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Commentary

Regulatory Gene Sequence and Changes in the Immunoglobulin Class

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DESCRIPTION

It is possible for B cells to go from producing isotype IgM to producing isotype IgG by a biological process known as immunoglobulin class switching, also known as isotype switching, isotypic commutation, or Class-Switch Recombination (CSR). During this process, the constant-region portion of the antibody heavy chain is altered, while the variable area of the heavy chain is left unaltered (the terms variable and constant refer to changes or lack thereof between antibodies that target different epitopes). Antigen specificity is unaffected by class switching since the variable region is unaltered. Instead, the antibody can interact with various effector molecules while still maintaining affinity for the same antigens.

After a mature B cell is activated by the membrane-bound antibody molecule (also known as the B cell receptor), different classes of antibodies are produced, each with the same variable domains as the initial antibody made in the immature B cell during V(D)J recombination, but with different constant domains in their heavy chains.

Naive mature B cells produce IgM and IgD, the first two heavy chain segments in the immunoglobulin loci. After becoming stimulated by an antigen, these B cells multiply. These activated B cells produce IgG, IgA, or IgE antibodies when they come into touch with particular signalling molecules via their CD40 and cytokine receptors (both of which are controlled by T helper cells). The immunoglobulin heavy chain's constant region changes during class switching, while the variable sections, and consequently the antigenic specificity, stay the same. This leads to the development of several isotypes or subtypes of antibodies (such as IgG1, IgG2, etc.) in distinct daughter cells from the same activated B cell.

Class Switch Recombination (CSR) binding is the mechanism used to switch between classes. A biological process called class switch recombination causes the antibody class of an active B cell to change during the isotype or class switching process. A functional antibody gene that produces a specific isotype of antibody is produced as a result of CSR, which involves the removal of portions of the antibody heavy chain locus from the chromosome and the rejoining of the gene segments covering the deleted section. Switch (S) regions, conserved nucleotide motifs upstream of gene segments encoding antibody heavy chain constant regions, are present adjacent to all heavy chain constant region genes with the exception of the -chain constant region gene, and are the sites of double-stranded breaks in DNA. DNA is nicked and broken at two distinct S-regions by a number of enzymes, including activation-induced (cytidine) deaminase (AID), uracil DNA glycosylase, and apyrimidic/apurinic (AP)-endonucleases. Then, the DNA from the chromosome between the S-regions is deleted, getting rid of any heavy chain constant region exons that weren't necessary and enabling the substitution of a, or constant region gene fragment. The free ends of the DNA are connected by a procedure known as Non-Homologous End Joining (NHEJ) in order to connect 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 can be rejoined by a different mechanism that is biassed against microhomology joins. With the exception of the and genes, a B cell can only express one antibody class at a time. Class switch recombination can also happen as an inter-chromosomal translocation mixing immunoglobulin heavy chain genes from both alleles (in 10 to 20% of cases, depending on the Ig class), even though it is frequently a deletional mechanism that rearranges a chromosome in "cis."

In addition to the target S regions' highly repetitive structure, class switching necessitates transcription and splicing out of S regions from transcripts of immunoglobulin heavy chains (where they lie within introns). The more distant Calpha gene's downstream neighbour, the 3' regulatory region (3'RR), controls chromatin remodelling, transcriptional accessibility, AID, and the synapsis of broken S sections. In some circumstances, AID will target the 3'RR super-enhancer, resulting in DNA breaks and a junction with S, which determines Locus Suicide Recombination (LSR) and deletion of the Ig heavy chain locus.

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