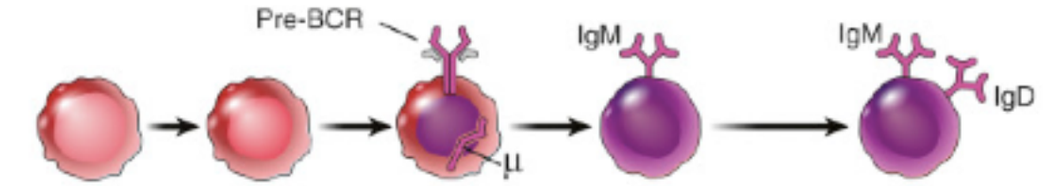
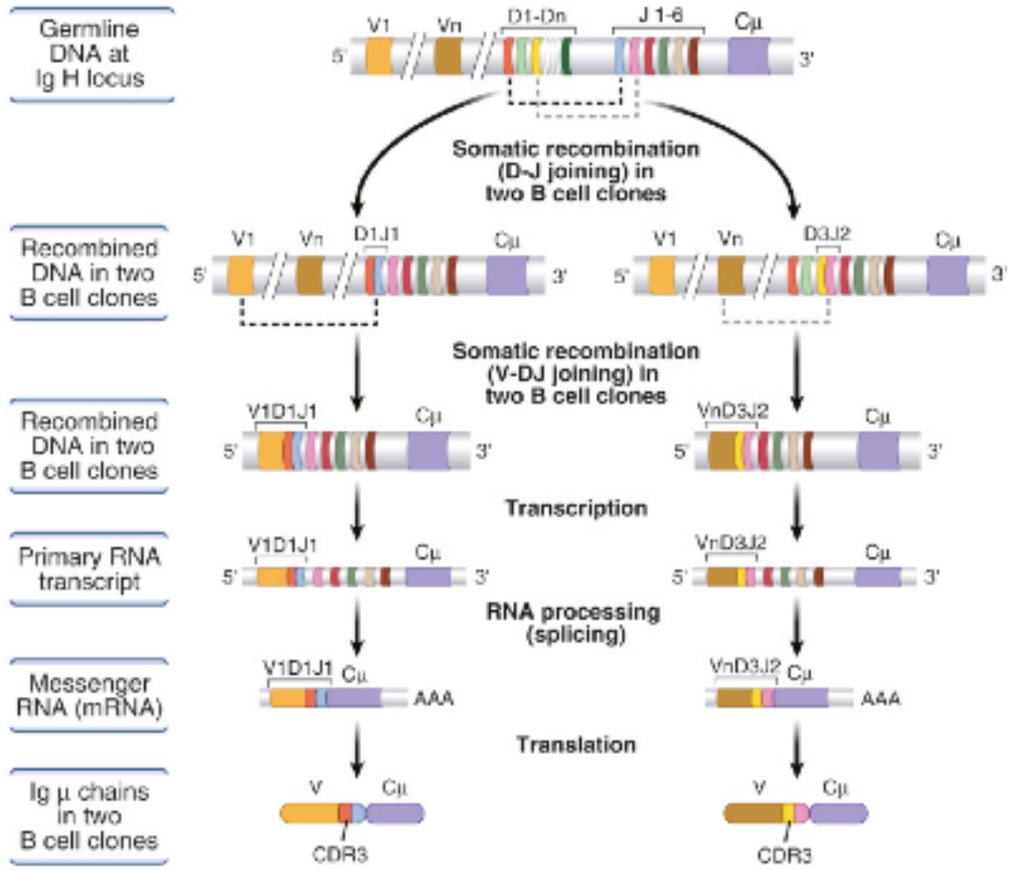
How do B cells become antigen-specific?



