numbers of follicular helper T cells have been detected in the blood of SLE patients.

- **TLR engagement by nuclear DNA and RNA** contained in immune complexes may activate B lymphocytes. These TLRs function normally to sense microbial products, including nucleic acids. Thus, B cells specific for nuclear antigens may get second signals from TLRs and may be activated, resulting in increased production of antinuclear autoantibodies.
- **Type I interferons** play a role in lymphocyte activation in SLE. High levels of circulating type I interferons and a molecular signature in blood cells suggesting exposure to these cytokines has been reported in SLE patients and correlates with disease severity. Type I interferons are antiviral cytokines that are normally produced during innate immune responses to viruses. It may be that nucleic acids engage TLRs on dendritic cells and stimulate the production of interferons. In other words, self nucleic acids mimic their microbial counterparts. How interferons contribute to the development of SLE is unclear; these cytokines may activate dendritic cells and B cells and promote T_H1 responses, all of which may stimulate the production of pathogenic autoantibodies.
- Other cytokines that may play a role in unregulated B-cell activation include the TNF family member BAFF, which promotes survival of B cells. In some patients and animal models, increased production of BAFF has been reported, prompting attempts to block the cytokine or its receptor as therapy for SLE.

Environmental Factors. There are many indications that environmental factors must also be involved in the pathogenesis of SLE.

- **Exposure to ultraviolet (UV) light** exacerbates the disease in many individuals. UV irradiation may induce apoptosis in cells and may alter the DNA in such a way that it becomes immunogenic, perhaps because of enhanced recognition by TLRs. In addition, UV light may modulate the immune response, for example, by stimulating keratinocytes to produce IL-1, a cytokine known to promote inflammation.
- The **gender bias** of SLE is partly attributable to actions of sex hormones and partly related to genes on the X chromosome, independent of hormone effects.
- **Drugs** such as hydralazine, procainamide, and D-penicillamine can induce an SLE-like response in humans.

A Model for the Pathogenesis of SLE. It is clear from this discussion that the immunologic abnormalities in SLE—both documented and postulated—are varied and complex. Nevertheless, an attempt can be made to synthesize results from human studies and animal models into a hypothetical model of the pathogenesis of SLE (Fig. 6-25). UV irradiation and other environmental insults lead to the apoptosis of cells. Inadequate clearance of the nuclei of these cells results in a large burden of nuclear antigens. Underlying abnormalities in B and T lymphocytes are responsible for defective tolerance, because of which self-reactive lymphocytes survive and remain functional. These lymphocytes are stimulated by nuclear self antigens, and

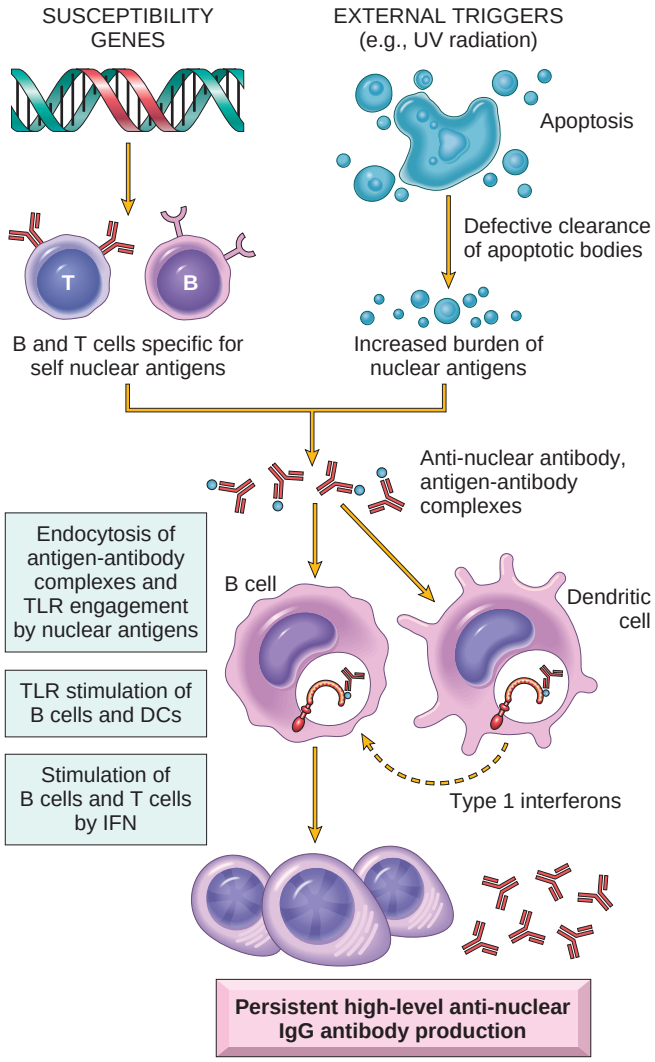

Figure 6-25 Model for the pathogenesis of systemic lupus erythematosus. In this hypothetical model, susceptibility genes interfere with the maintenance of self-tolerance and external triggers lead to persistence of nuclear antigens. The result is an antibody response against self nuclear antigens, which is amplified by the action of nucleic acids on dendritic cells (DCs) and B cells, and the production of type 1 interferons. TLRs, Toll-like receptors.

antibodies are produced against the antigens. Complexes of the antigens and antibodies bind to Fc receptors on B cells and dendritic cells, and may be internalized. The nucleic acid components engage TLRs and stimulate B cells to produce more autoantibodies. TLR stimuli also activate dendritic cells to produce interferons and other cytokines, which further enhance the immune response and cause more apoptosis. The net result is a cycle of antigen release and immune activation resulting in the production of high-affinity autoantibodies.

Mechanism of Tissue Injury. Different autoantibodies are the cause of most of the lesions of SLE.

- **Most of the systemic lesions are caused by immune complexes (type III hypersensitivity).** DNA-anti-DNA complexes can be detected in the glomeruli and small blood vessels. Low levels of serum complement