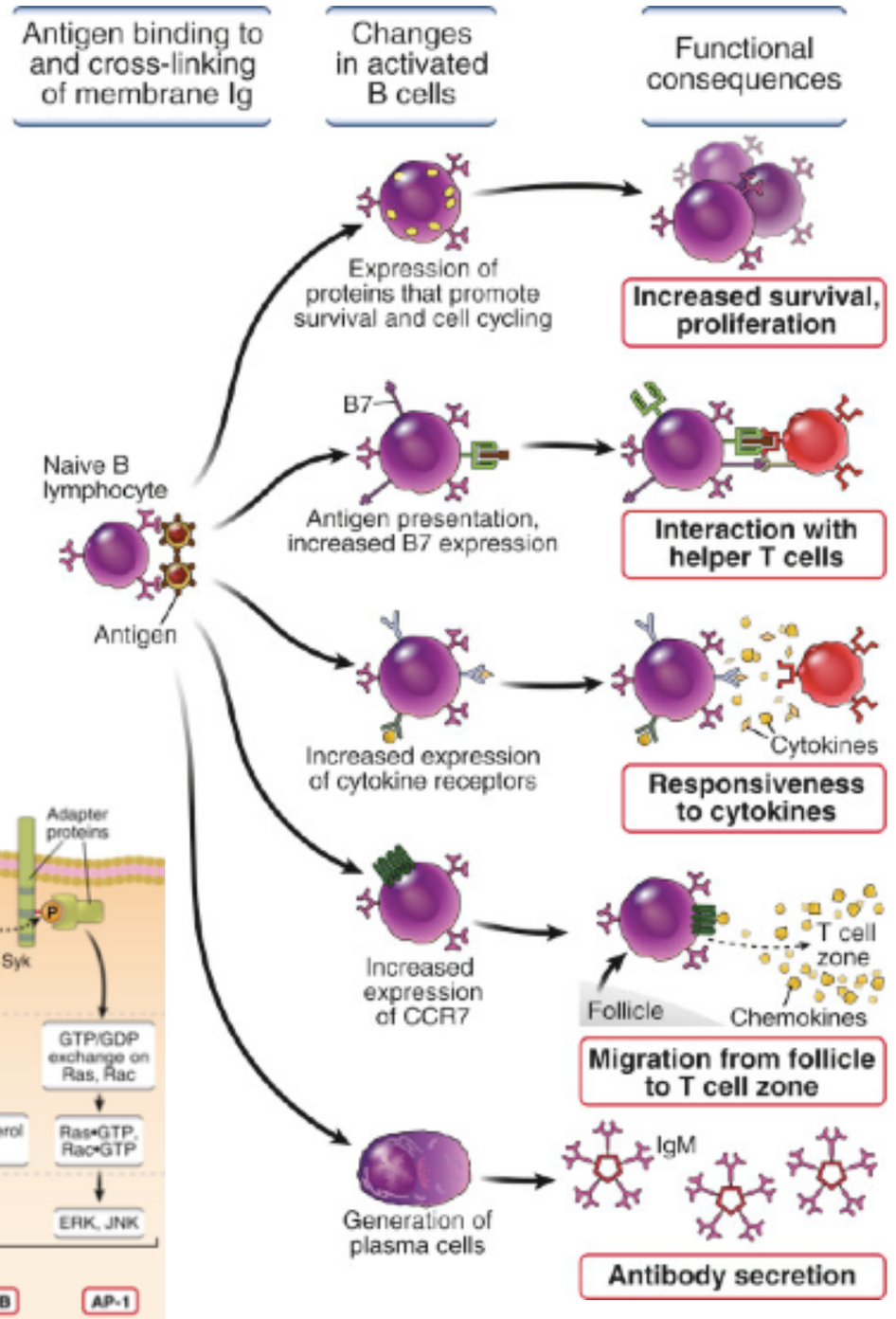
How are B cells activated?

