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Commentary

Immunoglobulin Class Switching

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DESCRIPTION

Immunoglobulin class switching, also known as isotype switching, isotypic commutation, or class-switch recombination (CSR), is a biological process that allows B cells to switch from producing isotype IgM to producing isotype IgG. The constant-region portion of the antibody heavy chain is modified during this process, but the variable region of the heavy chain remains unchanged (the terms variable and constant refer to changes or lack thereof between antibodies that target different epitopes). Class switching has no effect on antigen specificity since the variable region remains unchanged. Instead, the antibody retains affinity for the same antigens, but can interact with different effector molecules.

Class Switching occurs after activation of a mature B cell through its membrane-bound antibody molecule (or B cell receptor), different classes of antibody are produced, each with the same variable domains as the original antibody created in the immature B cell during V(D)J recombination, but different constant domains in their heavy chains.

IgM and IgD, the first two heavy chain segments in the immunoglobulin locus, are generated by naive mature B cells. These B cells proliferate after being activated by antigen. If these activated B cells come into contact with specific signalling molecules through their CD40 and cytokine receptors (both of which are modulated by T helper cells), they develop IgG, IgA, or IgE antibodies. The constant region of the immunoglobulin heavy chain shifts during class switching, but the variable regions, and thus antigenic specificity, remain the same. This causes different daughter cells from the same activated B cell to develop different isotypes or subtypes of antibodies (e.g., IgG1, IgG2, etc.

Class switching is accomplished by a process known as class switch recombination (CSR) binding. Class switch recombination is a biological mechanism that causes an activated B cell's antibody class to shift during the isotype or class switching process. During CSR, parts of the antibody heavy chain locus are removed from the chromosome, and the gene segments covering the deleted portion are rejoined, resulting in a functional antibody gene that creates a particular isotype of antibody. Double-stranded breaks occur in DNA at conserved nucleotide motifs known as switch (S) regions, which are located upstream from gene segments that encode antibody heavy chain constant regions; these are found adjacent to all heavy chain constant region genes with the exception of the -chain constant region gene. A series of enzymes, including activation-induced (cytidine) deaminase (AID), uracil DNA glycosylase, and apyrimidic/apurinic (AP)-endonucleases, nick and break DNA at two specific S-regions. The DNA between the S-regions is then removed from the chromosome, eliminating any unnecessary or heavy chain constant region exons and allowing the replacement of a, or constant region gene fragment. To connect the variable domain exon to the desired downstream constant domain exon of the antibody heavy chain, the free ends of the DNA are rejoined by a process known as non-homologous end joining (NHEJ).Free ends of DNA can be rejoined by an alternate pathway biased against microhomology joins in the absence of non-homologous end joining. Only one antibody class is expressed by a B cell at any given time, with the exception of the genes. Though class switch recombination is often a deletional mechanism that rearranges a chromosome in "cis," it may also occur as an inter-chromosomal translocation mixing immunoglobulin heavy chain genes from both alleles (in 10 to 20% of cases, depending on the Ig class).

GENE REGULATORY SEQUENCES RESPONSIBLE FOR CLASS SWITCHING

In addition to the target S regions' extremely repetitive structure, class switching requires S regions to be transcribed and spliced out of immunoglobulin heavy chain transcripts (where they lie within introns). The 3' regulatory region (3'RR), which is located downstream of the more distal Calpha gene, regulates chromatin remodelling, accessibility to transcription and AID, and synapsis of broken S regions. In certain cases, AID will target the 3'RR super-enhancer, causing DNA breaks and a junction with S, which deletes the Ig heavy chain locus and determines locus suicide recombination (LSR).

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