11.7D: Isotype Class Switching

Isotype class switching is a biological mechanism that changes a B cell’s production of antibody from one class to another.

Learning Objectives

• Describe the process of class switch recombination that results in changes in the antibody-heavy chain

Key Points

• The antibody isotype of a B cell changes during cell development and activation. Immature B cells have never been exposed to an antigen and are known as naïve B cells. B cells begin to express both IgM and IgD when they reach maturity and renders the B cell ‘mature’ and ready to respond to antigen.

• If activated B cells encounter specific signaling molecules via their CD40 and cytokine receptors (both modulated by T helper cells), they undergo antibody class switching to produce IgG, IgA or IgE antibodies that have defined roles in the immune system.

• During class switch recombination the constant region portion of the antibody-heavy chain is changed, but the variable region of the heavy chain stays the same; thus, class switching does not affect antigen specificity.

• The antibody retains affinity for the same antigens, but can interact with different effector molecules. This allows different daughter cells from the same activated B cell to produce antibodies of different isotypes or subtypes (e.g. IgG1, IgG2 etc.).

Key Terms

• **isotype**: Antibodies can come in different varieties known as isotypes, which refer to the genetic variations or
differences in the constant regions of the heavy and light chains of the antibody.

- **class switch recombination**: A biological mechanism that changes a B cell’s production of antibody from one class to another; for example, from an isotype called IgM to an isotype called IgG.

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**Isotype Class Switching**

Antibodies can come in different varieties, known as isotypes or classes. In placental mammals there are five antibody isotypes: IgA, IgD, IgE, IgG and IgM. They are each named with an “Ig” prefix that stands for immunoglobulin (another name for antibody) and differ in their biological properties, functional locations, and ability to deal with different antigens.

The antibody isotype of a B cell changes during cell development and activation. Immature B cells, which have never been exposed to an antigen, are known as naïve B cells and express only the IgM isotype in a cell surface bound form. B cells begin to express both IgM and IgD when they reach maturity; the co-expression of both of these immunoglobulin isotypes renders the B cell ‘mature’ and ready to respond to an antigen. B cell activation follows engagement of the cell-bound antibody molecule with an antigen, causing the cell to divide and differentiate into an antibody-producing cell, called a plasma cell. In this activated form, the B cell starts to produce antibody in a secreted form rather than a membrane-bound form. If these activated B cells encounter specific signaling molecules via their CD40 and cytokine receptors (both modulated by T helper cells), they undergo antibody class switching to produce IgG, IgA or IgE antibodies (from IgM or IgD) that have defined roles in the immune system.

Immunoglobulin class switching (or isotype switching, or isotypic commutation, or class switch recombination (CSR)) is a biological mechanism that changes a B cell’s production of antibody from one class to another; for example, from an isotype called IgM to an isotype called IgG. During this process, the constant region portion of the antibody-heavy chain is changed, but the variable region of the heavy chain stays the same (the terms “constant” and “variable” refer to changes or lack thereof between antibodies that target different epitopes). Since the variable region does not change, class switching does not affect antigen specificity. Instead, the antibody retains affinity for the same antigens, but can interact with different effector molecules. This allows different daughter cells from the same activated B cell to produce antibodies of different isotypes or subtypes (e.g. IgG1, IgG2 etc.).

Class switching occurs by a mechanism called class switch recombination (CSR) binding. Class switch recombination is a biological mechanism that allows the class of antibody produced by an activated B cell to change during a process known as isotype or class switching. During CSR, portions of the antibody-heavy chain locus are removed from the chromosome, and the gene segments surrounding the deleted portion are rejoined to retain a functional antibody gene that produces antibody of a different isotype. Double-stranded breaks are generated in DNA at conserved nucleotide motifs, called switch (S) regions, which are upstream from gene segments that encode the constant regions of antibody-heavy chains; these occur adjacent to all heavy chain constant region genes with the exception of the δ-chain. DNA is nicked and broken at two selected S-regions by the activity of a series of enzymes, including Activation-Induced (Cytidine) Deaminase (AID), uracil DNA glycosylase and apyrimidic/apurinic (AP)-endonucleases. The intervening DNA between the S-regions is subsequently deleted from the chromosome, removing unwanted μ or δ heavy chain constant region exons and allowing substitution of a γ, α or ε constant region gene segment. The free ends of the DNA are rejoined by a process called non-homologous end joining (NHEJ) to link the variable domain exon to the desired downstream constant domain exon of the antibody-heavy chain. In the absence of non-homologous end joining, free ends of DNA may be rejoined by an alternative pathway biased toward microhomology joins. With the exception of the μ
and δ genes, only one antibody class is expressed by a B cell at any point in time.

Figure: **Class Switch Recombination**: Mechanism of class switch recombination that allows isotype switching in activated B cells.