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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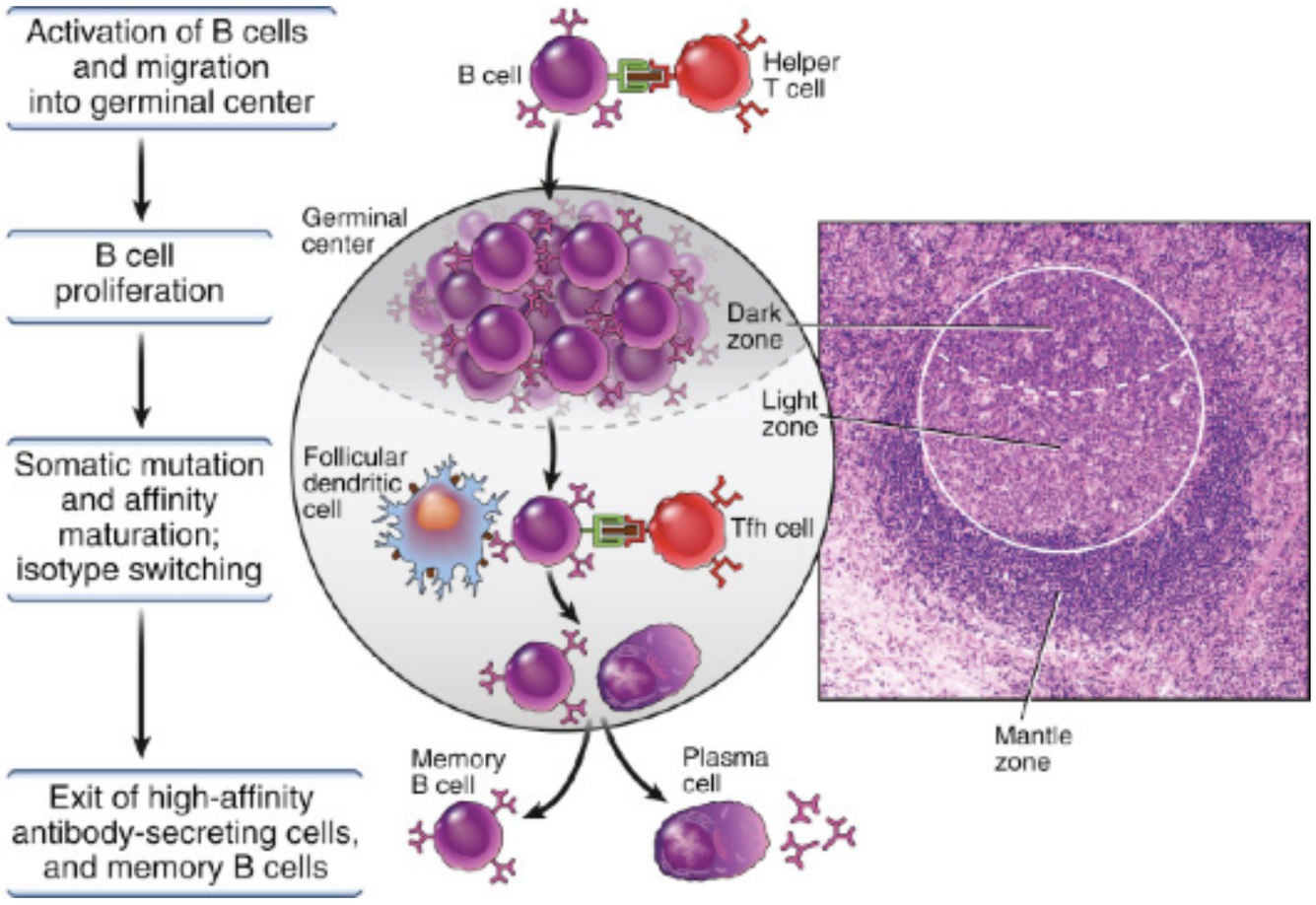
How do B cells differentiate?

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.

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