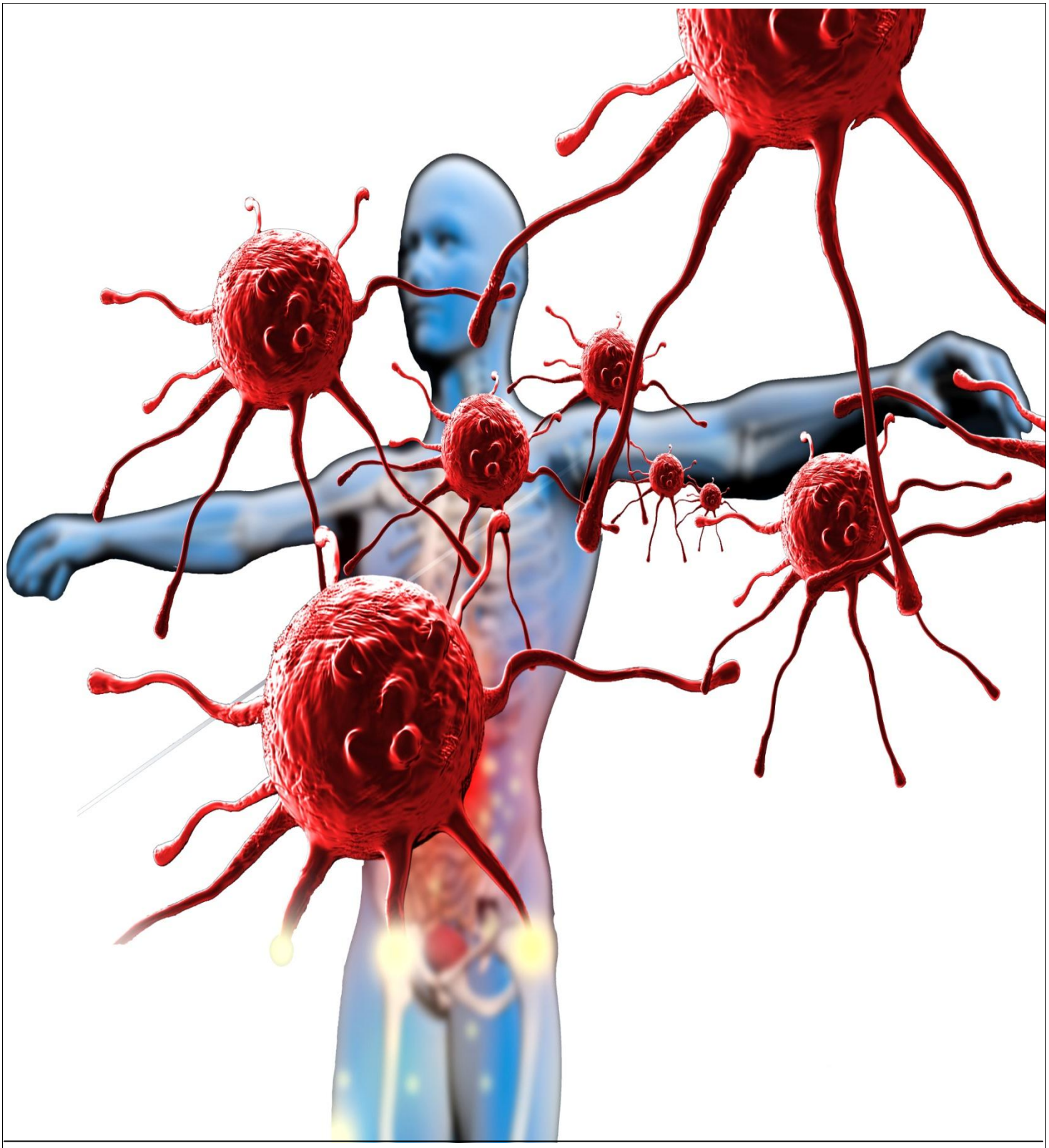

IMMUNOLOGY

Done By: Abdullah Odeh

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#5

By Mohammed Nawasreh

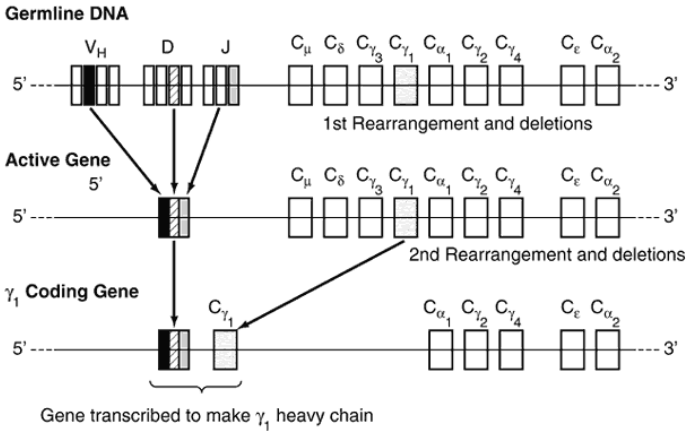
Continue immunoglobulin & TCR

1-Immunoglobulins:

We said that when the synthesis of the heavy chain is successfully finished, we start the synthesis of the light chain (either the Kappa or Lambda) and they combine together ((light & heavy)) to produce an Immune-globulin molecule. The Ig molecule will be expressed on B-cell surface .

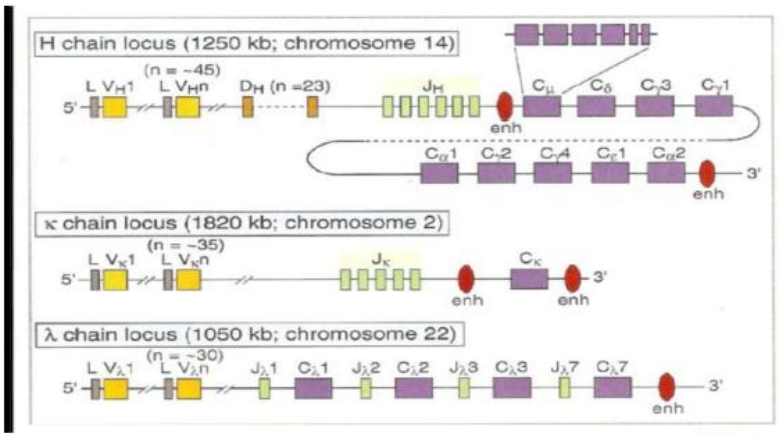
Now looking at the figure below we can see the VDJ on the heavy chain which represents the variable region, as well the constant domain of the heavy chain that could consist of 3 or 4 according to isotype or class of Ig (this depends on the genes downstream of the variable domain).

(eg. Cμ codes for the 4 constant domain of IgM antibody .))



The first gene next to the VDJ is Cμ (this gene is responsible for production of M heavy chain) and next to it Cδ (IgD) and then we have the sequence of IgG , IgA , IgE etc.

Each of these gene segments has a sequence of DNA before it known as a switch region, there's a switch region before the Cμ but if you look at the Cδ there's no switch region.



When you start the synthesis of the heavy chain the switch region of Cμ will join the VDJ with the μ chain. So the B-cell first synthesizes a μ-heavy chain and after that a Kappa or Lambda chain is added to get an IgM . (Remember that the first Ig that will be expressed on B-cell surface is IgM). A B-cell that **only** has IgM on its surface is known as an immature B-cell.

The messenger RNA in this case will have a VDJ region followed by a μ and a δ. In alternative splicing we will sometime get an mRNA which contains μ and other times a δ. This leads to the expression of both IgM & IgD on the surface of B-cell and now it becomes a mature B-cell which will leave the bone marrow and go to secondary immune tissue.

VDJ with μ →IgM VDJ with δ →IgD

B-cell + IgM = Immature B cell

B-cell + IgM + IgD = mature B cell

The specificity to the antigen is the same because the VDJ doesn't change so although they are different isotypes they still have the same specificity.

A student asked why an immature B-cell only expresses IgM and the doctor answered that it's probably for the deletion and the education of B-cells. In case an immature B-cell with only IgM expressed on it encounters a certain antigen the message will be deletion of that B-cell by apoptosis or anergy. If however an IgD is also expressed, the message that's propagated upon binding of an antigen is activation of this mature B-cell.

