How do B cells develop?

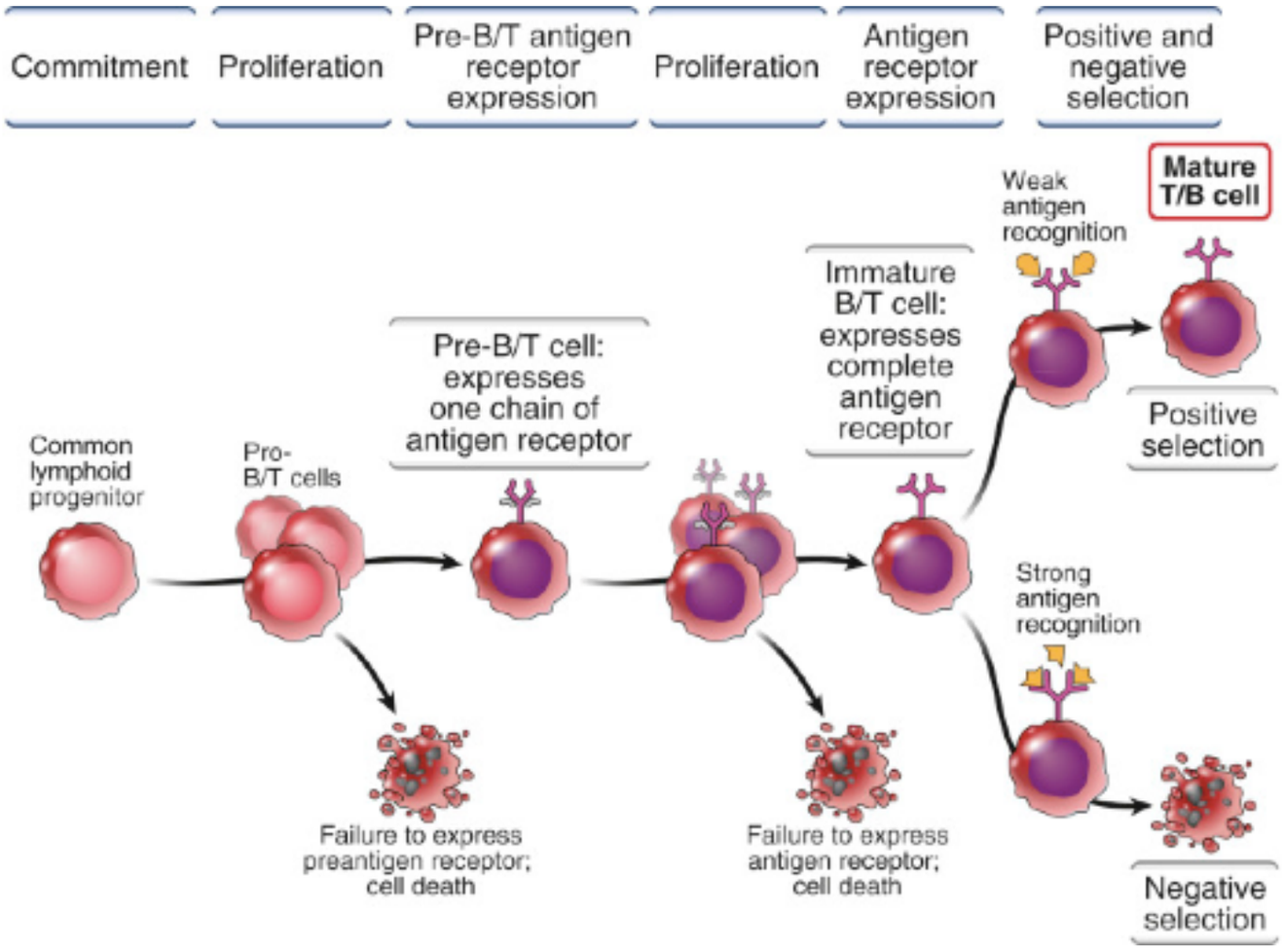
The development of lymphocytes from bone marrow stem cells involves commitment of hematopoietic progenitors to the B or T cell lineage, the proliferation of these progenitors, the rearrangement and expression of antigen receptor genes, and selection events to preserve and expand cells that express potentially useful antigen receptors. These steps are common to B and T lymphocytes, even though B lymphocytes mature in the bone marrow and T lymphocytes mature in the thymus. Each of the processes that occurs during lymphocyte maturation plays a special role in the generation of the lymphocyte repertoire.

Developing lymphocytes undergo proliferation at several stages during their maturation. Survival and proliferation of the earliest lymphocyte precursors are stimulated mainly by the growth factor interleukin-7 (**IL-7**), which is produced by stromal cells in the bone marrow and the thymus. Further proliferative expansion of the B and T cell lineages occurs after the developing lymphocytes have completed their first antigen receptor gene rearrangement and assembled a preantigen receptor. This step is a quality control checkpoint in lymphocyte development that ensures preservation of cells with functional receptors.

