4. B-Cell Development and Antibody Maturation

LEARNING OBJECTIVES:

1. Understand the coordinated process how a B cell that expresses a single antibody is generated during the rearrangement of the V, D, J gene segments in the bone marrow.
2. Become familiar with the concepts of allelic exclusion and B-cell tolerance.
3. Understand the mechanism of clonal selection and affinity maturation that generates B cells with high-affinity antibodies against pathogens.
4. Recognize that the germinal center reaction generates high-affinity memory B cells and plasma cells through somatic hypermutation and class switch recombination.
5. Recognize that the DNA-modifying processes occurring during the germinal center reaction can occasionally cause oncogenic chromosome translocations.

SUMMARY

1. The rearrangement of immunoglobulin genes during B-cell development in the bone marrow is ordered: *i)* rearrangement of the heavy chain genes, *ii)* testing of a successful rearrangement that produces a functional heavy chain expressed as pre-B cell receptor, *iii)* rearrangement of the light chain genes, *iv)* testing of a successful rearrangement yielding a functional B cell receptor, *v)* ablation of auto-reactive B-cell receptors.

2. Allelic exclusion ensures that each B-cell clone expresses a single antibody on the cell surface and thus establishes specificity. Two checkpoints confer allelic exclusion: the expression of the pre-B cell receptor and, following successful light chain rearrangement, that of the B-cell receptor.

3. Deletion of self-reactive clones establishes immunological tolerance. *Central tolerance* is the tolerance to self antigens established in lymphocytes developing in central lymphoid organs and is mediated by clonal deletion. *Peripheral tolerance* is established in the peripheral tissues and is mediated by clonal deletion, anergy, or ignorance.

4. B cells activated by exogenous antigen with the help of T cells undergo the germinal center reaction. Here, the rearranged antibody genes are diversified by somatic hypermutation and class switch recombination to generate high-affinity antibodies against the invading pathogen. The descendents of the germinal center reaction are plasma cells that help to eliminate the infection and memory B cells that are able to mount an effective antigen-recall response.

5. Mistakes in the DNA-modifying processes of somatic hypermutation and class switch recombination may cause chromosome translocations that could lead to the constitutive activation of proto-oncogenes, potentially culminating in the development of lymphomas.