Another student asked about Igα and Igβ and the doctor said that these are co-receptors that help convey the signal inside the B-cell since the IgM is a small molecule and cannot convey messages on its own. They also help stabilize IgM in the membrane.

Once a cell produces one isotype of Igs it cannot go back to producing IgM because that bit of DNA will be deleted. Class switching (which we will talk about it later) is controlled by CYTOKINES.

Now as far as the Ig's we are concerned with IgM , IgD , IgA1 , IgA2 and Igε. These are present in everybody, so we all have them and that's why they are called ISOTYPES.

ISOTYPE: classes of Ig and subclasses are found in ALL individuals of a species .

ALLOTYPE: some allelic variation in amino acid sequences lead to allotype of Ig in CERTAIN individuals , there are allotypes of gamma and kappa chains as well as alpha chains .

IDIOTYPE: ((antigenicity of paratope)). Paratopes should be different and they're immunogenic due to their heterogeneity. Antibodies that are produced against paratopes are called anti-idiotypes ((anti-antibody))

Biological properties of immune-globulins:

Not all types of Igs can perform all of these functions

1- Precipitation: linking soluble antigens to form precipitate (cross linking of antigens together by antibodies forming an immune-complex → the complex will get bigger and bigger and produce a lattice formation and eventually will precipitate). This happen in abnormal pathologic condition .

2- Agglutination : if the antigen is part of a cell we will have clumping together of particulate antigens producing insoluble aggregates.
*Wiki:Agglutination occurs if an antigen is mixed with its corresponding antibody

3- Opsonisation: coating of bacteria by antibodies facilitating phagocytosis. When a bacteria is encapsulated (the capsule is negatively charged) and a macrophage tries to attack it (its membrane is also negatively charged), repulsion forces make it harder for the macrophage to reach the bacteria. For this same reason antibodies are produced against the capsule to allow the macrophage to pull the bacteria closer to it by recognizing the Fc fragment of the antibody through some receptors on its surface (like a cowboy pulls a cow closer using rope).

4- Complement activation: the antibody on its own cannot activate the complement, it has to bind an antigen so the CH2 site becomes exposed and can attach complement. The activated complement causes opsonisation , cell lysis and chemotaxis.

5- Neutralization of viruses: viruses need receptors to attach to cells and gain access to them, so when a receptor is blocked by means of an antibody viruses are really neutralized.

6- Neutralization of toxins : by binding of antibody to active site

7-ADCC “antibody dependent cell-mediated cytotoxicity ": through NK cells and eosinophil . If a parasite has an IgE on it the eosinophil will stick to it and degranulate releasing the basic protein (so it’s killing mediated through antibody). NK cells can recognize other cells non-specifically but the killing effect when there's antibodies on these cell becomes more apparent. NK cell kills by:
A- **Granzyme**→ activate caspases→ apoptosis
B- **Perforins**→ pore in plasma membrane → cell die .

8-crossing the placenta: only IgG subclasses (except IgG2) .

9-Immobilisation of bacteria: binding to flagella and cilia .

T-cell Receptor

TCR: it is the receptor that belongs to T cells → it's always cell bound & there's no secreted soluble form of this molecule.

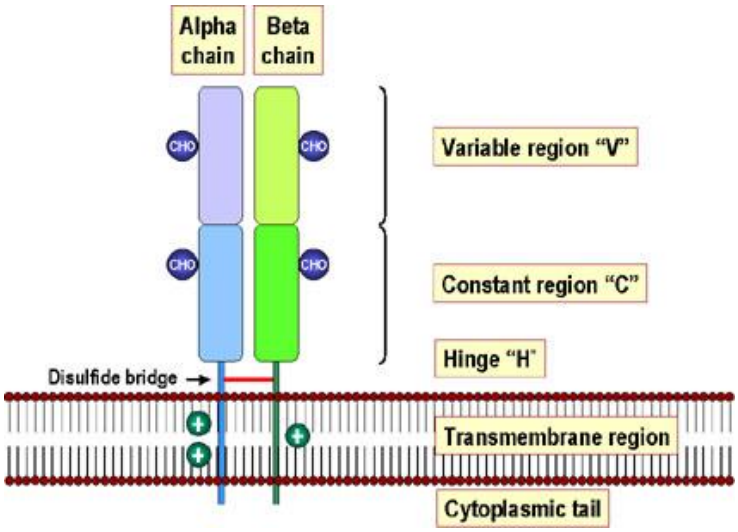
TCR is made of two polypeptide chain: alpha & beta chains
Beta chain is equivalent to heavy chain of Ig's.
Alpha chain is equivalent to light chain of Ig's.
Both undergo gene rearrangement.
Beta is formed first then alpha chain, both of them will give you a TCR.

