B cell activation by Thymus dependent (TD) antigen

Activation of B cells by soluble protein antigens requires the involvement of TH cells. Binding of antigen to B-cell mIg does not itself induce an effective competence signal without additional interaction with membrane molecules on the TH cell. In addition, a cytokine-mediated progression is required for B-cell proliferation. Figure 1 outlines the probable sequence of events in B-cell activation by a thymus-dependent (TD) antigen. This process is considerably more complex than activation induced by thymus independent (TI) antigens.

Formation of T-B conjugate

After binding of antigen by mIg on B cells, the antigen is internalized by receptor-mediated endocytosis and processed within the endocytic pathway into peptides. Antigen binding also initiates signaling through the BCR that induces the B cell to up-regulate a number of cell-membrane molecules, including class II MHC molecules and the co-stimulatory ligand B7 (see Figure 1). Increased expression of both of these membrane proteins enhances the ability of the B cell to function as an antigen-presenting cell in TH-cell activation. B-cells could be regarded as helping their helpers because the antigenic peptides produced within the endocytic processing pathway associate with class II MHC molecules and are presented on the B-cell membrane to the TH cell, inducing its activation. It generally takes 30 - 60 min after internalization of antigen for processed antigenic peptides to be displayed on the B-cell membrane in association with class II MHC molecules.

Because a B cell recognizes and internalizes antigen specifically, by way of its membrane-bound Ig, a B cell is able to present antigen to TH cells at antigen concentrations that are 100 to 10,000 times lower than what is required for presentation by macrophages or dendritic cells. When antigen concentrations are high, macrophages and dendritic cells are effective antigen-presenting cells, but, as antigen levels drop, B cells take over as the major presenter of antigen to TH cells. Once a TH cell recognizes a processed antigenic peptide displayed by a class II

MHC molecule on the membrane of a B cell, the two cells interact to form a T-B conjugate.

CONTACT-DEPENDENT HELP MEDIATED BY CD40/CD40L INTERACTION

Formation of a T-B conjugate not only leads to the directional release of TH-cell cytokines, but also to the up-regulation of CD40L (CD154), a TH-cell membrane protein that then interacts with CD40 on B cells to provide an essential signal for T- cell– dependent B-cell activation. Interaction of CD40L with CD40 on the B cell delivers a signal (signal 2) to the B cell that, in concert with the signal generated by mIg crosslinkage (signal 1), drives the B cell into G1 (see Figure 1c).

SIGNALS PROVIDED BY TH-CELL CYTOKINES

Although B cells stimulated with membrane proteins from activated TH cells are able to proliferate, they fail to differentiate unless cytokines are also present; this finding suggests that both a membrane-contact signal and cytokine signals are necessary to induce B-cell proliferation and differentiation. Electron micrographs of T-B conjugates reveal that the antigen-specific interaction between a TH and a B cell induces a redistribution of TH-cell membrane proteins and cytoskeletal elements that results in the polarized release of cytokines toward the interacting B cell. Once activated, the B cell begins to express membrane receptors for various cytokines, such as IL-2, IL-4, IL-5, and others. These receptors then bind the cytokines produced by the interacting TH cell. The signals produced by these cytokine-receptor interactions support B-cell proliferation and can induce differentiation into plasma cells and memory B cells, class switching, and affinity maturation.

