.

They will undergo maturation so they will mature normally and and but they will remain clonally ignorant because they might not have the ability to interact with the ligands. So and but still they will remain in the population and they will remain in the population and their receptors since they have very low affinity for these antigens. So they can be activated at very high concentration of the ligands very high concentration of these antigens.

So they will remain as clonally ignorant population because they are unable to bind or no ligand can actually activate them binding of any ligand can actually activate them. So what happens in the case number two is that when there is a binding in binding of the most important cases are at least case number one in case number two so a first one where there is a mature B cell formation without any reactiveness and the second case where there is our reactiveness that is if there is a strong reaction to the cell surface antigens self antigens remember so they interact with the cell surface self antigens and if that occurs.

So if that occurs that it interacts with the cell surface antigens the B cell receptor if it can interact with the cell surface antigens. So now there can be a second round of light chain rearrangement and the B cell development will be arrested. So here there will be an arrest of the B cell development and then you can have a second round of receptor editing leading to the light chain rearrangement and you will expression you will have expression of new set of light chains.

And then it will be again checked it will be again checked for the with a new receptor specificity with this new receptor specificity. So the receptor specificity will change and with this new receptor specificity it will be again checked. So these cells will again undergo a quality control check and even then if still there is a cell-free activity then these cells will die by apoptosis. And if they do not have this reactivity then they will continue to mature with the new light chains on the IgM.

So they will then develop into the mature B cells or they will they will mature and leave the bone marrow. So this is the situation from this case number two. So these are the four different situations that can arise with the B cells an immature B cell. So what we learnt in today's lecture

in overall is that how these stem cells they after entering into the early Pro progenitor B cells into the stage of early progenitor B cells there is DJ a recombination rearrangement.

And then VDJ area arrangement occurs and then you have the surrogate light chains being expressed which then starts to express on the surface of the pre B cells. And then finally now you have the immature B cells where you in this pre B cell stage it will start having the light chain rearrangement and then you will have the complete IgM molecule will being formed and these IgM molecules. So at this pre B cell stage there is again another stage where this these cells becomes bigger in size and then they become again smaller in size with the IgM in the soluble form.

And then the IgM is expressed on the surface of the molecule of this of the cell and they are also called the membrane IgM or the surface IgM. And the surface IgM will associate with this Ig alpha and Ig beta the signaling subunits of the receptor and then finally it will mature into the mature B cells. Now at this stage when the immature B cells before it finally matures and leaves the bone marrow there is a match of B cells they can again interact with the cell surface antigens and undergo four different fates.

So they have four different situations can arise one is that they can interact with the surface antigens the different surface proteins like for example the MHC molecules and if it recognizes it as an antigen and it interacts it reacts. So that means it has a self reactivity then then it will not go into the maturation stage it will either undergo apoptosis or it will undergo a second round of reading of the B cell receptors that is case 2.

Case one is that it does not interact with any cell surface self and antigens and that can lead to complete maturation of the B cells and development of the IgM and IgD and the mature B cells will be produced a case 3 is where they develop an energy cell energy B cell means which is unresponsive to any antigen and that occurs when the B cell receptors are they still interact with self antigens but soluble antigens.

And a case for is that when it still interacts with the soluble antigens but with low affinity. So there's they develop into a clonal ignorant population of the B cells. So we kind of try to understand if you look in the whole picture we try to understand the B cell maturation the different stages of B cell maturation and selection of the correct B cells which actually finally matures and there then it can go to the lymph the lymphoid organs for activation and differentiation.

So we will keep continuing we will keep continue discussing about the B cell development activation and differentiation parts of the B cell, what occurs with; what happens to this mature B cells then we will keep discussing about this and for today's lecture we stop here and thank you very much.