antigen to the TCR. Together with the TCR, these proteins form the *TCR complex*.

A small population of mature T cells expresses another type of TCR composed of γ and δ polypeptide chains. The γδ TCR recognizes peptides, lipids, and small molecules, without a requirement for display by MHC proteins. γδ T cells tend to aggregate at epithelial surfaces, such as the skin and mucosa of the gastrointestinal and urogenital tracts, suggesting that these cells are sentinels that protect against microbes that try to enter through epithelia. However, the functions of γδ T cells are not established. Another small subset of T cells expresses markers that are also found on NK cells; these cells are called NK-T cells. NK-T cells express a very limited diversity of TCRs, and they recognize glycolipids that are displayed by the MHC-like molecule CD1. The functions of NK-T cells are also not well defined.

In addition to CD3 and ζ proteins, T cells express several other proteins that assist the TCR complex in functional responses. These include CD4, CD8, CD28, and integrins. CD4 and CD8 are expressed on two mutually exclusive subsets of αβ T cells. Approximately 60% of mature T cells are CD4+ and about 30% are CD8+. Most CD4+ T cells function as cytokine-secreting helper cells that assist macrophages and B lymphocytes to combat infections. Most CD8+ cells function as cytotoxic (killer) T lymphocytes (CTLs) to destroy host cells harboring microbes. CD4 and CD8 serve as *coreceptors* in T-cell activation, so called because they recognize a part of the same ligand that the antigen receptor sees. During antigen recognition, CD4 molecules bind to class II MHC molecules that are displaying antigen (Fig. 6-5), and CD8 molecules bind to class I MHC molecules, and the CD4 or CD8 coreceptor initiates signals that are necessary for activation of the T cells. Because of this requirement for coreceptors, CD4+ helper T cells can recognize and respond to antigen displayed only by class II MHC molecules, whereas CD8+ cytotoxic T cells recognize cell-bound antigens only in association with class I MHC molecules; this segregation is described later. Integrins are adhesion molecules that promote the attachment of T-cells to APCs.

To respond, T cells have to recognize not only antigen-MHC complexes but additional signals provided by antigen-presenting cells. This process, in which CD28 plays an important role, is described later, when the steps in cell-mediated immune responses are summarized.

B Lymphocytes

B lymphocytes are the only cells in the body capable of producing antibody molecules, the mediators of humoral immunity. B lymphocytes develop from precursors in the bone marrow. Mature B cells constitute 10% to 20% of the circulating peripheral lymphocyte population and are also present in peripheral lymphoid tissues such as lymph nodes, spleen, and mucosa-associated lymphoid tissues. B cells recognize antigen via the B-cell antigen receptor complex. Membrane-bound antibodies of the IgM and IgD isotypes, present on the surface of all mature, naive B cells, are the antigen-binding component of the B-cell receptor complex (Fig. 6-6). After stimulation by antigen and other signals (described later), B cells develop into *plasma cells*, veritable protein factories for antibodies. It is estimated that a single plasma cell can secrete hundreds to thousands

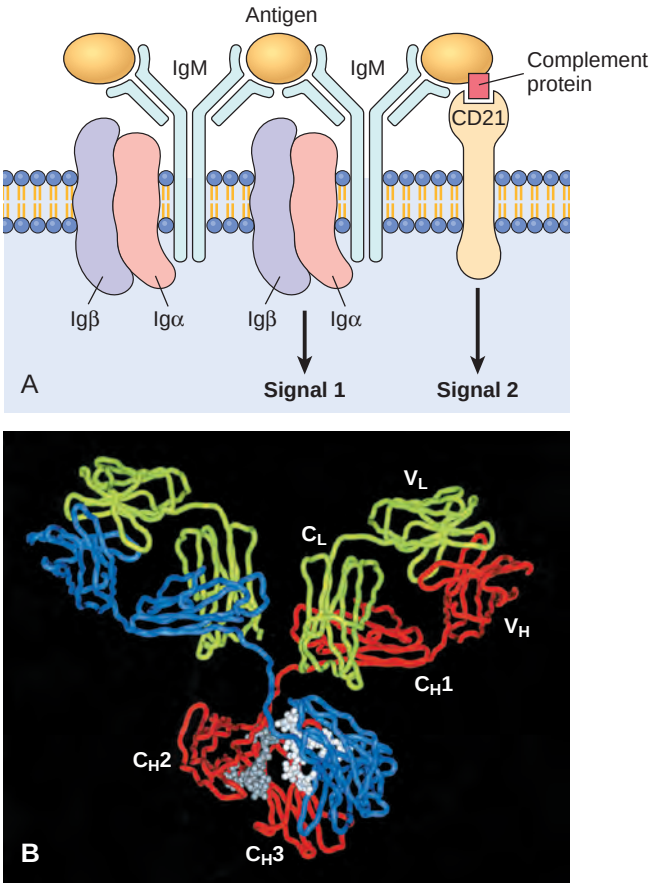

Figure 6-6 Structure of antibodies and the B-cell antigen receptor. **A,** The B-cell antigen receptor complex is composed of membrane immunoglobulin M (IgM; or IgD**,** not shown), which recognizes antigens, and the associated signaling proteins Igα and Igβ. CD21 is a receptor for a complement component that also promotes B-cell activation. **B,** Crystal structure of a secreted IgG molecule, showing the arrangement of the variable (V) and constant (C) regions of the heavy (H) and light (L) chains. (Courtesy Dr. Alex McPherson, University of California, Irvine, Calif.)

of antibody molecules per second, a remarkable measure of the power of the immune response for combating pathogens. Antibody-secreting cells are also detected in human peripheral blood; these are called *plasmablasts*.

In addition to membrane Ig, the B-cell antigen receptor complex contains a heterodimer of two invariant proteins called Igα and Igβ. Similar to the CD3 and ζ proteins of the TCR complex, Igα (CD79a) and Igβ (CD79b) are essential for signal transduction through the antigen receptor. B cells also express several other molecules that are essential for their responses. These include the type 2 complement receptor (CR2, or CD21), which recognizes complement products generated during innate immune responses to microbes, and CD40, which receives signals from helper T cells. CR2 is also used by the Epstein-Barr virus (EBV) as a receptor to enter and infect B cells.

Dendritic Cells

Dendritic cells (sometimes called *interdigitating dendritic cells*) **are the most important antigen-presenting cells for initiating T-cell responses against protein antigens.** These