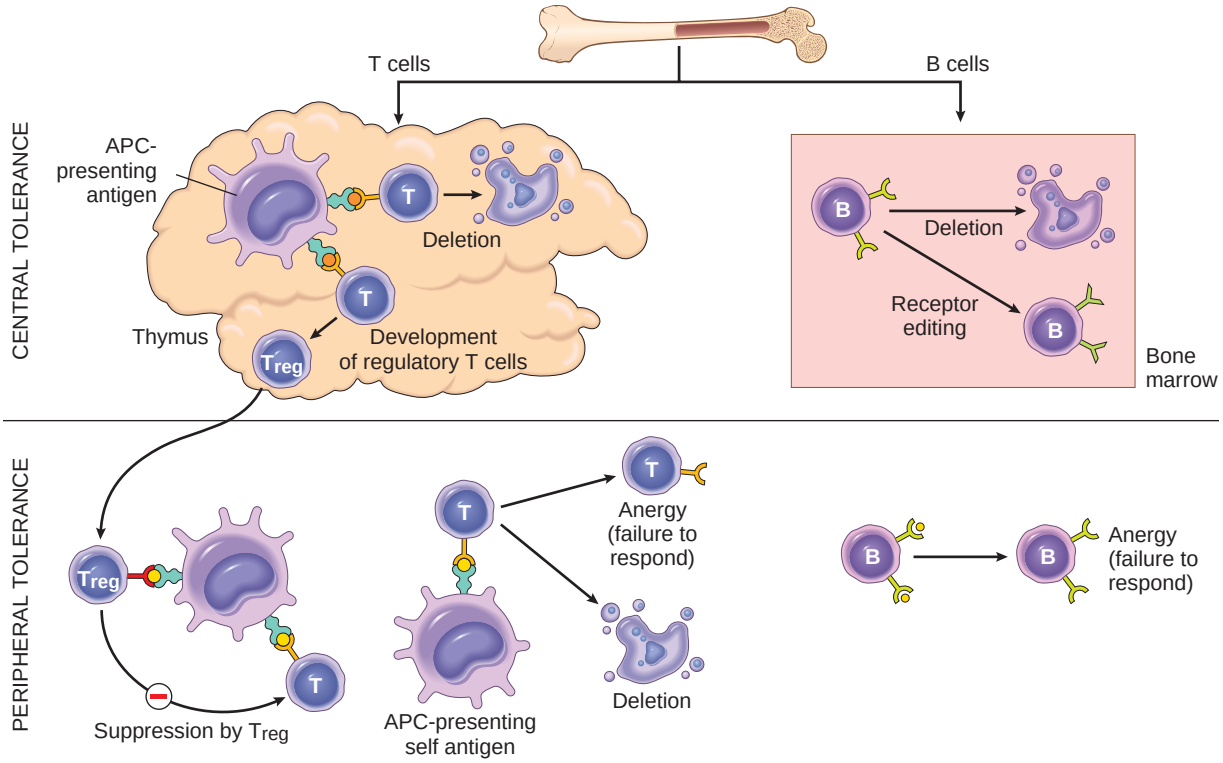

Figure 6-21 Mechanisms of immunologic tolerance to self antigens. The principal mechanisms of central and peripheral self-tolerance in T and B cells are illustrated. APC, Antigen-presenting cell.

response may be directed against normally harmless microbes such as gut commensal bacteria.

The clinical manifestations of autoimmune disorders are extremely varied. On one end are conditions in which the immune responses are directed against a single organ or tissue, resulting in *organ-specific disease*, and on the other end are diseases in which the autoimmune reactions are against widespread antigens, resulting in *systemic* or *generalized disease*. Examples of organ-specific autoimmune diseases are type 1 diabetes mellitus, in which the autoreactive T cells and antibodies are specific for β cells of the pancreatic islets, and multiple sclerosis, in which autoreactive T cells react against central nervous system myelin. The best example of systemic autoimmune disease is SLE, in which a diversity of antibodies directed against DNA, platelets, red cells, and protein-phospholipid complexes result in widespread lesions throughout the body. In the middle of the spectrum falls Goodpasture syndrome, in which antibodies to basement membranes of lung and kidney induce lesions in these organs.

It is obvious that autoimmunity results from the loss of self-tolerance, and the question arises as to how this happens. Before we look for answers to this question, we review the mechanisms of immunologic tolerance to self antigens.

Immunologic Tolerance

Immunologic tolerance is the phenomenon of unresponsiveness to an antigen induced by exposure of lymphocytes to that antigen. *Self-tolerance* refers to lack of responsiveness to an individual's own antigens, and it underlies our ability to live in harmony with our cells and tissues. Because the antigen receptors of lymphocytes are generated by somatic recombination of genes in a random fashion, lymphocytes with receptors capable of recognizing self antigens are generated constantly, and these cells have to be eliminated or inactivated as soon as they recognize self antigens, to prevent them from causing harm.

The mechanisms of self-tolerance can be broadly classified into two groups: central tolerance and peripheral tolerance (Fig. 6-21). Each of these is considered briefly.

Central Tolerance

In this process, immature self-reactive T and B lymphocyte clones that recognize self antigens during their maturation in the central (or generative) lymphoid organs (the thymus for T cells and the bone marrow for B cells) are killed or rendered harmless. The mechanisms of central tolerance in T and B cells show some similarities and differences.

- In developing T cells, random somatic gene rearrangements generate diverse TCRs. Such antigen-independent TCR generation produces many lymphocytes that express high-affinity receptors for self antigens. When immature lymphocytes encounter the antigens in the thymus, many of the cells die by apoptosis. This process, called *negative selection* or *deletion*, is responsible for eliminating self-reactive lymphocytes from the T-cell pool. A wide variety of autologous protein antigens, including antigens thought to be restricted to peripheral tissues, are processed and presented by thymic antigen-presenting cells in association with self MHC molecules and can, therefore, be recognized by potentially