	Stem cell	Pro-B	Pre-B	Immature B	Mature B
Ig DNA, RNA	Germline DNA	Germline DNA	Recombined H chain gene (VDJ); μ mRNA	Recombined H chain gene, κ or λ genes; μ and κ or λ mRNA	Alternative splicing of primary transcript to form C_μ and C_δ mRNA
Ig expression	None	None	Cytoplasmic μ and pre-B receptor-associated μ	Membrane IgM (μ+κ or λ light chain)	Membrane IgM and IgD



The maturation of B lymphocytes proceeds through sequential steps, each of which is characterized by particular changes in immunoglobulin (Ig) gene expression and in the patterns of Ig protein expression. At the transition from pro-B to pre-B or pre-B to immature B cells, failure to express Ig heavy chain or Ig light chain proteins, respectively, results in death of the cells by a default pathway of apoptosis. The pre-BCR (B cell receptor) consists of a membrane-associated Ig μ protein attached to two other proteins called surrogate light chains because they take the place of the light chain in a complete Ig molecule.

During B cell development, the expression of an Ig heavy chain involves two gene recombination events (D-J joining, followed by joining of a V region to the DJ complex, with deletion and loss of intervening gene segments). The recombined gene is transcribed, and the VDJ complex is spliced onto the C region exons of the first heavy-chain RNA (which is μ), to give rise to the μ messenger RNA (mRNA). The mRNA is translated to produce the μ heavy-chain protein. The recombination of the Ig light chain follows similarly, except it lacks D segments, so a V gene recombines directly with a J gene segment. The T cell receptor (TCR) follows essentially the same sequence using α and β chains. The TCR rearrangements result in T cell Receptor Excision Circles, or **TRECs**, which can be detected in newborn screening. *Very low or absent TRECs would suggest a T cell deficiency.*

The somatic recombination of V and J, or of V, D, and J, gene segments is mediated by a lymphoid-specific enzyme, the VDJ recombinase, and additional enzymes, most of which are not lymphocyte specific and are involved in repair of double-stranded DNA breaks introduced by the recombinase. The VDJ recombinase is composed of the recombination-activating gene 1 and 2 (**RAG-1 and RAG-2**) proteins.

