LECTURE: 19

Title B-LYMPHOCYTE ACTIVATION AND ANTIBODY PRODUCTION

LEARNING OBJECTIVES:

The student should be able to:

- **Enumerate the two different ways of B-cell activation.**
- **Explain the mechanism of naïve or virgin B-cell activation.**
- **Explain the mechanism of re-activating experienced B cells.**
- **Explain the mechanism of B-cell activation via the T-cell dependent.**
- **Explain the mechanism of B-cell activation via the T-cell independent.**
- **Explain the mechanism of B-cell activation via follicular dendritic cells.**
- **Explain the mechanism of the BCR signals.**
- **Describe the plasma cell, and indicate where they found.**
- **Identify the appropriate immunological technique used in visualizing the immunoglobulins in the cytoplasm of the plasma cells.**
- **Define the type of immunoglobulins produced first.**
- **Enumerate the different immunoglobulin isotypes.**

LECTURE REFRENCE:

1. TEXTBOOK: ROITT, BROSTOFF, MALE IMMUNOLOGY. 6th edition. Chapter 2. pg. 29-30.

2. TEXTBOOK: ABUL K. ABBAS. ANDREW H. LICHTMAN. CELLULAR AND MOLECULAR IMMUNOLOGY. 5TH EDITION. Chapter 9 .pg 189-214.

3. TEXTBOOK: LAUREN SOMPAYRAC. HOW THE IMMUNE SYSTEM WORKS. Chapter 3. pg 29-35.

B-LYMPHOCYTE ACTIVATION AND ANTIBODY PRODUCTION

B CELL RECEPTOR COMPLEX

Most of the peripheral blood B cells express two immunoglobulin isotypes on their surfaces **IgM** and **IgD.** Very **few** cells in the **circulation** express IgG, IgA, or IgE. But these cells bearing immunoglobulins are found in large quantity in specific location, for example; B lymphocytes bearing IgA are found in large quantity in intestinal mucosa. The B-lymphocyte complex is formed by the association of the surface immunoglobulins with other molecules on the B cell surface as well. These molecules are disulphide-bonded heterodimer of:

Igα (CD79 a, a 34 kDa molecule and a product of the mb-1 gene)
Igβ (CD 79b, a 39 kDa molecule and product of the B29 gene)

OTHER B CELL MARKERS

1. MHC class II antigens (which is important in the cooperative interaction with T cells. The class II molecules consist of HLA- DP, DQ, and DR antigens.

2. Complement receptors for C3b (CR1, CD35), and C3d (CR2, CD21)

3. Fc receptors for IgG (Fcγ RII, CD32)

4. The main markers currently used to identify human B cell are CD19, CD20, and CD22.

5. CD 72-78 are markers found in both human and murine

6. CD40 is an important marker on B cells and is involved in the cognate interaction between T and B cells.

7. CD5 is usually present on the T cells but it was detected on one set of the B cells as well. B cells expressing CD5 is called B1a cell, where the conventional B cell is called B2 cells.

MECHANISM OF IMMUNOGLOBULIN

About one billion B-cells are produced each day during the entire life of human. B-cells select B-cell receptor "BCR" gene segments during their early days in the bone marrow. Gene segments usually assembled to make **a complete gene** and the BCR encoded by this gene is then displayed on the surface of the cell where it can receive signals.

The specificity of the antibodies produced by a particular B-cell is identical to that of the B-cell receptors "BCR", **except** that it **lacks** the protein sequences that anchor the BCR to the outside of the cell. Lacking this anchor, the antibody then can be easily **secreted** to the outside of the cell to do its duties.

The BCR is formed from two types of proteins, the heavy and light chain, each of them is encoded by genes that are assembled from gene segments. The gene segments that will be chosen to make up the final heavy chain gene are located on chromosome fourteen and each B cell has two chromosome fourteens (one from the father and the other form the mother). This will cause a problem because each B cell makes only one type of antibody. Therefore, because there are two sets of heavy chain segments, it will be necessary to "silence" the segments on one chromosome fourteen to keep from getting two different heavy chain proteins made by the same B cell. Of course, ALLAH could have chosen to make one chromosome a "dummy", so that the other would always be the one that was used to make the heavy chain protein, but ALLAH did not. That would have been too boring. Instead, ALLAH came up with a much sweeter scheme, which it exhibited as a game of cards with the two chromosomes. It is a game a winner takes all, in which each chromosome tries to rearrange its cards (gene segments) until it finds an arrangement that works. The first player to do this wins.

