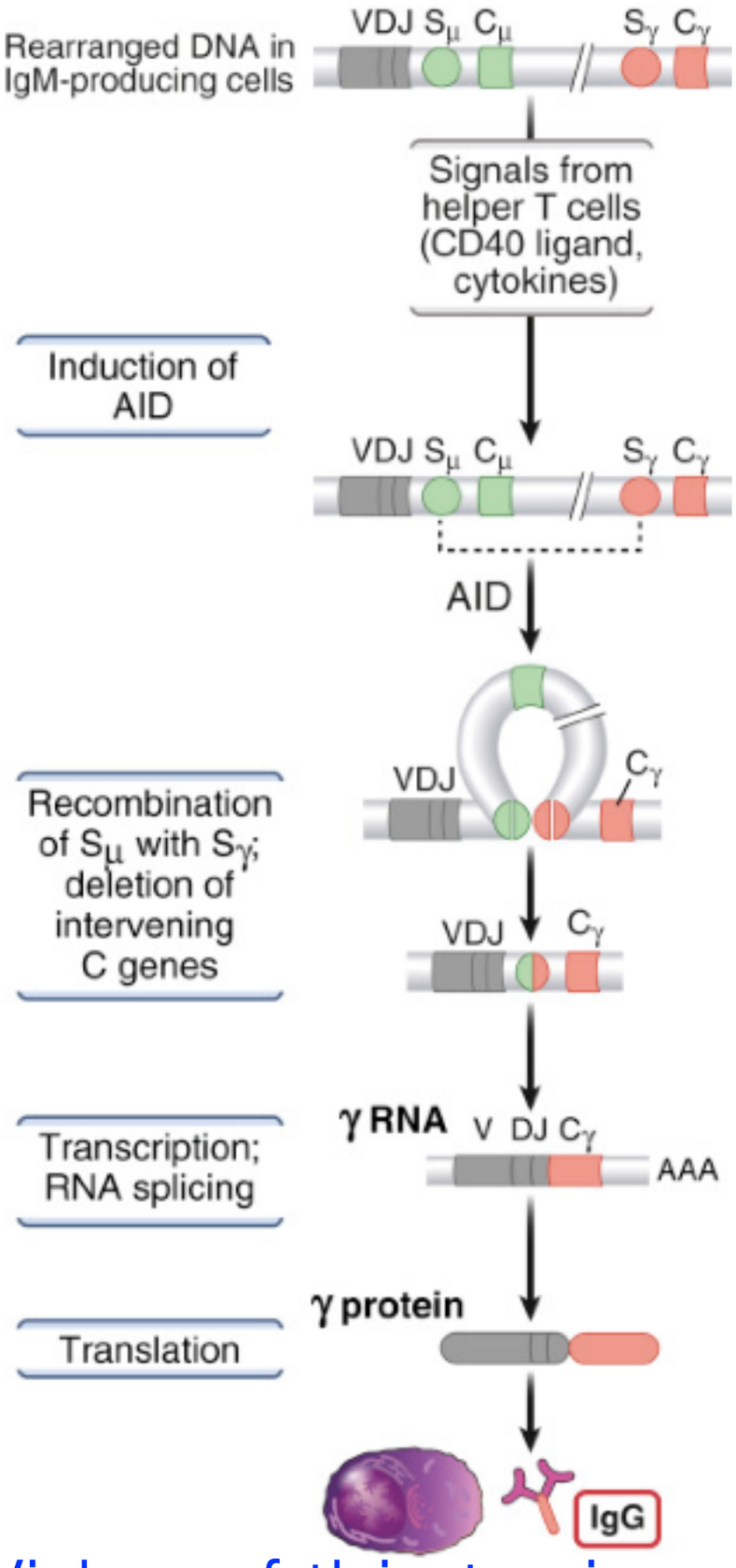
How do B cells change the antibody isotype?