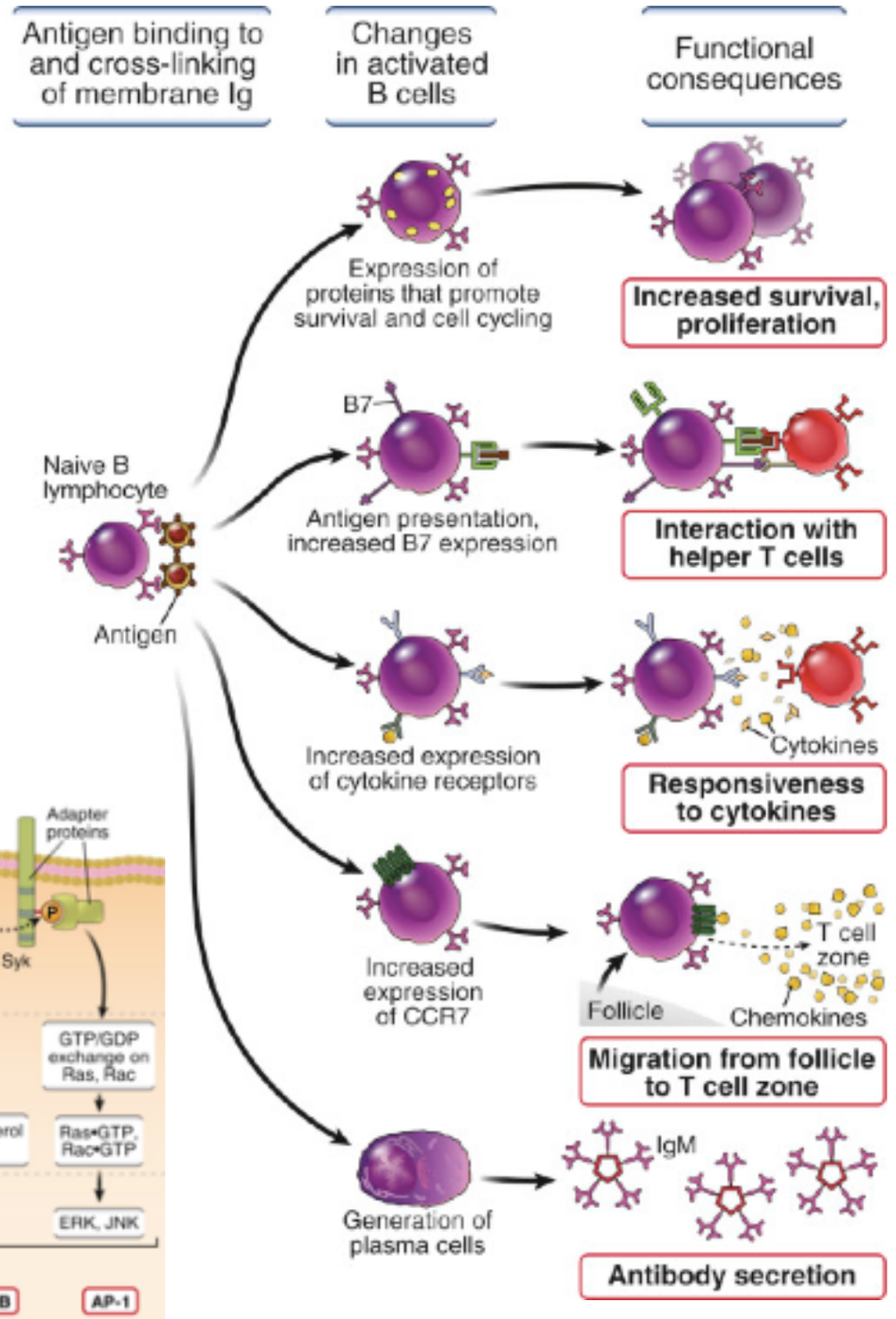
In B cells, the Ig heavy-chain locus rearranges first, and only cells that are able to make an Ig μ heavy-chain protein are selected to survive and become pre-B cells. Pre-B cells are defined by the presence of the Ig μ heavy-chain protein, mainly in the cytoplasm. Some of the μ protein is expressed on the cell surface in association with two other, invariant proteins, called surrogate light chains because they resemble light chains and associate with the μ heavy chain. The complex of μ chain and surrogate light chains associates with the Igα and Igβ signaling molecules to form the pre-B cell receptor (pre-BCR) complex. After completion, mature B cells leave the bone marrow.

How are B cells activated?

Naive B lymphocytes recognize antigens but do not secrete **antibodies**, and activation of these cells stimulates their differentiation into antibody-secreting plasma cells. The activation of naive, mature B lymphocytes upon antigen recognition results in the proliferation of antigen-specific cells, leading to **clonal expansion**, and in their differentiation into **plasma cells**, which actively secrete antibodies and are thus the effector cells of humoral immunity. This process is also under the influence of helper T cells and other stimuli. Some of the activated B cells undergo heavy-chain isotype switching and affinity maturation, and some become long-lived memory cells.

Remember that B cells and plasma cells secrete antibodies for **humoral immunity**, which is the principal defense mechanism against microbes with capsules rich in polysaccharides and lipids, because antibodies can be produced against polysaccharides and lipids but T cells cannot respond to nonprotein antigens.

Humoral immune responses are initiated when antigen-specific B lymphocytes in the spleen, lymph nodes, and mucosal lymphoid tissues recognize antigens. Some of the antigens in tissues or in the blood are transported to and concentrated in the B cell–rich follicles and marginal zones of these peripheral lymphoid organs. In lymph nodes, macrophages may capture and display bound antigens to B cells. B lymphocytes specific for an antigen use their membrane-bound immunoglobulin (Ig) as receptors that recognize the antigen directly, without any need for processing. B cells are capable of recognizing the native (unprocessed) antigen, so the antibodies that are subsequently secreted (which have the same specificity as the B cell antigen receptors) are able to bind to the native microbe or microbial product.



The activation of B cells by antigen in lymphoid organs initiates the process of B cell proliferation and IgM secretion and prepares the B cell for interaction with helper T cells. B cell activation proceeds through multiple different pathways and transcription factors.

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