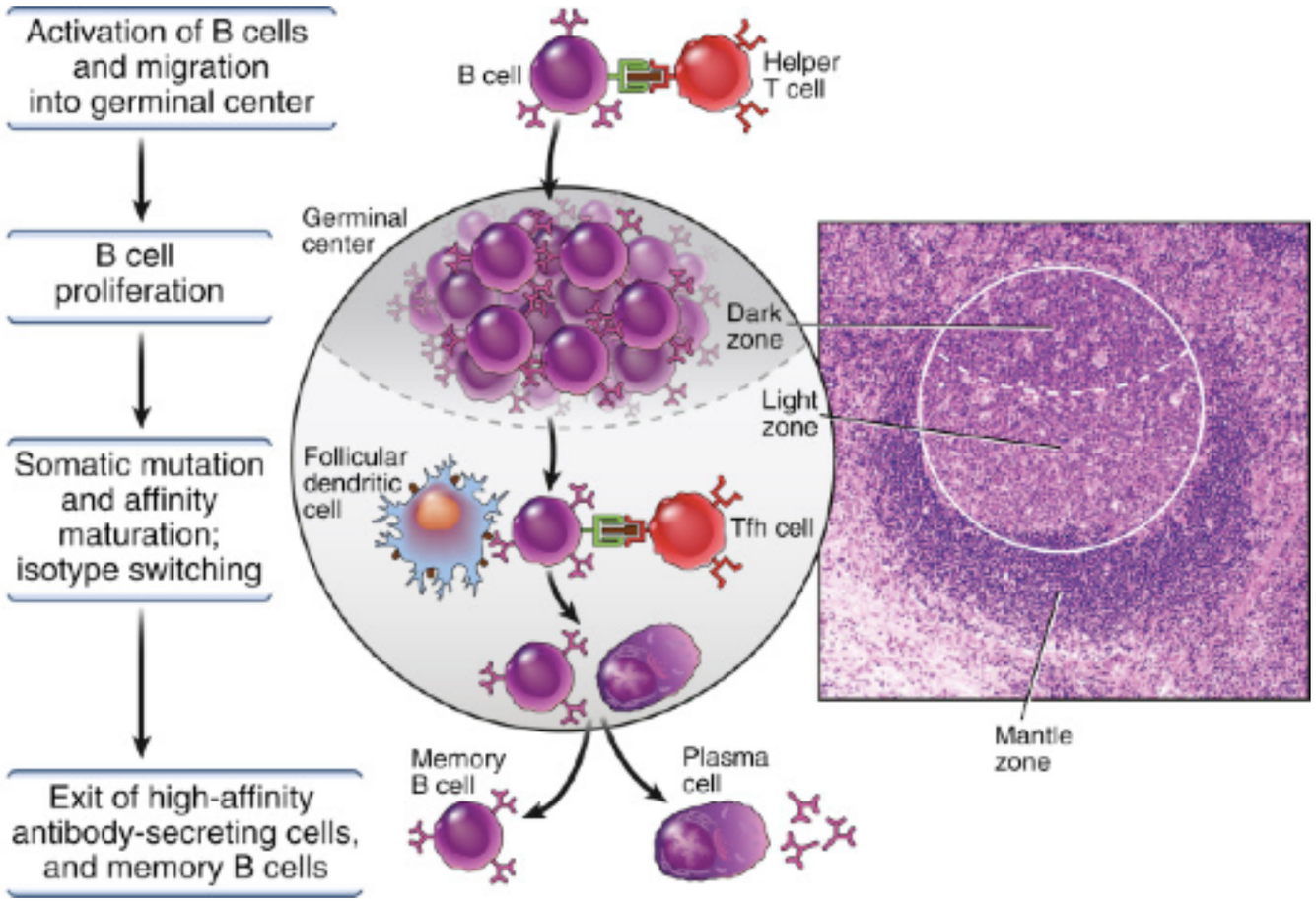
How do B cells differentiate?

B cell activation by antigen (and other signals) initiates the proliferation and differentiation of the cells and prepares them to interact with helper T lymphocytes if the antigen is a protein. The activated B lymphocytes enter the cell cycle and begin to proliferate. The cells may also begin to synthesize more IgM and to produce some of this IgM in a secreted form.