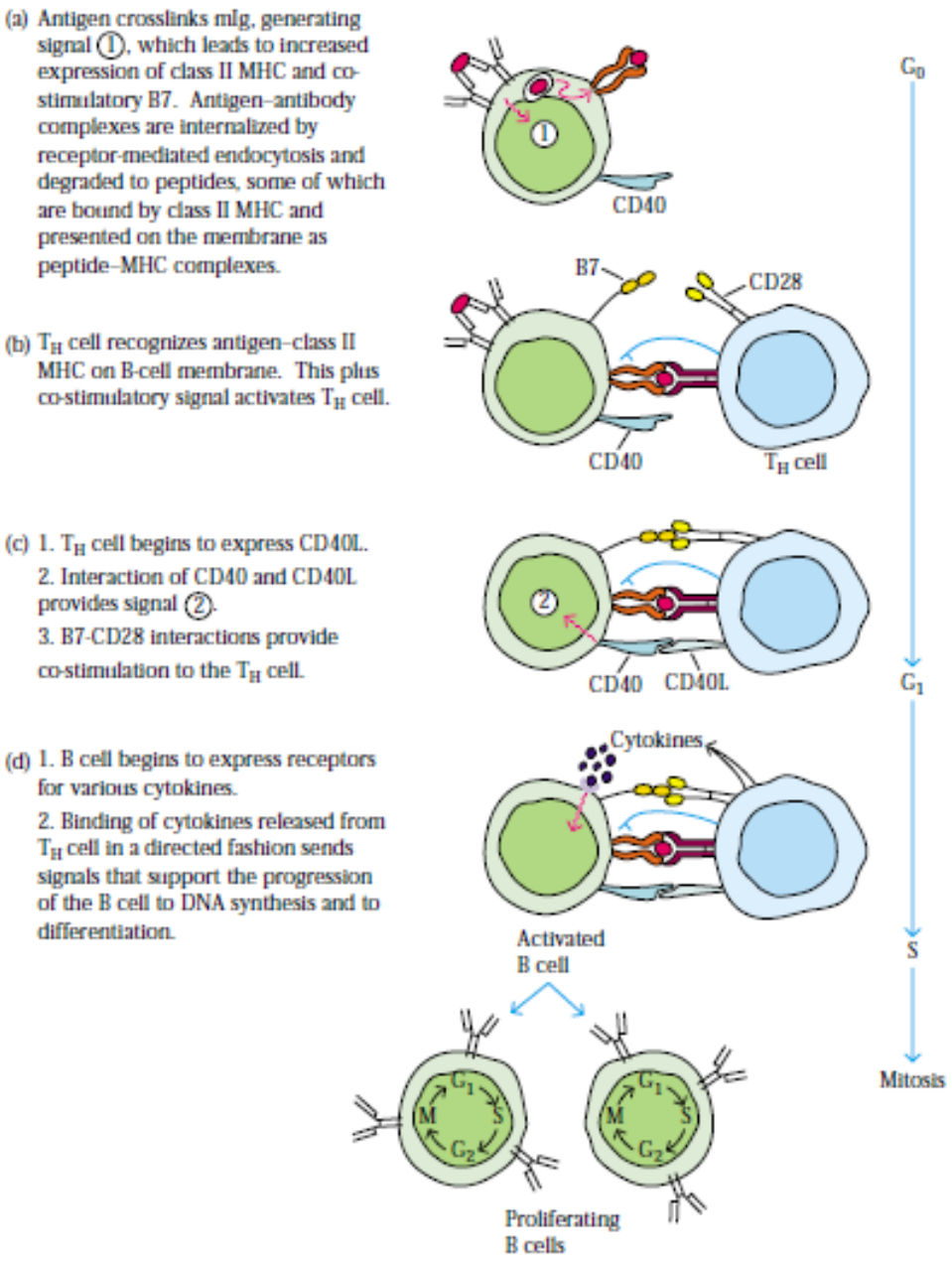

Figure1. Sequence of events in B-cell activation by a thymus-dependent antigen

Anatomical distribution of B cells

In vivo activation and differentiation of B cells occurs in defined anatomic sites whose structure places certain restrictions on the kinds of cellular interactions that can take place. When an antigen is introduced into the body, it becomes

concentrated in various peripheral lymphoid organs. Blood borne antigen is filtered by the spleen, whereas antigen from tissue spaces drained by the lymphatic system is filtered by regional lymph nodes or lymph nodules. The following description focuses on the generation of the humoral response in lymph nodes. A lymph node is an extremely efficient filter capable of trapping more than 90% of any antigen carried into it by the afferent lymphatics. Antigen or antigen-antibody complexes enter the lymph nodes either alone or associated with antigen transporting cells (e.g., Langerhans cells or dendritic cells) and macrophages. As antigen percolates through the cellular architecture of a node, it will encounter one of three types of antigen-presenting cells: interdigitating dendritic cells in the paracortex, macrophages scattered throughout the node, or specialized follicular dendritic cells in the follicles and germinal centers. Antigenic challenge leading to a humoral immune response involves a complex series of events, which take place in distinct microenvironments within a lymph node (Figure 2). Once antigen-mediated B-cell activation takes place, small foci of proliferating B cells form at the edges of the T-cell–rich zone. These B cells differentiate into plasma cells secreting IgM and IgG isotypes. Most of the antibody produced during a primary response comes from plasma cells in these foci. A similar sequence of events takes place in the spleen, where initial B-cell activation takes place in the T-cell–rich periarterial ymphatic sheath, PALS.

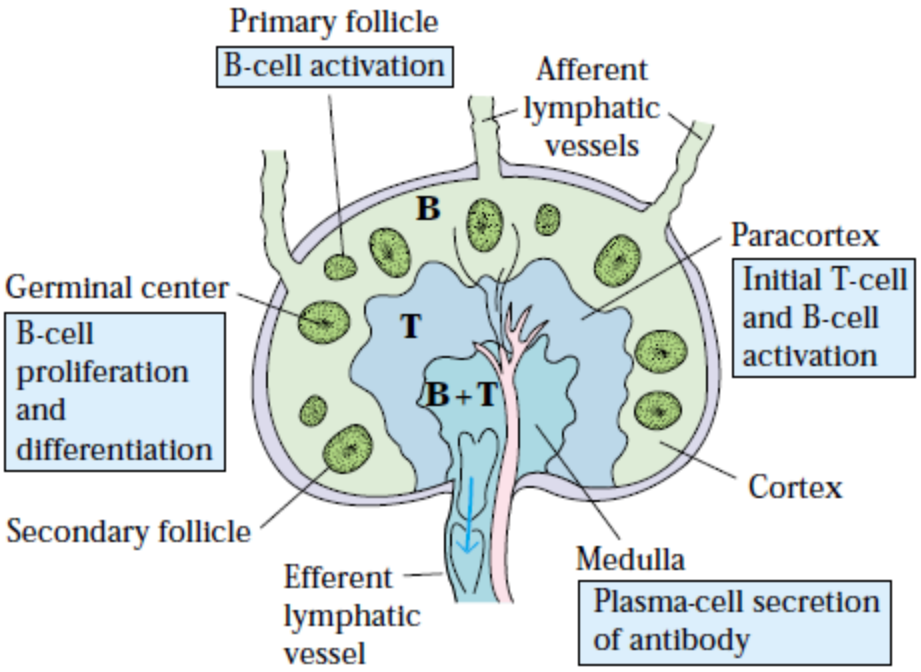

Figure 2: Schematic diagram of a peripheral lymph node showing anatomic sites at which various steps in B-cell activation, proliferation, and differentiation occur. The cortex is rich in B cells and the paracortex in T cells; both B and T cells are present in large numbers in the medulla. A secondary follicle contains the follicularmantle and a germinal center.