13.1D: Generation of Antibody Diversity

Skills to Develop

1. Define gene translocation and relate it to each B-lymphocyte being able to produce an antibody with a unique shaped Fab.

2. Define the following:
   a. combinatorial diversity
   b. junctional diversity
   c. affinity maturation

In this section we will look at generation of antibody diversity through gene translocation. As mentioned earlier, the immune system of the body has no idea as to what antigens it may eventually encounter. Therefore, it has evolved a system that possesses the capability of responding to any conceivable antigen. The immune system can do this because both B-lymphocytes and T-lymphocytes have evolved a unique system of gene-splicing called gene translocation, a type of gene-shuffling process where various different genes along a chromosome are cut out of one location and joined with other genes along the chromosome.

To demonstrate this gene translocation process, we will look at how each B-lymphocyte becomes genetically programmed to produce an antibody functioning as a B-cell receptor (BCR) having a unique shaped Fab. As mentioned above, the Fab portion of an antibody is composed of 2 protein chains: a heavy and a light (see Figure 1).

The variable heavy chain portion of the Fab is coded for by a combination of 3 genes, called VH (variable heavy), DH (diversity heavy), and JH (joining heavy). The variable light chain portion of the Fab consists of either a kappa chain or a lambda chain coded for by a combination of 2 genes, VL (variable light) and JL (joining light). In the DNA of each B-lymphocyte there are multiple forms of each one of these variable determinant genes. Although the exact number of each gene isn't known and varies from person, there are approximately 38-46 VH genes; 23 DH genes; 6 JH genes;
34-38 kappa VL genes; 5 kappa JL genes; 29-33 lambda VL genes; and 4-5 lambda JL genes.

While a person inherits alleles for the various V(D)J genes from each parent, an individual B-lymphocyte will only express an inherited allele set from one parent. This increases a greater diversity of antibodies in that individual.

Through random gene translocation, any combination of the multiple forms of each gene can join together (see Figure 2) resulting in thousands of possible gene combinations. This is known as combinatorial diversity.

Gene translocation of the V(D)J genes is initiated when an enzyme called V(D)J recombinase recognizes recombination signal sequences located at the 3' end of V genes, the 5' end of J genes, and both ends of D genes. As a result, the chromosome forms a loop allowing different genes from different regions along the chromosome to align (see Figure 3). In the heavy chain any J-heavy gene and any D-heavy gene align and bind together as the genes are cut from one location and pasted into another. Subsequently, any one of the V-heavy genes is attached to this DJ segment. In the light chain, chromosomal looping enables any V-light gene to attach to any J-light gene.

During gene translocation, specialized enzymes in the B-lymphocyte cause splicing inaccuracies wherein additional nucleotides are added or deleted at the various gene junctions. This change in the nucleotide base sequence generates even greater diversity in Fab shape. This is called junctional diversity.

Furthermore, as B-lymphocytes proliferate, they undergo affinity maturation, a process that "fine tunes" the shape of the Fab epitope binding site. This is because the immunoglobulin V genes of B-lymphocytes have a mutation rate between 1000 to 10,000 times greater than other human genes in the body. This somatic hypermutation creates a great opportunity for selection of variant B-lymphocytes with even better fitting antigen-binding sites that fit the epitope more precisely. The longer and more tightly the antigen binds to the B-cell receptor, the greater the chance that B-lymphocyte has of surviving and replicating. In other words, the "fit" of the antibody can be improved over time. Affinity maturation occurs in the germinal centers of the lymph nodes.

Most likely humans produce at least $10^{11}$ different shaped BCRs. Keep in mind that the 3-dimensional shape of a protein is ultimately determined by the sequence of its amino acids and the sequence of amino acids is determined by the order of nitrogenous bases in the genes coding for that protein. Between combinatorial diversity, junctional diversity, and affinity maturation, there are probably billions of possible gene combinations and rearrangements that can code for the Fab portions of an antibody. Chances are, then, each B-lymphocyte will carry out a unique series of gene translocations and be able to produce an antibody with a unique shaped epitope-binding site.

Because gene translocation is a random process, some immature B-lymphocytes do wind up making B-cell receptors that fit the body's own antigens. Immature B-lymphocytes with self-reactive B-cell receptors may be stimulated to undergo a new gene rearrangement to make a new receptor that is no longer self-reactive. Recognition of self antigen can reactivate genes that allow the B-lymphocyte to carry out new light chain V-J recombinations and enabling that cell to express a new B-cell receptor. This process is called receptor editing.
Alternately, self-reactive B-lymphocytes can also undergo negative selection. Since the bone marrow, where the B-lymphocytes are produced and mature, is normally free of foreign substances, any B-lymphocytes that bind substances there must be recognizing "self" and are eliminated by apoptosis, a programmed cell suicide. Apoptosis results in the activation of proteases within the target cell which then degrade the cell's structural proteins and DNA.

Summary

1. The adaptive immune responses have evolved a system that possesses the capability of responding to any conceivable antigen the body might eventually encounter through a process called gene translocation.
2. Gene translocation is a type of gene-shuffling process where various different genes along a chromosome are cut out of one location and joined with other genes along the chromosome to create a maximum number of different B-cell and T-cell receptors.
3. Each B-lymphocyte becomes genetically programmed to produce an antibody functioning as a B-cell receptor (BCR) having a unique shaped Fab.
4. The variable portion of both the heavy and light chain of the antibody is coded for by multiple genes and there are multiple forms of each one of these variable genes.
5. Through random gene translocations, any combination of the multiple forms of each gene can join together resulting in thousands of possible gene combinations. This is known as combinatorial diversity.
6. During gene translocation, specialized enzymes in the B-lymphocyte cause splicing inaccuracies wherein additional nucleotides are added or deleted at the various gene junctions and this change in the nucleotide base sequence generates even greater diversity in Fab shape. This is called junctional diversity.
7. As B-lymphocytes proliferate, they undergo affinity maturation, a process that "fine tunes" the shape of the Fab epitope binding site through a high rate of somatic hypermutation. This creates a great opportunity for selection of variant B-lymphocytes with even better fitting antigen-binding sites that fit the epitope more precisely.
8. Immature B-lymphocytes with self-reactive B-cell receptors may be stimulated to undergo a new gene rearrangement to make a new receptor that is no longer self-reactive through a process called receptor editing. Alternately, self-reactive B-lymphocytes can also undergo negative selection whereby any B-lymphocytes that bind substances recognized as "self" and are eliminated by apoptosis.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Define gene translocation. (ans)
2. Relate gene translocation to each B-lymphocyte being able to produce an antibody with a unique shaped Fab. (ans)
3. Define the following:
   a. combinatorial diversity (ans)
   b. affinity maturation (ans)
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