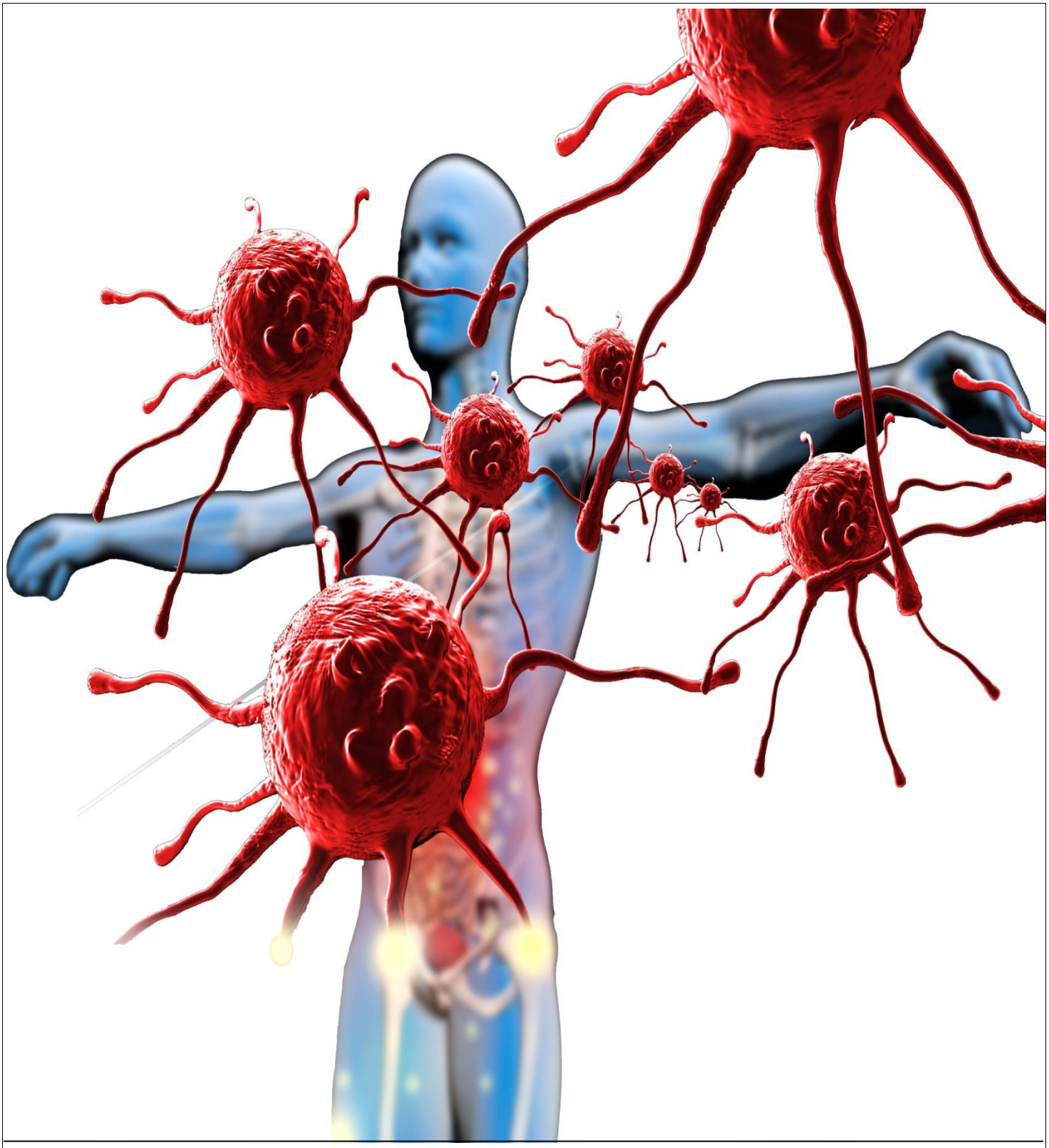

IMMUNOLOGY

Done By: Areej Jaber

Dr. Hassan Abu Al-Ragheb

#10

By Mohammed Nawaiseh

Structure & Development of immune system's cells

Before we are going to talk about the activation of the B- & T- Lymphocytes, we will talk about their structure and maturation.

Lymphocytes start their development from the **stem cells**, in the bone marrow, along the lymphoid lineage. This line gives rise for B- & T-lymphocytes. The T-lymphocytes leave the bone marrow early, and go to the thymus to continue its maturation there.