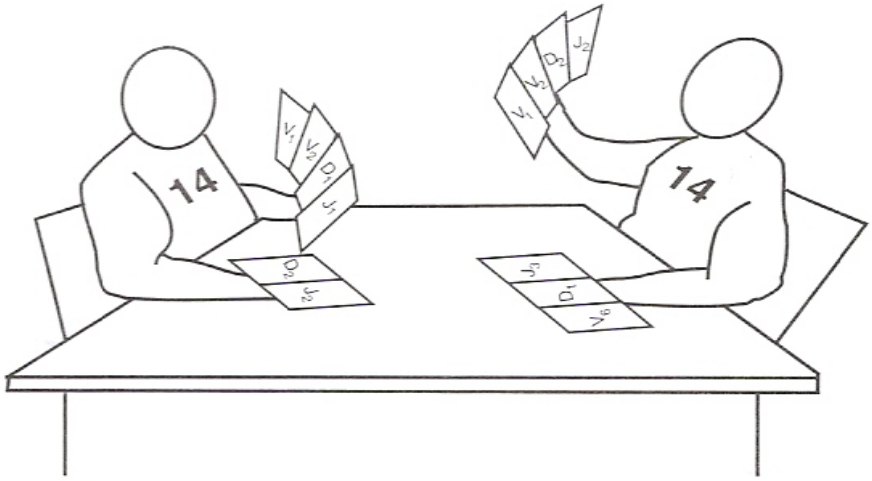
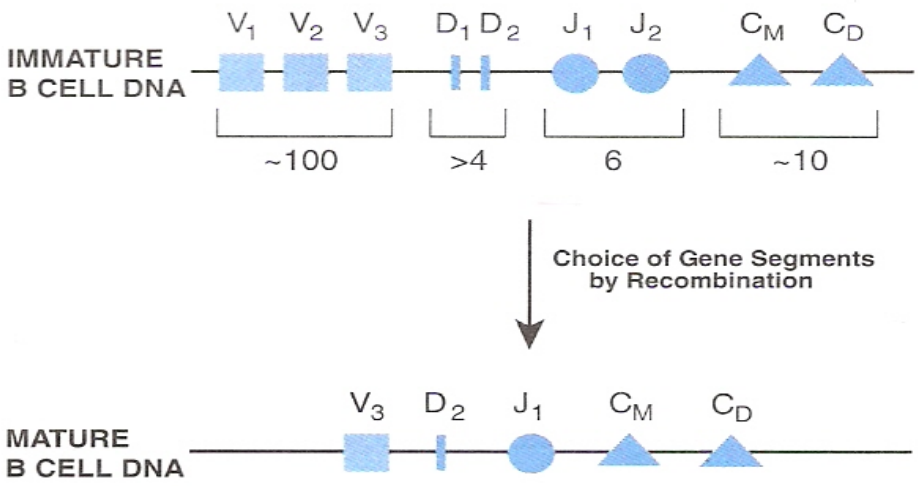


Figure-1 the process of selecting gene segments to make a B cell receptor

Usually the finished heavy chain protein is made up of four segments (V, D, J, and C), and these are lined up along chromosome fourteen are multiple, slightly different copies of each kind of segment.



The player in this card game first choose one each of the possible D and J segments, and these are joined together by deleting the DNA sequences in between them. Then one of the many V segments is chosen, and this "card" is joined to the DJ segment, again by deleting the DNA in between. Next to the rearranged J segment is a string of gene segments that code for various constant regions. By default, the constant region for IgM and IgD are used to make the BCR, just because they are first in line.

Immunologists call these joined together gene segment a "gene rearrangements", but it is rally more the result of cutting and pasting than rearranging. Anyway, the chosen V, D, and J segments and the constant region segments all lined up adjacent to each other on the chromosome 14.

Next the rearranged gene segments are tested. What's the test? As you know, prot3ein translation stops codons, so if the gene segments are not joined up just right ("in frame"), the protein translation machinery will encounter a stop codon and terminate protein assembly right in the middle of ht heavy chain. If this were the happen, the result would be a useless little piece of protein. In fact, you can calculate that each player has only about one chance in nine of assembling a winning combination of gene segments that will produce a full length heavy chain protein. Immunologists call such a combination of gene segments a "productive rearrangement". If one of the chromosomes tat is playing this game ends up with a productive rearrangement, the winning heavy chain protein is made and transported to the cell surface where it signals to the losing chromosome that the game is over.

Since each player has only about a one in nine chance of success, you may be wondering what happens if both chromosomes fail to assemble gene segments that result in a productive rearrangement. Well the B cell dies. That's right, it commit suicide! It's a high stakes game, because a B cell that can not express a receptor is totally useless.

If the heavy chain is rearrangement is productive, the light chain players step up to the table. The rules of this game are very similar to the rules of the heavy chain game except that there is a second test which must be passed to win: the completed heavy and light chain proteins must fit together properly to make a complete antibody.

If the B cell fails to productively rearrange heavy and light chains, or if the two chains don't match up correctly, the B cell commits suicide. So every mature B cell produces one and only one kind of BCR or antibody, made up of one and only one kind of heavy and light chain. Because of the mix and match strategy that is used t5o make the final heavy and light chain genes, the receptors on different B cells are so diverse that collectively, they can probably recognize any organic molecule that could exist. When you consider how many molecules that might be, the fact that a simple scheme like this can cr3eate such diversity is truly breathtaking.

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