Remember, lymphocytes are selected at multiple steps during their maturation to preserve the useful specificities, with checkpoints ensuring only cells with intact, functional antigen receptors are selected to survive and proliferate. Selection is based on the expression of intact antigen receptor components and what they recognize. Pre-lymphocytes and immature lymphocytes that fail to express antigen receptors die by apoptosis.

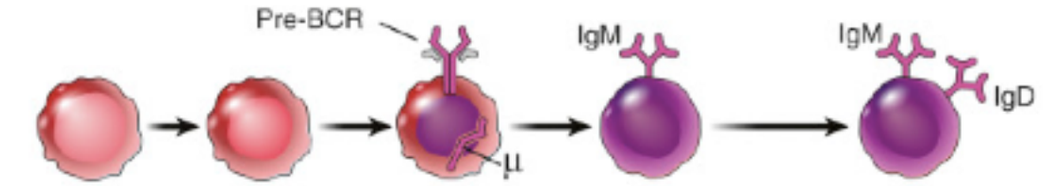
Gene rearrangements in the developing lymphocytes randomly generate antigen receptors with highly diverse specificities. T cells undergo **positive selection**, ensuring that cells that complete maturation will be capable of recognizing antigens displayed by the same major histocompatibility (MHC) molecules on antigen-presenting cells (APCs), which are the only MHC molecules these cells can normally encounter. Thus, immature T cells are selected to survive only if they recognize MHC molecules in the thymus.

B and T lymphocytes also undergo **negative selection**, which eliminates strongly self-reactive cells to prevent antigen receptors from recognizing peptides of self proteins. Negative selection is used to eliminate these potentially dangerous lymphocytes and prevent the development of autoimmune responses.

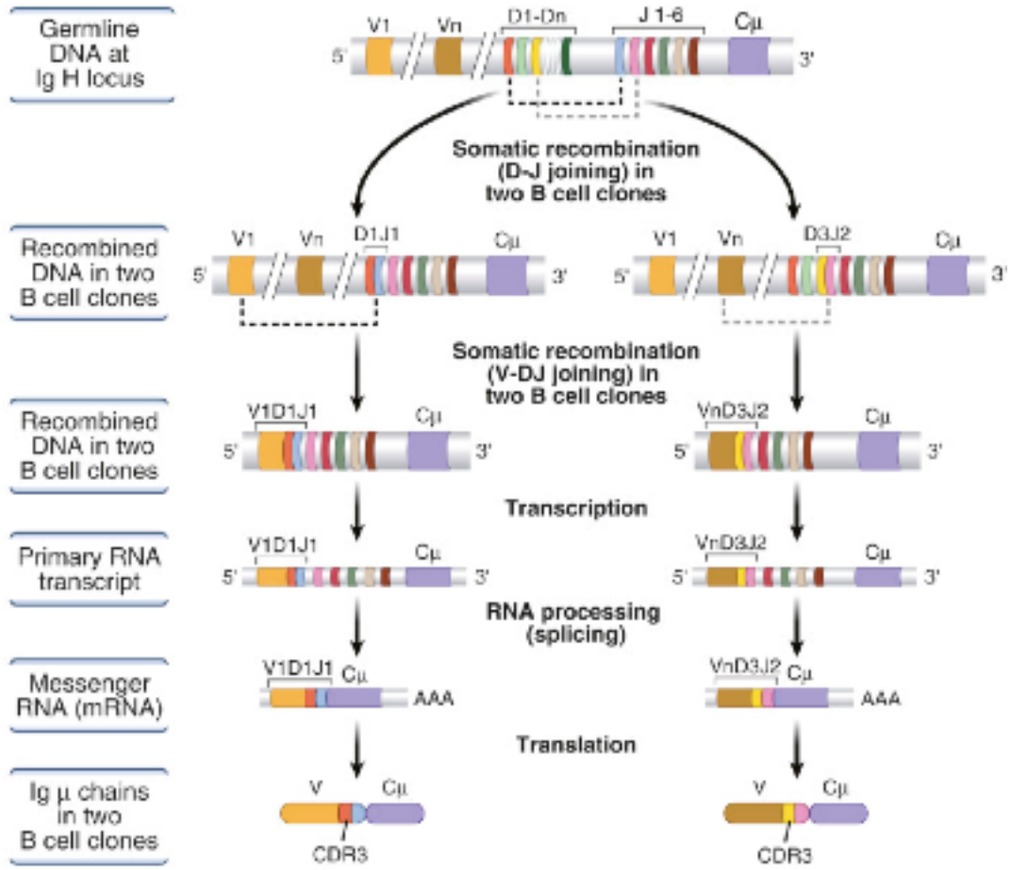


During their maturation, B and T lymphocytes go through cycles of proliferation and expression of antigen receptor proteins by gene recombination. Cells that fail to express intact, functional receptors die by apoptosis, because they do not receive the necessary survival signals. At the end of the process, the cells undergo positive and negative selection. The lymphocytes shown may be B or T cells.

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.

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If you would like to learn more or review any particular topic, the links below will take you to a text-based review of these concepts, or to the correlating video. You may also skip ahead to the post-module assessment.