TCR is a member of the super immune-globulin family due to the presence of the disulfide bonds. It has a variable region on the alpha chain and a constant region. A small subset of T-cells (5%) can have different chains like gamma and delta, these are of different makeup than alpha and beta.

α & β→ 95% of all TCR in T-cells.

λ & δ → 5% of all TCR in T-cells .

The development and production of diversity is exactly similar to what occurs in immunoglobulins → Beta chain is equivalent to the heavy chain , so during the gene rearrangement which drives the activation you will find that we have V ,D , J rearrangement , and then the variable domain will attach to the constant domain forming the beta chain of the TCR , just like the heavy chain in Ig's. but here we have one constant domain coded by 1 gene , not 3 or 4 constant domain as in ig's .



Activation of T-cells is done through signaling but actually TCR is not the only molecule responsible for activation of T-cells; since the tail region is small and cannot transmit signals to the inside of the cell or gives very little amount of signaling upon recognizing the antigen. Activation occurs mostly by accessory molecules which are always in association with the TCR and they are adjacent to it → CD3, Zeta & Eta molecules.

1- CD3: a tri-molecular compound (it has 3 polypeptide chain: λ, δ and ε) that is always associated with TCR. As cluster of differentiation protein it is called CD3 not because it has 3 molecules but because it's the third one to be included/ discovered in the CD nomenclature. It's involved in the signaling pathway for activation of T-cells (upon recognition of the antigen, CD3 molecules transmits signals to the inside of the cell)

2- In order to produce more signaling for more activation there are further accessory molecules that are also included → these molecules are called Zeta & Eta , these molecules can transmit signals to the inside of the cell better, as you can see from their tails.

So recognition occurs through TCR itself, but signaling is mainly achieved by the adjacent molecules. All together form the TCR complex.

During their development, T-cells exit the bone marrow at a very early stage then they go to the thymus "cortex". At that stage these cell don't have any molecules on their surface ((NO TCR, NO CD4, NO CD8)) and they are negative cells known as → double negative (double negative means there is no CD4 or CD8)

As they go in, TCR "alpha & beta chain" start forming and at the same time they express two other molecules → CD4 & CD8. And now they are known as double positive.

Positive selection occurs in these cells that have expressed TCR, CD4, CD8 in order to keep them alive.

Eventually they will loop towards the cortico-medullary junction into the medulla and one of the two positive CD4 & CD8 will be lost, either CD4 or CD8. This determines whether the cell will become a helper T-cell or a cytotoxic T-cell.

CD4 → Helper T-cell CD8 → Cytotoxic T-cell.

We have the other group that makes 4-5 % of T-cells in the body. Not much is known about them or how they develop!! They do not express CD4 or CD8 but they do form TCR ((which will be λ and δ instead of α and β, making them less diverse)). We also don't know if they undergo positive or negative selection, however, these go to the sub-mucosal areas and they will be the first line defense against micro-organisms. Some people say that they are the transition state from innate to acquired immunity.

There are also some T-cells that have CD25 on their surface known as regulatory T-cell ((suppressor)) that develop in different way and come out of the thymus.

And there is another very very small portion of T-cells known as NK T-cells that have TCR and **markers** such as CD60 & CD64. NK T-cells recognize antigen which is most likely to be lipid in conjunction with another molecule similar to MHC.

Thank you ☺

Sorry for any mistakes