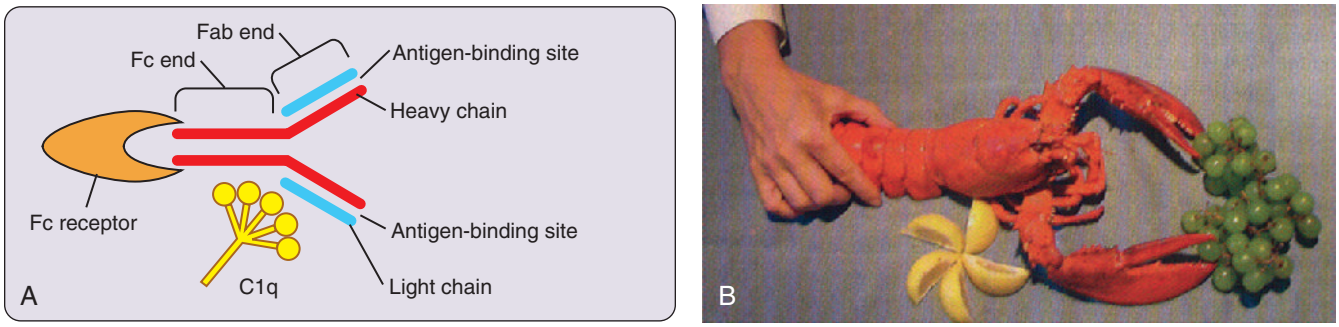

FIGURE 86-2 Structure of antibodies. Antibody molecules are composed of two heavy chains *(red lines)* and two light chains *(blue lines)* held together by disulfide bonds. The two heavy chains join to form a tail (Fc end), which can interact with receptors (FcR) on a variety of cells. The heavy and light chains contribute to the Fab end. At the 5′ or amino-terminal end, these chains form two identical antigen-binding sites, much like two lobster claws. Near the hinge region of the antibody, there is a binding site for C1q, the first component of the complement cascade. (From Birdsall H: Adaptive immunity: antibodies and immunodeficiencies. In Bennett JE, Dolin R, Blaser M, editors: Mandell, Douglas, and Bennett's principles and practice of infectious diseases, ed 8, Philadelphia, 2015, Saunders.)

antibody production. B cells may also differentiate into plasma cells that do not contain surface antibody but secrete large amounts of a single specific isotype immunoglobulin.

B cells may also undergo somatic hypermutation. In this process, cells producing antibody develop point source mutations in the immunoglobulin DNA that may increase the affinity to antigen. This may stimulate increased production of the higher-affinity antibody, thus fine tuning the B-cell response. Driven by T-cell interaction, a portion of the B cells are formed for life, and these *memory cells* have the capacity to secrete antibodies rapidly on antigen reexposure that have extremely high avidity for a particular antigen.

B cells can be activated by two routes. Some antigens can stimulate B cells to proliferate and produce antibody directly without the presence of helper $CD4^+$ T cells. They include microbial-derived molecules such as LPS, which have broad stimulatory properties. Others, such as microbial-derived repetitive motifs on polysaccharides, stimulate mature B cells more specifically. More commonly, B cells are stimulated through synergistic action with $CD4^+$ T cells. Specific antigen is bound to the surface immunoglobulin of the B cell, which triggers endocytosis, degradation of the antigen, and presentation of peptide fragments in association with MHC class II molecules on the cell surface. $CD4^+$ T cells with TCR specificity for the antigen interacts with the B cell through adhesion molecules and costimulatory activation molecules such as CD28 and CD80/86. $CD4^+$ T cells then produce cytokines such as IL-4 that drive antibody production by the B cells.

T Lymphocytes

T cells are produced in the bone marrow and then are processed and selected in the thymus. T lymphocytes have CD4 or CD8 molecules on their surface along with a TCR that has exquisite antigen specificity. During development, the TCR is produced in a process involving gene rearrangement and selection of V, D, and J clusters similar to B-cell antibody differentiation. The potential number of epitopes that T cells can respond to is greater than those that induce B cells.

As maturation takes place in the thymus, T cells whose TCRs have too high an affinity for self-molecules are eliminated. Naïve T cells, usually in regional lymph nodes or similar tissues such as Peyer's patches in the gut, are sensitized by interaction with an APC such as the dendritic cell. The APC processes a microbial peptide antigen and then presents the antigen to the associated T cell. Presentation of antigen occurs in association with human leukocyte antigen (HLA) class II molecules for $CD4^+$ cells or HLA class I molecules for $CD8^+$ cells. $CD4^+$ cells are called helper T cells and develop into T_H1, T_H2, and T_H17 subsets. $CD8^+$ cells are cytotoxic T cells (Fig. 86-3).

$CD4^+$ T cells are key enhancing cells that are permissive and amplify the response of B lymphocytes, other $CD4^+$ T cells, and $CD8^+$ T cells. They also can activate cells such as phagocytes. $CD4^+$ T cells orchestrate host defenses against pathogens that are initially recognized by phagocytic cells during phagocytosis or pinocytosis. Dendritic cells, for example, incorporate external pathogens or antigens by phagocytosis or pinocytosis and then degrade them within phagosomes.

Short-chain peptide antigens, which are produced by proteolytic degradation, attach to a grove in the MHC class II molecules. The complex is then transported to the surface for presentation to naïve T lymphocytes expressing CD4 molecules on their surface. $CD4^+$ T lymphocytes with specificity for the antigen then adhere to the MHC class II/antigen complex on the surface of the APC. Accessory molecules, such as the adhesion molecule lymphocyte function–associated antigen 1(LFA-1) on T cells, which interacts with intercellular adhesion molecule 1 (ICAM-1) on the APC, are necessary to stabilize the interaction. Activating adhesion complexes such as CD28 (on T cells) and CD80/86 (on APCs) are necessary for sensitization, proliferation, and activation of T cells. Activation and proliferation is also driven by IL-2.

Activated $CD4^+$ T cells (initially called T_H0 cells) can be driven by IL-12 and other cytokines to become T_H1 cells or by IL-4 and IL-10 to become T_H2 cells. T_H17 cell differentiation is driven by transforming growth factor-β (TGF-β), IL-6, and IL-23. T_H1 cells mediate host defenses against intracellular pathogens such as *M. tuberculosis or Toxoplasma gondii.* They do so by producing γ-interferon that activates APCs such as macrophages that then destroy the invading intracellular pathogen. T_H1 cells also produce Il-12, Il-2, and TNF-α, which can enhance the immune response. They also activate cytotoxic T lymphocytes to lyse infected cells.