prevent immune reactions against fetal antigens that are inherited from the father and therefore foreign to the mother. In line with this idea, during evolution, placentation appeared simultaneously with the ability to stably express the Foxp3 transcription factor. Experiments in mice have shown that fetal antigens induce long-lived Foxp3+ regulatory T cells, and depletion of these cells results in fetal loss. There is great interest in determining the contribution of regulatory T cells in human pregnancy and possible defects in these cells as the basis for recurrent spontaneous abortions.

- **Deletion by apoptosis. T cells that recognize self antigens may receive signals that promote their death by apoptosis.** Two mechanisms of deletion of mature T cells have been proposed, based mainly on studies in mice. It is postulated that if T cells recognize self antigens, they may express a pro-apoptotic member of the Bcl family, called Bim, without antiapoptotic members of the family like Bcl-2 and Bcl-x (whose induction requires the full set of signals for lymphocyte activation). Unopposed Bim triggers apoptosis by the mitochondrial pathway (Chapter 2). A second mechanism of activation-induced death of CD4+ T cells and B cells involves the Fas-Fas ligand system. Lymphocytes as well as many other cells express the death receptor Fas (CD95), a member of the TNF-receptor family. Fas ligand (FasL), a membrane protein that is structurally homologous to the cytokine TNF, is expressed mainly on activated T lymphocytes. The engagement of Fas by FasL induces apoptosis of activated T cells (Chapter 2). It is postulated that if self antigens engage antigen receptors of self-reactive T cells, Fas and FasL are co-expressed, leading to elimination of the cells via Fas-mediated apoptosis. Self-reactive B cells may also be deleted by FasL on T cells engaging Fas on the B cells. The importance of this mechanism in the peripheral deletion of autoreactive lymphocytes is highlighted by two mice that are natural mutants of Fas or FasL. These mice develop an autoimmune disease somewhat resembling human SLE, associated with generalized lymphoproliferation. In humans a similar disease is caused by mutations in the *FAS* gene; it is called the *autoimmune lymphoproliferative syndrome (ALPS)*.

  Some antigens are hidden (sequestered) from the immune system, because the tissues in which these antigens are located do not communicate with the blood and lymph. As a result, self antigens in these tissues fail to elicit immune responses and are essentially ignored by the immune system. This is believed to be the case for the testis, eye, and brain, all of which are called *immune-privileged sites* because it is difficult to induce immune responses to antigens introduced into these sites. If the antigens of these tissues are released, for example, as a consequence of trauma or infection, the result may be an immune response that leads to prolonged tissue inflammation and injury. This is the postulated mechanism for post-traumatic orchitis and uveitis.

Mechanisms of Autoimmunity: General Principles

The immune system normally exists in an equilibrium in which lymphocyte activation, which is required for defense against pathogens, is balanced by the mechanisms of tolerance, which prevent reactions against self antigens. The underlying cause of autoimmune diseases is the failure of tolerance, which allows responses to develop against self antigens. Understanding why tolerance fails in these diseases is an important goal of immunologists.

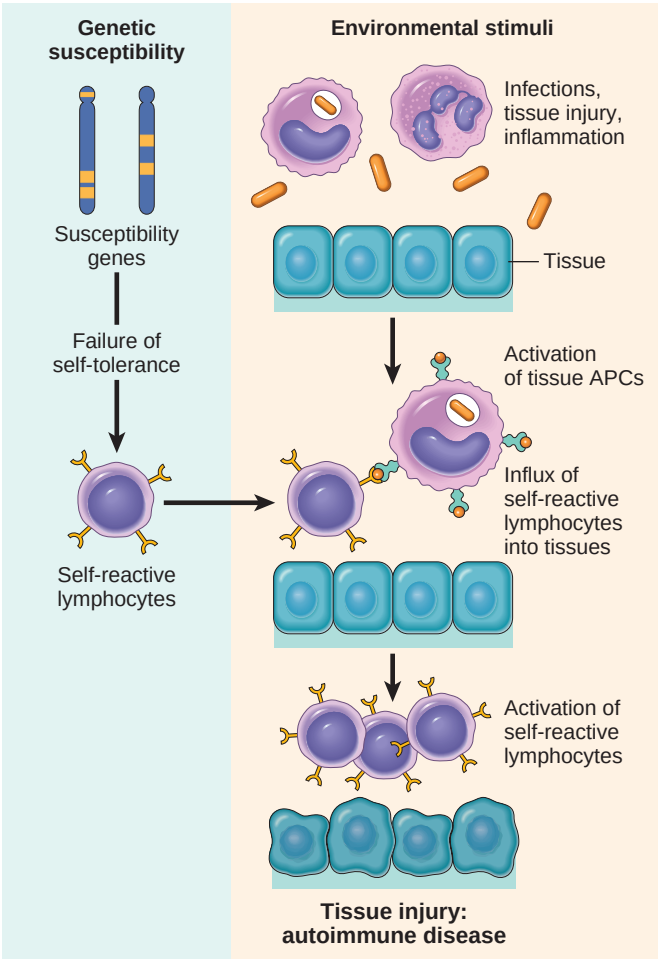

Figure 6-22 Pathogenesis of autoimmunity. Autoimmunity results from multiple factors, including susceptibility genes that may interfere with self-tolerance and environmental triggers (such as infections, tissue injury, and inflammation) that promote lymphocyte entry into tissues, activation of self-reactive lymphocytes, and tissue damage.

Autoimmunity arises from a combination of the inheritance of susceptibility genes, which may contribute to the breakdown of self-tolerance, and environmental triggers, such as infections and tissue damage, which promote the activation of self-reactive lymphocytes (Fig. 6-22). The genetics, as well as the gene-environment interactions, are complex and difficult to dissect, because of which much remains unknown about the enigma of autoimmunity. Nevertheless, some interesting clues have begun to emerge with the development of better technologies for defining genetic susceptibility and for studying patients.

It is thought that susceptibility genes and environmental triggers induce a number of changes that contribute to the development of autoimmunity:

- **Defective tolerance or regulation.** Fundamental to the development of autoimmune diseases is a failure of the