Helper T cells stimulate the progeny of IgM– and IgD–expressing B lymphocytes to produce antibodies of different heavy-chain isotypes (classes). Different antibody isotypes perform different functions, and therefore the process of isotype switching broadens the functional capabilities of humoral immune responses. Heavy-chain isotype switching is induced by a combination of CD40 ligand (**CD40L**)-mediated signals and cytokines. These signals act on antigen-stimulated B cells and induce switching in some of the progeny of these cells. In the absence of CD40 or CD40L, B cells secrete only IgM and fail to switch to other isotypes, indicating the essential role of this ligand-receptor pair in isotype switching. Cytokines produced by follicular helper T cells determine which heavy-chain isotype is produced.

The molecular mechanism of isotype switching, called **class switch recombination (CSR)**, takes the previously formed VDJ exon encoding the V domain of an Ig μ heavy chain and moves it adjacent to a downstream C region. IgM-producing B cells, which have not undergone switching, contain in their Ig heavy-chain locus a rearranged VDJ gene adjacent to the first constant-region cluster, which is Cμ. The heavy-chain mRNA is produced by splicing a VDJ exon to Cμ exons in the initially transcribed RNA, and this mRNA is translated to produce a μ heavy chain, which combines with a light chain to give rise to an IgM antibody. Thus, the first antibody produced by B cells is IgM. Signals from CD40 and cytokine receptors stimulate transcription through one of the constant regions that is downstream of Cμ. In the intron 5′ of each constant region (except Cδ) is a conserved nucleotide sequence called the switch region. During switch recombination, the switch region 5′ of Cμ recombines with the switch region adjacent to the transcriptionally active downstream constant region, and the intervening DNA is deleted. An enzyme called **activation-induced deaminase (AID),** which is induced by CD40 signals, plays a key role in this process. AID converts cytosines in DNA to uracil (U). The sequential action of other enzymes results in the removal of the U's and the creation of nicks in the DNA. Such a process on both strands leads to double-stranded DNA breaks. When double-stranded DNA breaks in two switch regions are brought together and repaired, the intervening DNA is removed, and the rearranged VDJ exon that was originally close to Cμ may now be brought immediately upstream of the constant region of a different isotype (e.g., IgG, IgA, IgE). The result is that the B cell begins to produce a new heavy-chain isotype (determined by the C region of the antibody) with the same specificity as that of the original B cell, because specificity is determined by the sequence of the VDJ exon, which is not altered. Note that although the C region changes, the VDJ region, and thus the specificity of the antibody, is preserved. (Each C region gene consists of multiple exons, but only one is shown for simplicity.)

How do B cells acquire memory?

In the germinal centers, the activated B cells not only under class switch recombination (CSR) but they also undergo rapid proliferation and accumulate mutations in their immunoglobulin (Ig) V genes. These B cells produce antibodies with different affinities for the antigen. Follicular dendritic cells (FDCs) display the antigen, and B cells that recognize the antigen are selected to survive. FDCs display antigens by utilizing Fc receptors to bind immune complexes or by using C3 receptors to bind immune complexes with attached C3b and C3d complement proteins. B cells also bind the antigen, process it, and present it to follicular helper T (Tfh) cells in the germinal centers, and signals from the Tfh cells promote survival of the B cells. As more antibody is produced, the amount of available antigen decreases, so only the B cells that express receptors with higher affinities can bind the antigen and are selected to survive.

Activated B cells in germinal centers may differentiate into long-lived **plasma cells** or **memory cells**. The antibody-secreting cells enter the circulation and are called plasmablasts. From the blood they tend to migrate to the bone marrow or mucosal tissues, where they may survive for years as plasma cells and continue to produce high-affinity antibodies, even after the antigen is eliminated. It is estimated that more than half of the antibodies in the blood of a normal adult are produced by these long-lived plasma cells; thus, circulating antibodies reflect each individual's history of antigen exposure. These antibodies provide a level of immediate protection if the antigen (microbe or toxin) reenters the body. Think about the antibody titers you've had checked post-vaccination before enrolling in medical school.