-B- Lymphocytes:

☝ Pro-B cell stage:

As the B- cell starts developing, the earliest cell to be detected in the line of its development is the "**Pro-B cell**". It is detected by the presence of two surface molecules: **CD10** and **CD 19**. Next, there will be an activation for **RAG-1** and **RAG-2** genes (**R**ecombination **A**ctivation **G**enes). Those, the two genes, are responsible for the gene rearrangement. The first thing to be assembled by these gene rearrangement is the **heavy chains**, the μ chain type (because it is the first one to appear in the cytoplasm of these cells). For these cells to continue growing, they need to have, also, **BCRS** "B-Cell Receptors" on their surfaces.

So keep in mind that: Gene Rearrangement started in the Pro-B cell stage.

By this time (in the **Pro-B cell stage**), the light chain isn't assembled yet. Actually, the heavy chain(the μ one) is associated with a surrogate chain "أُموميّة" in place of the light chain. Then, they are expressed on the surface of the B-cell "actullay the Pro-B cell" and called the "Pre- BCR". It is ,of course, associated with Igα & Igβ which are really necessary for the integrity of the receptors in the surface.

- Why we call it a "Pre-BCR" NOT a "BCR" ?

Actually, because the BCR is composed of a heavy chain and a light chain, but here we don't have a light chain, instead we have a surrogate chain.

✌ Immature B-cell stage:

Once this Pre-BCR is assembled and exposed on the surface, the cell will have a signal to continue its maturation. After that, there will be a production of the light chain, then, it will associate with the μ-heavy chain to be exposed on the surface of

Written by Areej Jaber

the cell. At this stage the BCR will be formed, which is really made of IgM. The BCR is associated with Igα & Igβ, just like the Pre-BCR.

The cell at this stage, expressing of BCR, is known as the **Immature B-cell**. Note that IgD hasn't really been expressed yet.

- **Fate of the Immature B-cells :**

The complete maturation of the B-cells is actually occurs in the bone marrow, but more recently it was found that the Immature B-cells leave the bone marrow, and go to the spleen, mainly, completing their maturation there. In the spleen, the cells will lay, mainly, in the marginal zone to complete its maturation (expressing the IgD on the surface).

Once there is an expression of **both IgM** and **IgD** on the surface of B-cells, this is Known as "**Mature B-cell stage**".

After being **matured** in the spleen, they will be classified into two varieties:

1-Follicular B-cells "FO-B cells": these cells go to the follicles in the second lymphoid tissues. This type is the one that get **activated** by encountering antigens which are made of proteins, producing first IgM and then other isotypes of the immunoglobulins, then, giving rise to memory cells and plasma cells.

2-Marginal Zone B-cells "MZ-B cells": remain in the marginal zone. They may circulate in the blood, but before that, they will undergo **some transitional processes**; designated as T1- and T2- B cells. MZ-B cells apparently are responsible for encountering the antigens which are made of polysaccharids, expressing only IgM on their surface (there is no switching here), having No Memory Cells. However, they can give rise to naïve memoryB-cells expressing only IgM.

Note That :

- For a cell to give rise to "memory cells" it must have the ability to express IgG. Because MZ-B cells have no IgG's, they will not give rise to memory cells.

- MZ-B cells are mature ones, so they have on their surface both IgM and IgD.

-Some references say that MZ-B cells can give rise to IgG3 !

There is another, **third**, type of B-cells called: **B1-cells** or CD5 B-cells, because it expresses the **CD5** molecule on their surfaces. These cells are apparently produced in the fetus , propagate themselves and continue dividing there.

They express only IgM(for antigens made of polysaccharides, mainly for: Bacteria and foreign bodies come to the mucosal membranes), having no memory cells.

"B1-Cells called the CD5 +ve cells"

MZ- and FO- B cells are originally produced in the bone marrow and continue generated there, not tolerated in the periphery. However, the B1-cells can renew themselves in the periphery, confined mainly to the peritoneum and the pleura.

