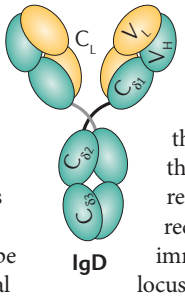
MILESTONE 8

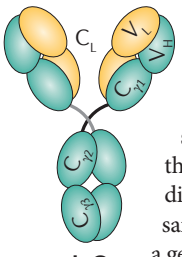
Functional switching

Whereas recombination and hypermutation of immunoglobulin variable (V) regions generate antibody diversity and a broad range of specificities (MILESTONE 10), the immunoglobulin heavy-chain constant region (C) determines the immunoglobulin class (or isotype) and ultimately defines how the immune system is activated. Each antibody isotype leads to distinct immunological functions: immunoglobulin M (IgM) and IgD are a first-line defense mechanism; IgA is secreted in mucosal tissues to prevent pathogen colonization; IgE binds to allergens and parasitic worms; and the various IgG subclasses provide the bulk of antibody-based immunity to pathogens.



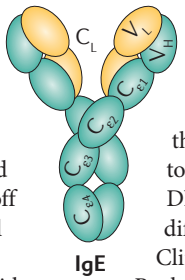
IgD

The identification of the mechanism by which B cells switch isotype, a process called 'class-switch recombination' (CSR), came in a step-wise fashion. The first evidence of isotype switching was reported in 1970, when Alfred Nisonhoff and colleagues found identical light chains on IgM and IgG antibodies from one patient with multiple myeloma and identified an identical 27-amino-acid sequence in the V region of both heavy chains. Given that immunoglobulin V regions are heavily modified, the presence of a shared sequence indicated that the two antibodies of different isotypes had the same origin; therefore, a genetic switching event must have occurred during the expansion of that particular B cell clone. Ten years later, support for this theory came as researchers found that the production of IgA and IgG antibodies requires two distinct recombination events.



IgG

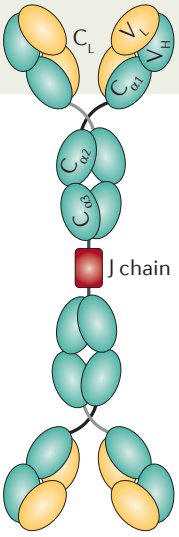
Subsequent studies showed that naive B cells develop as producers of IgM (containing a C_μ region), but during maturation and differentiation, CSR is triggered and replaces their isotype, which increases the efficiency of the immune response. CSR is a DNA-recombination event on the immunoglobulin heavy-chain locus that leads to substitution of the C_μ region for a C_γ region (IgG), C_ε region (IgE) or C_α region (IgA) and thereby switches the B cell's antibody isotype. The presence of different, contiguous C regions in the immunoglobulin heavy-chain locus probably originated from duplication of an ancient C_μ exon and of its flanking sequences; the homology in the different C-loci flanking sequences, later called 'switch' (S) sequences, is key for CSR (MILESTONE 7).



IgE

Research efforts in the field were not restricted to the identification of the DNA events that generate different isotypes. In 1987, Clifford Snapper and William Paul described how the T cell cytokines IFN-γ and IL-4 have strong but opposite effects on the antibody isotypes produced by B cells. Whereas IFN-γ stimulates the production of antibodies of the IgG2a subclass and inhibits that of IgE and other IgG isotypes, IL-4 promotes the expression of IgG1 and IgE but inhibits that of IgM and other IgG subtypes, including IgG2a. It quickly became clear that T cell help is critical in shaping B cell responses.

The molecular mechanism underlying the recombination of C regions of the immunoglobulin heavy-chain locus during CSR was elucidated further by Tasuku Honjo and colleagues, who in 2000 identified the cytidine deaminase AID as a key enzyme in class switching from IgM to IgA. It is now known that CSR events are triggered by AID-mediated deamination of deoxycytosines into deoxyuracils in the C_μ S region and that uracil DNA glycosylase generates DNA breaks by removing those deoxyuracils. The final step of recombination occurs as members of the non-homologous end-joining or alternative end-joining pathways, such as 53BP1, resolve these double-stranded DNA breaks, effectively replacing the C_μ region with C_γ, C_ε or C_α by joining distal S regions.



IgA

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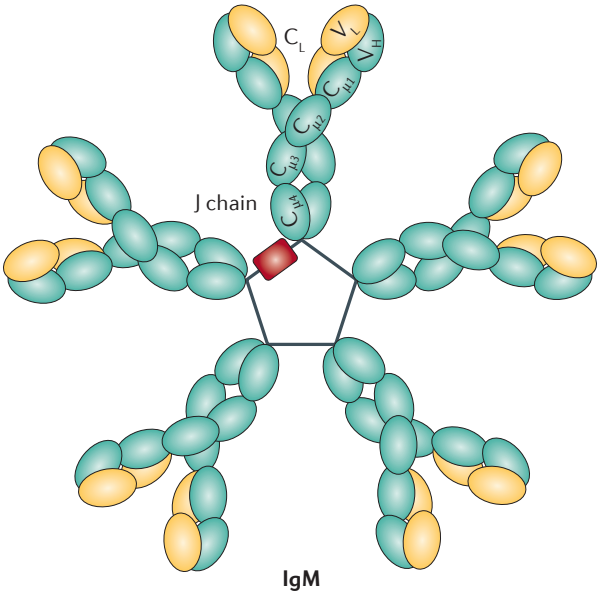

IgM

Whereas V(D)J recombination creates diversity in the antigen-binding region of antibodies, class-switch recombination determines how an antibody will interact with the immune system. Shown here are monomeric IgD, IgE and IgG, along with the dimeric and pentameric forms of IgA and IgM. Image credit: Nature Publishing Group.

ORIGINAL RESEARCH PAPERS Wang, A.C. *et al.* Evidence for control of synthesis of the variable regions of the heavy chains of immunoglobulins G and M by the same gene. *Proc. Natl Acad. Sci. USA* **66**, 337–343 (1970) | Davis, M.M. *et al.* An immunoglobulin heavy-chain gene is formed by at least two recombinational events. *Nature* **283**, 733–739 (1980) | Snapper, C.M. & Paul, W.E. Interferon-γ and B cell stimulating factor-1 reciprocally regulate Ig isotype production. *Science* **236**, 944–947 (1987) | Muramatsu, M. *et al.* Class switch recombination and hypermutation require activation-induced cytidine deaminase (AID), a potent RNA editing enzyme. *Cell* **102**, 553–563 (2000).
FURTHER READING Xu, Z. *et al.* Immunoglobulin class-switch DNA recombination: induction, targeting and beyond. *Nat. Rev. Immunol.* **12**, 517–531 (2012).