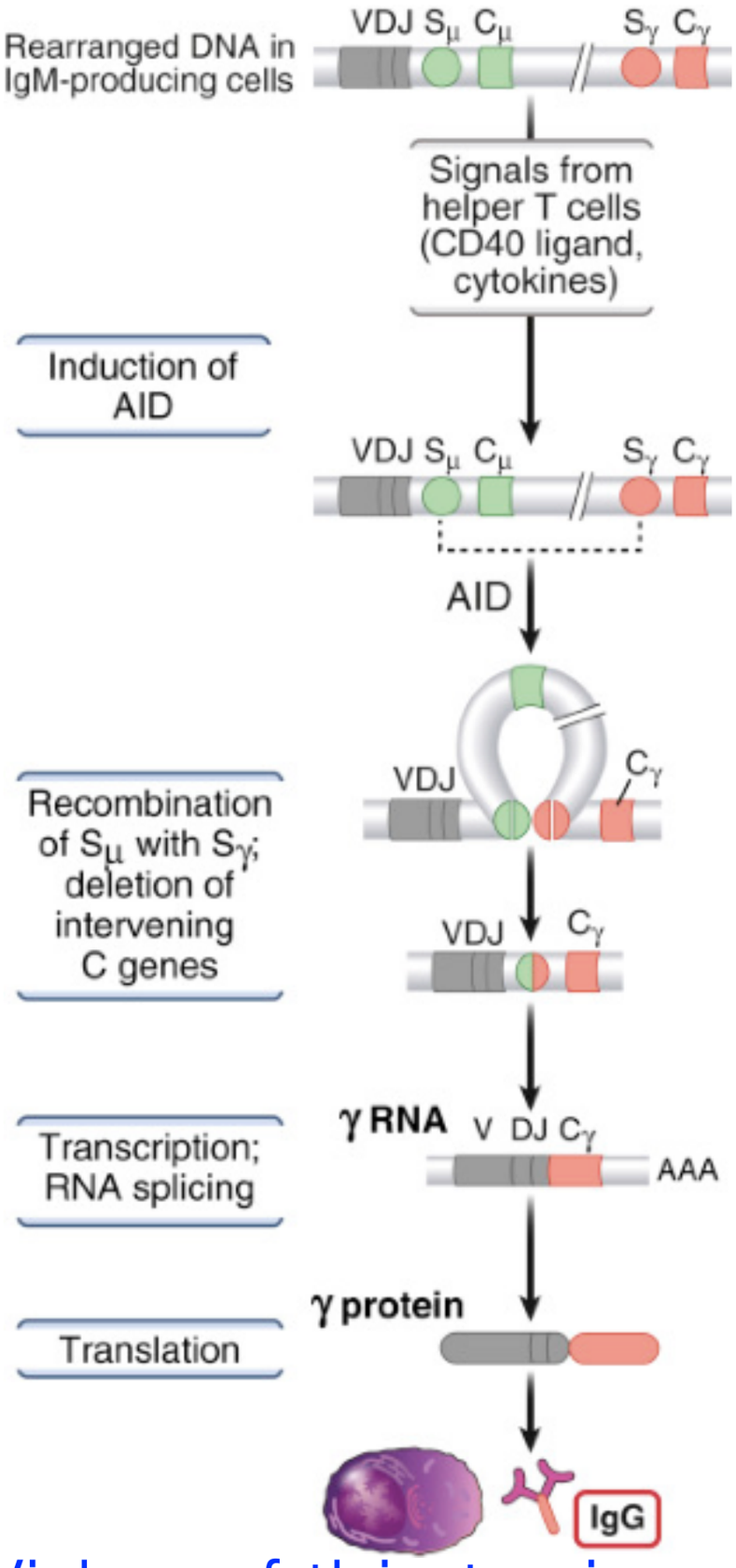
B cell activation is greatest when an antigen is multivalent, cross-links many antigen receptors, and activates complement and innate immune receptors strongly; all these features are typically seen with polysaccharides and other T-independent microbial antigens. Remember that by themselves, soluble proteins typically do not stimulate high levels of B cell proliferation and differentiation. This is because most soluble protein antigens do not contain multiple identical epitopes, so they are not capable of cross-linking many receptors on B cells. However, protein antigens can induce signals in B lymphocytes that lead to important changes in the cells that enhance their ability to interact with helper T lymphocytes.

Initial B cell activation occurs at an extra follicular focus, after which a few of the activated B cells migrate back into the lymphoid follicle and begin to divide rapidly in response to signals from T follicular helper (Tfh) cells. It is estimated that these B cells have a doubling time of approximately 6 hours, so one cell may produce several thousand progeny within a week. The region of the follicle containing these proliferating B cells is the germinal center. In the germinal center, B cells undergo extensive **isotype switching** and **somatic mutation** of Ig genes. The highest-affinity B cells are the ones that are selected during the germinal center reaction to differentiate into memory B cells and long-lived plasma cells. Proliferating B cells reside in the dark zone of the germinal center while selection occurs in the less dense light zone.



B cells that have been activated by T helper cells at the edge of a primary follicle migrate into the follicle and proliferate, forming the dark zone of the germinal center. Germinal center B cells undergo extensive **isotype switching** and **somatic mutation** of Ig genes, and migrate into the light zone, where B cells with the highest affinity Ig receptors are selected to survive, and they **differentiate into plasma cells or memory cells**, which leave the germinal center. The right panel shows the histology of a secondary follicle with a germinal center in a lymph node. The germinal center includes a basal dark zone and an adjacent light zone. The mantle zone is the part of the follicle outside the germinal center.

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.)

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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.