☞ **The Fate of the Immature B-cells if it encounter an antigen**

During the maturation of the B-cells, either in the bone marrow and even in the spleen as well, you can find these Immature B-cells(remember they have only IgM, no IgD). If they encounter an antigen specific to them, what will happen? They will be inactivated ☹, why? Because the antigens, they encounter, are self-antigens and thus these cells are self-reactive. In Order to be inactivated, one of **four** outcomes will happen (according to the signal is received by the cells) :

1) **Apoptosis**: here, the cell is killed by a signal which induces apoptosis.
2) **Anergy**: here, the cell goes to the periphery, still alive not killed but rather having no energy, so it will not be activated it encounter another antigen. Later, it will be killed because of the lack of energy.
3) **Receptor Editing**: the B-cells, here, is given a chance to reactivate RAG-1 & RAG-2 and try to assemble a different light chain(producing another BCR), by this assembling the cells will not become auto-reactive, and thus they will escape, continue maturation and go to the periphery.
4) **Immunological Ignorance**: either the amount of the antigen is very very small [they are ignored], or it is sequestrated somewhere else. So the cells here are allowed to mature, but they aren't really encounter that antigen in the periphery.

These cells, that use the immunological ignorance pathway, are important. They are believed to be responsible for the "**Auto-Immune Diseases**", potentially because they are really still auto-reactive but they ignore the antigens they encounter (because it is small or sequestered somewhere else). So they *may*, at one time, start to produce antibodies against these self-antigens.

This what is called: **Central-Tolerance → "**again, it is when the immature B-cells encounter and react with self-antigens"**, and we knew, above, how is dealt with this case.** There is also Peripheral Tolerance which will be discussed later.

✓ **Molecules present on the surface of the B-Cells:**

- BCR
- Igα and Igβ
- CD19: the **marker** of B-cells, it is found during ALL stages of maturation, so we can detect the B-cell by a fluorescent antibody against the CD19 marker.
- CR2"Complement Receptor 2": those complement receptors are for self-study, you should have been read about them. They are present on certain cells like B-cells, frontier cells and cervical cells. This molecule also functions as a receptor for EBV "Epstein Barr Virus" .
- CD81.

(CD19+CR2+CD81)→form a **tri-molecular complex** on the surface of B-cells that acts to **activate these cells** . *Please remember this molecule we will talk about it later*

- CR1"Complement Receptor 1".

- FC receptors: which are directed against the FC fragment of the Immunoglobulins, and they have something to do with the regulation of the activation of B-cells. *we will talk about later on*

-T- Lymphocytes:

☝ **Cortex**:

As we said, they leave the bone marrow at very early stage to complete their maturation in the thymus. The cells are naked(in the cortex of the thymus), have no molecules at their surfaces(no TCRs, no CD3, no CD4, no CD8), therefore, they are called at that stage **"Double Negative"**. The **double** specifically concerns about the "CD4 & CD8", and **negative** because they aren't expressed yet. These naked, immature T-cells are called **Pro-T cells**.

Next, the cell will start to assemble its TCRs. The first chain to be assembled in the TCR is the β-chain, which is equivalent to the "heavy chain" in the B-cell, in the cytoplasm. Then, it will associate with the surrogate chain ,that replaces the α-chain (not yet produced) of the TCR, producing a **Pre-TCR**. It will eventually associate with CD3 and be expressed on the surface of the T-cell. So it's the same as what you get in the B-cell as well.

For the cell to continue its maturation, something from this Pre-TCR must go inside the cell, this occurred when something "ligand that we don't know" bind to the Pre-TCR. Once this happened, the T-cell starts to produce its α-chain which will associate with the β-chain and then, express them on the surface.

Of course, they"α- and β- chains" will associate with CD3. Soon after that, the cell starts to produce & express its CD4 and CD8 at the same time. Now, we call these cells as "**Double Positive**"; because they express both **CD4 & CD8** beside the TCR and the CD3.

Most of the cells in the cortex are cortical epithelial cells of the thymus, they are considered as **APC** "**A**ntigen **P**resenting **C**ells" because they have MHC1 and MHC 2 on their surfaces. The interaction occurs between those "double positive" T-cells and these cortical thymic epithelial cells, more specifically it occurs between the TCR and the antigen, which is carried on the MHC (1 or 2). This kind of the **interaction**, if there is any "if the TCR recognize the antigen", is very useful to us. It will give the cell a signal to **continue its maturation.** If the TCR on the T-cell can't recognize the antigen presented by the MHC (1 or 2), the T-cell (it is of no use) will be neglected and eventually will die. **So the T-cell is either mature or will die by apoptosis.**

-By this we talk about the **"Positive Selection"**: when the **TCR** on the T-cell **recognizes** an **antigen** presented by either MHC 1 or MHC 2 . And this T-cell will continue its maturation and development because of the signal they received.

-T-cells as long as they are in the thymus we refer to them as "**Thymocytes**".