A fraction of the activated B cells, which often are the progeny of isotype-switched high-affinity B cells, do not differentiate into active antibody secretors but instead become memory cells. Memory B cells do not secrete antibodies, but they circulate in the blood and reside in mucosal and other tissues. They survive for months or years in the absence of additional antigen exposure, undergo slow cycling, and are ready to respond rapidly if the antigen is reintroduced. Therefore, memory from a T-dependent antibody response can last for a lifetime.

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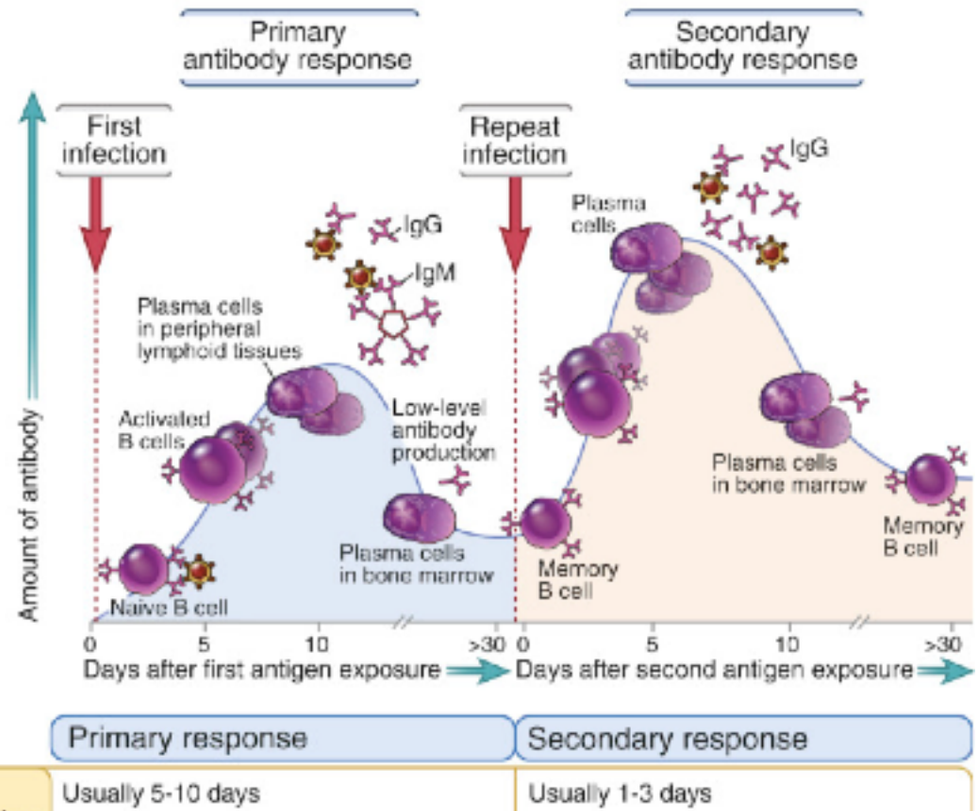

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Lag after immunization	Usually 5-10 days	Usually 1-3 days
Peak response	Smaller	Larger
Antibody isotype	Usually IgM>IgG	Relative increase in IgG and, under certain situations, in IgA or IgE (heavy-chain isotype switching)
Antibody affinity	Lower average affinity, more variable	Higher average affinity (affinity maturation)

Primary and secondary antibody responses differ in several respects. In a primary response, naive B cells in peripheral lymphoid tissues are activated to proliferate and differentiate into antibody-secreting plasma cells and memory cells. Some plasma cells may migrate to and survive in the bone marrow for long periods. In a secondary response, memory B cells are activated to produce larger amounts of antibodies, often with more heavy-chain class switching and affinity maturation. These features of secondary responses are seen mainly in responses to protein antigens, because these changes in B cells are stimulated by helper T cells, and only proteins activate T cells (not shown). The kinetics of the responses may vary with different antigens and types of immunization.

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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.