into effector and memory cells is summarized later. We start with a consideration of the diversity of lymphocytes.

### *Lymphocyte Diversity*

**Lymphocytes specific for a large number of antigens exist before exposure to antigen, and when an antigen enters, it selectively activates the antigen-specific cells.** This fundamental concept is called *clonal selection*. According to this hypothesis, lymphocytes express specific receptors for antigens and mature into functionally competent cells before exposure to antigen. Lymphocytes of the same specificity are said to constitute a *clone*; all the members of one clone express identical antigen receptors, which are different from the receptors in all other clones. There are about $10^{12}$ lymphocytes in a healthy adult, and it is estimated that these are capable of recognizing $10^7$ to $10^9$ different antigens. It follows that the number of cells specific for any one antigen is very small, probably less than 1 in 100,000 to 1 in 1 million lymphocytes. It is remarkable that so few cells with a particular specificity can accomplish the difficult task of combating various microbes; as discussed later, the immune system has developed many mechanisms for optimizing reactions to microbial antigens. It is also remarkable that the system is capable of producing so many receptors, far more than could be individually encoded in the genome. The mechanisms by which this happens are now well understood, and have many interesting clinical implications.

**Antigen receptor diversity is generated by somatic recombination of the genes that encode the receptor proteins.** All cells of the body, including lymphocyte progenitors, contain antigen receptor genes in the germline (inherited) configuration, in which the genes encoding these receptors consist of spatially separated segments that cannot be expressed as proteins. During lymphocyte maturation (in the thymus for T cells and the bone marrow for B cells), these gene segments recombine in random sets and variations are introduced at the sites of recombination, forming many different genes that can be transcribed and translated into functional antigen receptors. The enzyme in developing lymphocytes that mediates recombination of these gene segments is the product of *RAG-1* and *RAG-2* (recombination activating genes); inherited defects in RAG proteins result in a failure to generate mature lymphocytes. It is important to note that germline antigen receptor genes are present in all cells in the body, but only T and B cells contain recombined (also called rearranged) antigen receptor genes (the T-cell receptor [TCR] in T cells and immunoglobulin [Ig] in B cells). Hence, the presence of recombined TCR or Ig genes, which can be demonstrated by molecular analysis, is a marker of T- or B-lineage cells. Furthermore, because each T or B cell and its clonal progeny have a unique DNA rearrangement (and hence a unique antigen receptor), it is possible to distinguish polyclonal (nonneoplastic) lymphocyte proliferations from monoclonal (neoplastic) lymphoid tumors. Thus, **analysis of antigen receptor gene rearrangements is a valuable assay for detecting tumors derived from lymphocytes** (Chapter 13).

### *T Lymphocytes*

There are three major populations of T cells, which serve distinct functions. **Helper T lymphocytes stimulate B lymphocytes to make antibodies and activate other leukocytes (e.g., phagocytes) to destroy microbes; cytotoxic T lymphocytes (CTLs) kill infected cells; and regulatory T lymphocytes limit immune responses and prevent reactions against self antigens.**

T lymphocytes develop in the thymus from precursors that arise from hematopoietic stem cells. Mature T cells are found in the blood, where they constitute 60% to 70% of lymphocytes, and in T-cell zones of peripheral lymphoid organs (described later). Each T cell recognizes a specific cell-bound antigen by means of an antigen-specific TCR. In approximately 95% of T cells, the TCR consists of a disulfide-linked heterodimer made up of an α and a β polypeptide chain (Fig. 6-5), each having a variable (antigen-binding) region and a constant region. **The αβ TCR recognizes peptide antigens that are presented by major histocompatibility complex (MHC) molecules on the surfaces of antigen-presenting cells.** By limiting the specificity of T cells for peptides displayed by cell surface MHC molecules, called *MHC restriction*, the immune system ensures that T cells see only cell-associated antigens (e.g., those derived from microbes in cells or from proteins ingested by cells).

Each TCR is noncovalently linked to six polypeptide chains, which form the CD3 complex and the ζ chain dimer (Fig. 6-5). The CD3 and ζ proteins are invariant (i.e., identical) in all T cells. They are involved in the transduction of signals into the T cell that are triggered by binding of

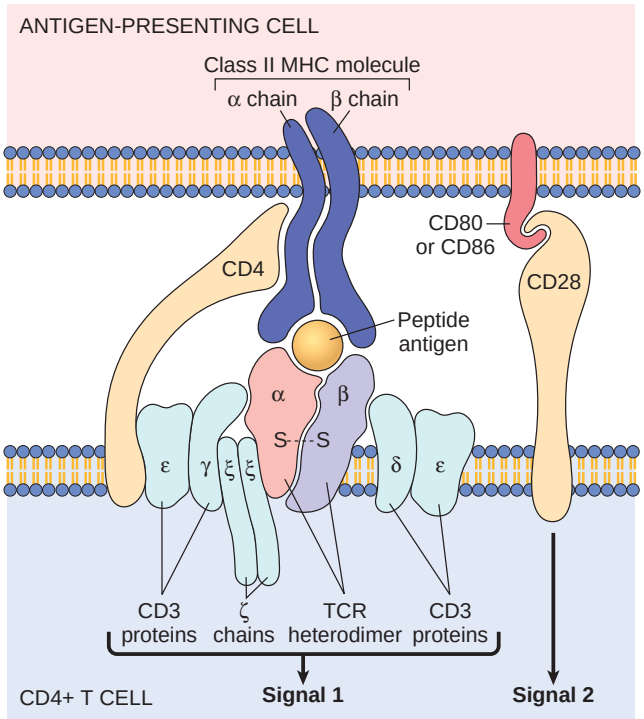


**Figure 6-5** The T-cell receptor (TCR) complex and other molecules involved in T-cell activation. The TCR heterodimer, consisting of an α and a β chain, recognizes antigen (in the form of peptide-MHC complexes expressed on antigen-presenting cells, or APCs), and the linked CD3 complex and ζ chains initiate activating signals. CD4 and CD28 are also involved in T-cell activation. (Note that some T cells express CD8 and not CD4; these molecules serve analogous roles.) The sizes of the molecules are not drawn to scale. MHC, Major histocompatibility complex.