✌ **At the Cortico-Medullary Junction:**

After that, thymocytes will transfer to the "**Cortico-Medullary Junction**" and undergo, there, what is called "**Negative Selection**", which most probably to occur in the "**Double Positive Stage**". At this junction, the thymocytes will interact with: those cortical thymic epithelial cells, dendritic cells and macrophages.

If the interaction (between the TCR & MHC "1 or 2") is strong(with **high affinity**), the T-cells will become very dangerous "auto-reactive cells" and they will be given a signal to kill them. That's what is called the "**Negative Selection**".

If the interaction is loose(with low affinity) between the TCR and the MHC (1 or 2), the T-cell will be allowed to mature and those are the one gain access to the periphery as mature T lymphocytes.

If the interaction is **intermediate**, it is suggested or believed that these cells will give rise to "**T-regulated T-cells**" or "**Suppressor cells**". These cells will go to the periphery, playing a role in tolerance rather than activation of the T-cells.

⊙ Some types of the T-cells:-

1) αβ –T cells: most common, are found in the: paracortex of the lymph nodes, brain, periarteriolar sheath "PAS" in the spleen and so on ..

2) γδ-T cells: less common, 3%-5%, they in the thymus, don't express CD4 nor CD8. We don't know much about them, what they do or how they interact. They leave as mature cells to the periphery, are confined, mainly, in the sub-mucosal surfaces of the gastrointestinal tract and are concerned with first line of defense against invasion by microorganisms.

3) T-regulated T-cells: can be identified by their **special marker** which is **CD25** which is the α-chain of the receptor. When these T-cells become activated, they will express the receptor, so naïve cells will not express it. These T-regulated T-cells will express one chain of the receptor (the **α-chain,** known as the **CD25**). They have **another marker** on their surface which is known as "**FOX3B**".

   Some of these cells originates in the thymus and called so "Natural T-regulated T-cells"→ "NT-regulated T-cells".
   Some go to the periphery , become there "Induced T-regulated T-cells". It is called Induced because it is induced by certain cytokines like "IL-10 and TGF-β". So it will become → "IT-regulated T-cells".

4) NK-T cells: They are called natural killer like T-cells and are less than **0.1**%. They are really T cells because they express "TCR and CD3", but they have markers shared with NK-cells like "CD 16 & CD56". They can serve with a different purpose, they can recognize an **antigen** which is in conjunction not with "MHC molecules" but rather with "**CD1**"(which is similar to the MHC molecules' structure) . CD1 usually presents **lipids' antigen**.

-This "**Negative Selection**" of the T-cells in the thymus is known also as the "**Central Tolerance**".
- As a conclusion, both B- and T- cells express "Central Tolerance" in the primary lymhoid tissues (bone marrow for B-cells and thymus for the T-cells).
- As we said before we have what is called "Peripheral Tolerance" for B-cell as well as for T-cells. *will be discussed later*

After the T-cells become **mature**, they will become **"Single Positive"**. It means that they either express **CD8** or **CD4**, not both.

But how it will choose between CD4 and CD8 ?

If the TRC recognises MHC1 Class molecule, we know that the CD8 on the T-cell will join up with Alpha 3 Domain, and this will allow the CD8 to stick around and CD4 will be lost, if the TRC recognises MHC 2 then the opposite will happen and CD8 will be lost and CD4 will be kept on board, either way

we'll end up with a single positive rather than a double positive .

- What is the idea behind the "Negative Selection"?

It means that we have cells not reactive to our antigens, can you make sure that every antigen in your body can be found in your bone marrow? – may be not .

So some B-cells, which are auto-reactive, don't encounter self-antigens. That's the importance of "**Peripheral Tolerance**".

According to T-cells, they rely mainly on "**Central Tolerance**", why? Because when they go to the medulla, there is "thymic medullary epithelial cells" which have a gene called "**AIRE** = **A**uto **I**mmune **R**egulatory **G**ene". This gene is able to produce any kind of proteins that are possible in your body. Suppose that this gene produces "insulin" protein, which isn't really found in the thymus, T-cells will not react with this "insulin" because it had passed the test and the insulin antigen presented to it but it recognised it and didn't attack it, if it did it will be eliminated.

Unfortunately, if you get a mutation in this "AIRE" gene, you will end up with "Auto immune diseases" directed against the endocrine system (by affecting the parathyroids, insulin, etc). This means that the gens are up working, and you will have many Auto-reactive cells, that will go to the periphery.

GOOD LUCK :")

"Be The Change You Wish To See In The World"

-Mahatma Gandhi

Corrected by ***Fuad***.