that increase the immunogenicity and immunostimulatory capacity of the microbial material. The adjuvants activate dendritic cells through TLRs, which in turn stimulate the activation of previously quiescent lymphocytes that recognize both microbial antigens and self-antigens. Similarly, cellular and tissue damage due to the release of *damage-associated molecular patterns* (DAMPs), including DNA, RNA nucleosomes, and other tissue debris, may activate cells of the inflammatory and immune systems through engagement of the same array of PRRs.

Endogenous derangements of the immune system may also contribute to the loss of immunologic tolerance to self-antigens and the development of autoimmunity (Table 377e-2). Some autoantigens reside in immunologically privileged sites, such as the brain or the anterior chamber of the eye. These sites are characterized by the inability of engrafted tissue to elicit immune responses. Immunologic privilege results from a number of events, including the limited entry of proteins from those sites into lymphatics, the local production of immunosuppressive cytokines such as transforming growth factor β, and the local expression of molecules (including Fas ligand) that can induce apoptosis of activated T cells. Lymphoid cells remain in a state of immunologic ignorance (neither activated nor anergized) with regard to proteins expressed uniquely in immunologically privileged sites. If the privileged site is damaged by trauma or inflammation or if T cells are activated elsewhere, proteins expressed at this site can become immunogenic and also be the targets of immunologic assault. In multiple sclerosis and sympathetic ophthalmia, for example, antigens uniquely expressed in the brain and eye, respectively, become the target of activated T cells.

Alterations in antigen presentation may also contribute to autoimmunity. Peptide determinants (*epitopes*) of a self-antigen that are not routinely presented to lymphocytes may be recognized as a result of altered proteolytic processing of the molecule and the ensuing presentation of novel peptides (*cryptic epitopes*). When B cells rather than dendritic cells present self-antigen, they may also present cryptic epitopes that can activate autoreactive T cells. These cryptic epitopes will not previously have been available to effect the silencing of autoreactive lymphocytes. Furthermore, once there is immunologic recognition of one protein component of a multimolecular complex, reactivity may be induced to other components of the complex after internalization and presentation of all molecules within the complex (epitope spreading). Finally, inflammation, environmental agents, drug exposure, or normal senescence may cause a post-transitional alteration in proteins, resulting in the generation of immune responses that cross-react with normal self-proteins. For example, the induction and/or release of protein arginine deiminase enzymes results in the conversion of arginine residues to citrullines in a variety of proteins, thereby altering their capacity to induce immune responses. Production of antibodies to citrullinated proteins has been observed in rheumatoid arthritis and chronic lung disease as well as in normal smokers and may contribute to organ pathology. Alterations in the availability and presentation of autoantigens may be important components of immunoreactivity in certain models of organ-specific autoimmune diseases. In addition, these factors may be relevant to an understanding of the pathogenesis of various drug-induced autoimmune conditions. However, the diversity of autoreactivity manifesting in non-organ-specific systemic autoimmune diseases suggests that these conditions may result from a more general activation of the immune system rather than from an alteration in individual self-antigens.

Many autoimmune diseases are characterized by the presence of antibodies that react with apoptotic material. Defects in the clearance of apoptotic material have been shown to elicit auto-immunity and autoimmune disease in a number of animal models. Moreover, such defects have been found in patients with systemic lupus erythematosus (SLE). Apoptotic debris that is not cleared quickly by the immune system can function as endogenous ligands for a number of PRRs on dendritic cells and B cells. Under such circumstances, dendritic cells and/or B cells are activated, and an immune response to apoptotic debris can develop. In addition, the presence of extracellular apoptotic material within germinal centers of secondary lymphoid organs in patients with SLE may facilitate the direct activation of autoimmune B cell clones or may function to select such clones during immune responses.

Studies in a number of experimental models have suggested that intense stimulation of T lymphocytes can produce nonspecific signals that bypass the need for antigen-specific helper T cells and lead to polyclonal B cell activation with the formation of multiple autoantibodies. For example, antinuclear, antierythrocyte, and antilymphocyte antibodies are produced during the chronic graft-versus-host reaction. In addition, true autoimmune diseases, including autoimmune hemolytic anemia and immune complex–mediated glomerulonephritis, can be induced in this manner. While such diffuse activation of helper T cell activity clearly can cause autoimmunity, nonspecific stimulation of B lymphocytes can also lead to the production of autoantibodies. Thus, the administration of polyclonal B cell activators, such as bacterial endotoxin, to normal mice leads to the production of a number of autoantibodies, including those to DNA and IgG (rheumatoid factor). A variety of genetic modifications resulting in hyperresponsiveness of B cells also can lead to the production of autoantibodies and, in animals of appropriate genetic background, a lupus-like syndrome. Moreover, excess B cell activating factor (BAFF), a B cell survival factor, can cause T cell–independent B cell activation and the development of autoimmunity. SLE can also be induced in mice through exuberant dendritic cell activation, through a redundancy of TLR7 on the Y chromosome (as in BXSB-Yaa mice), or through exposure to CpG, a ligand for TLR9. The ensuing induction of inflammatory mediators can cause a switch from the production of nonpathogenic IgM autoantibodies to the production of pathogenic IgG autoantibodies in the absence of antigen-specific T cell help. Aberrant selection of the B or T cell repertoire at the time of antigen receptor expression can also predispose to autoimmunity. For example, B cell immunodeficiency caused by an absence of the B cell receptor–associated kinase (Bruton's tyrosine kinase) leads to X-linked agammaglobulinemia. This syndrome is characterized by reduced B cell numbers. This leads to high levels of BAFF which alter B cell selection and lead to greater survival of autoreactive B cells. Likewise, negative selection of autoreactive T cells in the thymus requires expression of the autoimmune regulator (AIRE) gene that enables the expression of tissue-specific proteins in thymic medullary epithelial cells. Peptides from these proteins are expressed in the context of major histocompatibility complex (MHC) molecules and mediate the central deletion of autoreactive T cells. The absence of AIRE gene expression leads to a failure of negative selection of autoreactive cells, autoantibody production, and severe inflammatory destruction of multiple organs. Individuals deficient in AIRE gene expression develop autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED).

Primary alterations in the activity of T and/or B cells, cytokine imbalances, or defective immunoregulatory circuits may also contribute to the emergence of autoimmunity. Diminished production of tumor necrosis factor (TNF) and interleukin (IL) 10 has been reported to be associated with the development of autoimmunity. Overproduction or therapeutic administration of type 1 interferon has also been associated with autoimmunity. Overexpression of costimulatory molecules on T cells similarly can lead to autoantibody production.

Autoimmunity may also result from an abnormality of immunoregulatory mechanisms. Observations made in both human autoimmune disease and animal models suggest that defects in the generation and expression of regulatory T cell (Treg) activity may allow the production of autoimmunity. It has recently been appreciated that the IPEX (immunodysregulation, polyendocrinopathy, enteropathy X-linked) syndrome results from the failure to express the FOXP3 gene, which encodes a molecule critical in the differentiation of Tregs. Administration of normal Tregs or of factors derived from them can prevent the development of autoimmune disease in rodent models of autoimmunity, and allogeneic stem cell transplantation ameliorates human IPEX. Abnormalities in the function of Tregs have been noted in a number of human autoimmune diseases, including rheumatoid arthritis and SLE, although it remains uncertain whether these functional abnormalities are causative or are secondary to inflammation. One of the mechanisms by which Tregs control immune/inflammatory