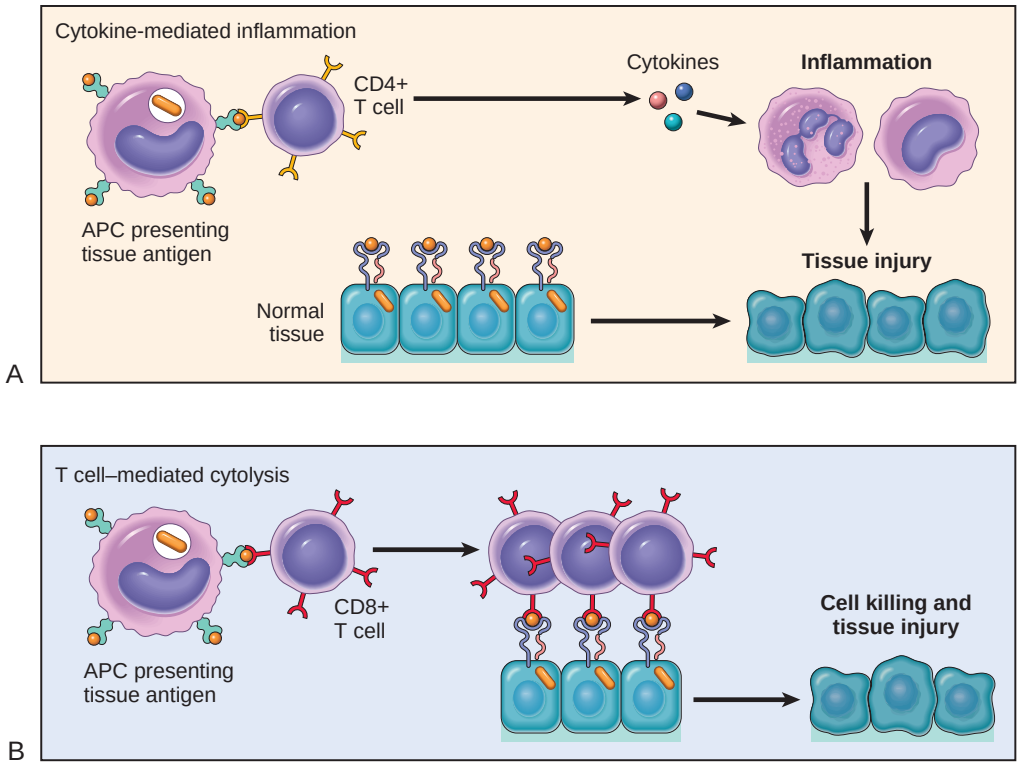

Figure 6-18 Mechanisms of T cell–mediated (type IV) hypersensitivity reactions. **A,** CD4+ T_H1 cells (and sometimes CD8+ T cells, not shown) respond to tissue antigens by secreting cytokines that stimulate inflammation and activate phagocytes, leading to tissue injury. CD4+ T_H17 cells contribute to inflammation by recruiting neutrophils (and, to a lesser extent, monocytes). **B,** In some diseases, CD8+ cytotoxic T lymphocytes (CTLs) directly kill tissue cells. APC, Antigen-presenting cell.

antigen-stimulated T cells to T_H1 or T_H17 cells is driven by the cytokines produced by APCs at the time of T-cell activation. In some situations the APCs (dendritic cells and macrophages) produce IL-12, which induces differentiation of CD4+ T cells to the T_H1 subset. IFN-γ produced by these effector cells promotes further T_H1 development, thus amplifying the reaction. If the APCs produce inflammatory cytokines such as IL-1, IL-6, and a close relative of IL-12 called *IL-23*, these stimulate differentiation of T cells to the T_H17 subset. Some of the differentiated effector cells enter the circulation and may remain in the memory pool of T cells for long periods, sometimes years.

Responses of Differentiated Effector T Cells. Upon repeat exposure to an antigen, T_H1 cells secrete cytokines, mainly IFN-γ, which are responsible for many of the manifestations of delayed-type hypersensitivity. IFN-γ-activated ("classically activated") macrophages are altered in several ways: their ability to phagocytose and kill microorganisms is markedly augmented; they express more class II MHC molecules on the surface, thus facilitating further antigen presentation; they secrete TNF, IL-1, and chemokines, which promote inflammation (Chapter 3); and they produce more IL-12, thereby amplifying the T_H1 response. Thus, activated macrophages serve to eliminate the offending

Table 6-5 T Cell–Mediated Diseases

Disease	Specificity of Pathogenic T Cells	Principal Mechanisms of Tissue Injury	Clinicopathologic Manifestations
Rheumatoid arthritis	Collagen? Citrullinated self proteins?	Inflammation mediated by T_H17 (and T_H1?) cytokines; role of antibodies and immune complexes?	Chronic arthritis with inflammation, destruction of articular cartilage
Multiple sclerosis	Protein antigens in myelin (e.g., myelin basic protein)	Inflammation mediated by T_H1 and T_H17 cytokines, myelin destruction by activated macrophages	Demyelination in CNS with perivascular inflammation; paralysis,
Type 1 diabetes mellitus	Antigens of pancreatic islet β cells (insulin, glutamic acid decarboxylase, others)	T cell–mediated inflammation, destruction of islet cells by CTLs	Insulitis (chronic inflammation in islets), destruction of β cells; diabetes
Inflammatory bowel disease	Enteric bacteria; self antigens?	Inflammation mediated by T_H1 and T_H17 cytokines	Chronic intestinal inflammation, obstruction
Psoriasis	Unknown	Inflammation mediated mainly by T_H17 cytokines	Destructive plaques in the skin
Contact sensitivity	Various environmental chemicals (e.g., urushiol from poison ivy or poison oak)	Inflammation mediated by T_H1 (and T_H17?) cytokines	Epidermal necrosis, dermal inflammation, causing skin rash and blisters

Examples of human T cell–mediated diseases are listed. In many cases, the specificity of the T cells and the mechanisms of tissue injury are inferred based on the similarity with experimental animal models of the diseases.