Calame Lecture #1

Clonotypic Antigen Receptors and Generation of Receptor Diversity

Teaching Objectives

1. Learn the relationship between structure and function of the clonotypic receptors for B and T lymphocytes, namely immunoglobulin and TCR proteins.

2. Learn the structural basis for specific recognition of foreign molecules by immunogloblulins.

3. Learn the organization of the loci encoding immunoglobulin and TCR proteins.

4. Learn how Ig and TCR genes are rearranged, transcribed and expressed.

5. Learn the functional consequences of gene rearrangement for Ig and TCR loci**.**

Summary

1. Antibodies are the clonotypic receptors for B cells.

2. T cell receptors are clonotypic receptors for T cells.

3. Antibodies are tetramers of 2 identical light chains and 2 identical heavy chains. Each chain has variable constant regions.

4. Antibody variable regions recognize antigen; antibody heavy chain constant regions eliminate antigen.

5. Hypervariable regions within the variable domains xare antigen-contact sites. HV regions from both light and heavy chains are necessary to form an antigen binding site.

6. TCRs resemble two Ig light chains; their sole function is to recognize antigen.

7. Ig and TCR genes are encoded by 30-150 V gene segments, several J and D gene segments and few C gene segments.

8. Unrearranged Ig and TCR genes are inactive (not expressed as either mRNA or protein).

9. VDJ recombination, involving random recombination between V, D, and J gene segments, in a single Ig or TCR locus, forms functional Ig and TCR genes.

10. VDJ recombination involves deletion and loss of DNA.

11. RAG1 and RAG2 genes are lymphoid specific components of the VDJ

recombination machinery and are required for formation of Ig and TCR genes. Some forms of Omenn's Syndrome involve mutation of RAG genes.

12. Non-lymphoid specific components of the DNA double strand break repair mechanism are also required for VDJ recombination

13. VDJ recombination provides a mechanism to generate huge amounts of diversity, primarily via combinatorial mechanisms.

14. VDJ recombination also juxtaposes regulatory elements that activate Ig or TCR gene transcription

Calame Lecture #2

B Cell Development

Learning Objectives

1. Learn the timing and location of both antigen-independent and antigen-dependent B cell development.

2. Learn the nature and consequences of germinal center reactions including isotype switch recombination and somatic hypermutation

3. Learn the function and characteristics of B cells following antigen-specific activation in the periphery.

4. Learn the molecular mechanisms responsible for allelic exclusion and its functional consequences.

5. Learn mechanisms responsible for both central and peripheral tolerance.

6. Learn the basis of genetic diseases affecting B cell development.

Summary

1. Antigen-independent B cell development occurs in the bone marrow and depends on signals from stroma cells.

2. DNA rearrangements establish the primary B-cell repertoire in the bone marrow, creating *diversity.*

3. Allelic exclusion ensures that each clone expresses a single antibody on the surface, establishing *specificity.*

4. PreBCR and BCR provide critical checkpoints for B cell development in the bone marrow.

5. Deletion and editing of self-reactive clones in the bone marrow establishes central *tolerance.*

6. Antigen-dependent B cell development occurs in the periphery (spleen, lymph nodes).

7. Antigen selects specific clones for proliferation and maturation.

8. Bacterial polysaccharides are T-cell independent activators of B cells. Protein antigens require T cells to help B cells mature.

9. T cells and B cells communicate in several ways:
   -B cells process antigen and present peptide-MHC to T cells; this stimulates the T cells.

-T cells provide cell-cell signals to B cells via CD40L/CD40
-T cells provide soluble cyotkine signals to B cells

10. T-cell dependent B cell maturation occurs in Germinal Centers.

11. Affinity maturation in GCs results from somatic hypermutation + selection for high antigen-binding affinity

12. Class switch recombination occurs in GCs and is directed by specific T cell cytokines

13. Deletion, editing or anergy of self-reactive clones provides peripheral tolerance.

14. Memory B cells and plasma cells emerge from the GC reaction.