Why are there different isotypes?

The effector functions of Abs are regulated by the constant region, as determined by its genetic sequence, called an **isotype**. Each constant region exhibits a distinct type of effector function. Remember that binding of Ab Fc regions to FcR expressed on the surface of phagocytes and other cells occurs only when Ab has bound Ag (the exception being IgE binding to FcR of mast cells, which is why allergic IgE-mediated reactions occur so rapidly).

One important defense mechanism against the extracellular stages of most bacteria and viruses is to coat (opsonize) these microbes with antibodies and cause them to be phagocytosed by neutrophils and macrophages. This reaction is best mediated by antibody classes, such as IgG1 and IgG3 (in humans), that bind to high-affinity phagocyte Fc receptors specific for the γ heavy chain (**IgG**). Helminths, in contrast, are too large to be phagocytosed, and they are best eliminated by eosinophils. Therefore, defense against these parasites involves coating them with antibodies to which eosinophils bind. The antibody class that is able to do this is **IgE**, because eosinophils have high-affinity receptors for the Fc portion of the ε heavy chain.

Ⓑ Antibody isotype	Isotype-specific effector functions
IgG	Neutralization of microbes and toxins Opsonization of antigens for phagocytosis by macrophages and neutrophils Activation of the classical pathway of complement Antibody-dependent cellular cytotoxicity mediated by NK cells Neonatal immunity: transfer of maternal antibody across placenta and gut Feedback inhibition of B cell activation
IgM	Activation of the classical pathway of complement
IgA	Mucosal immunity: secretion of IgA into lumens of gastrointestinal and respiratory tracts, neutralization of microbes and toxins
IgE	Defense against helminths Mast cell degranulation (immediate hypersensitivity reactions)

The antibody isotype produced is also influenced by the site of immune responses. For example, **IgA** antibody is the major isotype produced in mucosal lymphoid tissues, probably because cytokines such as transforming growth factor (TGF)-β that promote switching to IgA are made in these tissues. The B cells activated in these lymphoid tissues are also induced to express chemokine receptors and adhesion molecules that favor their migration into the sites just below mucosal epithelial barriers. IgA is the principal antibody isotype that can be actively secreted through mucosal epithelia.

The diversity of pathogens is why an effective host defense requires that the immune system make different antibody isotypes in response to different types of microbes, even though all naive B lymphocytes specific for all these microbes express antigen receptors of the IgM and IgD isotypes. Thus, the nature of the **helper T cell response** to a microbe guides the subsequent antibody response, making it optimal for combating that microbe. This is how different components of the immune system are regulated coordinately and function together in defense against different types of microbes. It also explains why deficiencies in antibody production may be due to B cell or T cell defects.

How do B cells develop?

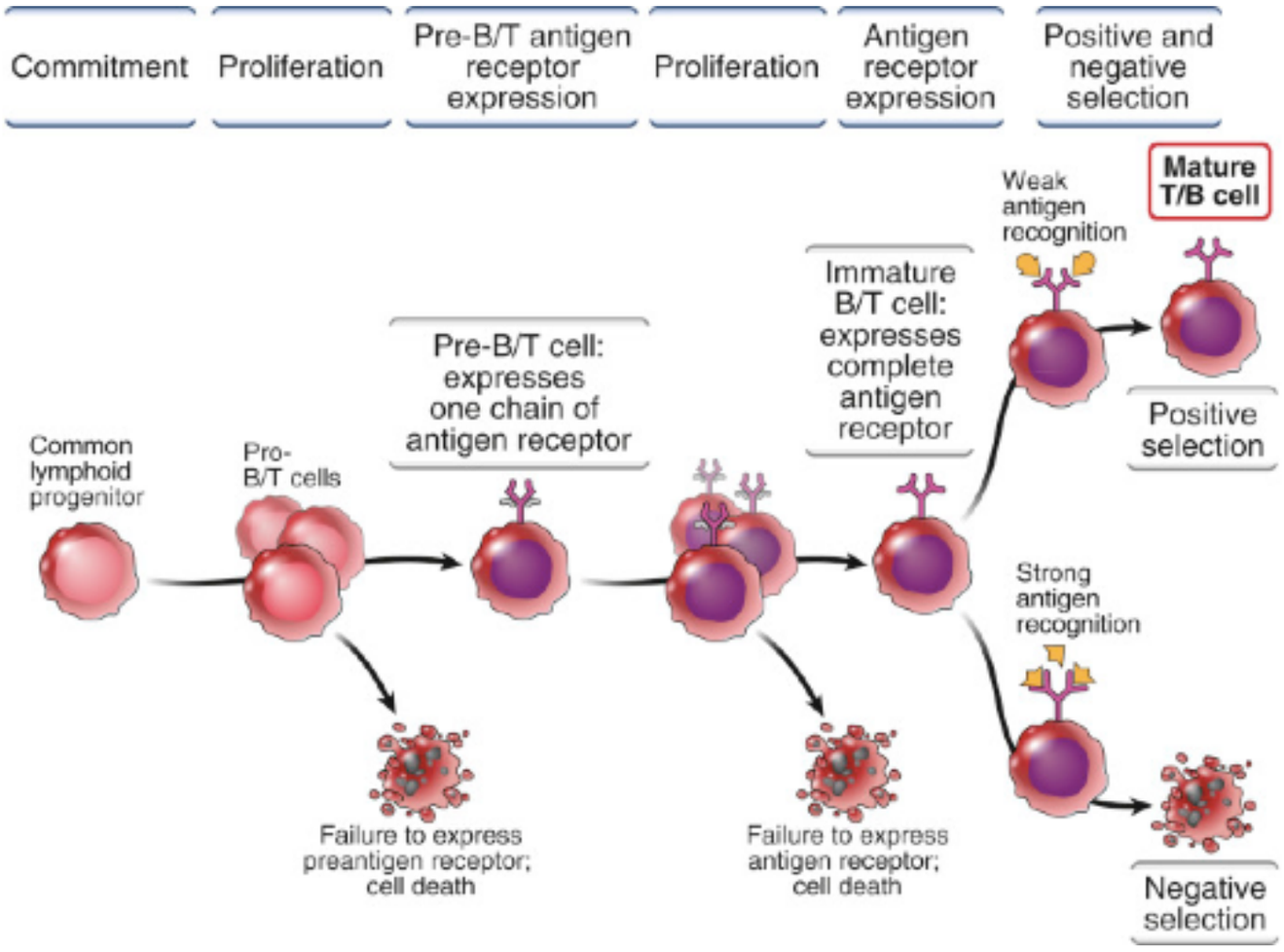
The development of lymphocytes from bone marrow stem cells involves commitment of hematopoietic progenitors to the B or T cell lineage, the proliferation of these progenitors, the rearrangement and expression of antigen receptor genes, and selection events to preserve and expand cells that express potentially 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.

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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.