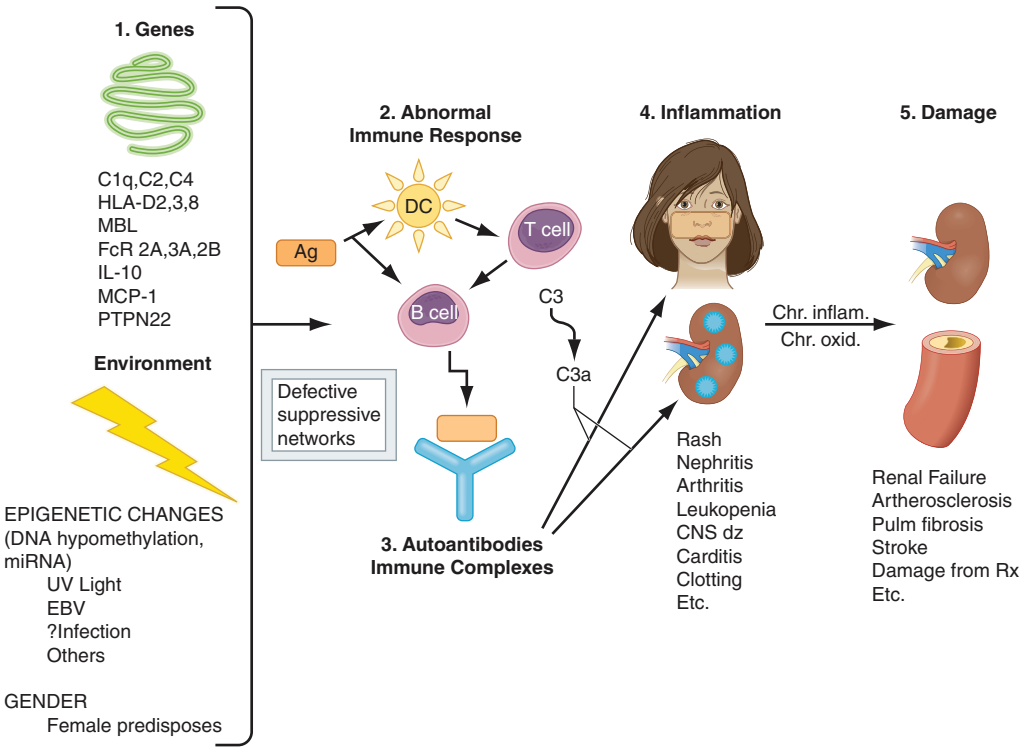

FIGURE 378-1 Pathogenesis of systemic lupus erythematosus (SLE). Genes confirmed in more than one genome-wide association analysis in northern European whites (several confirmed in Asians as well) as increasing susceptibility to SLE or lupus nephritis are listed (reviewed in SG Guerra et al: Arthritis Res Ther 14:211, 2012). Gene-environment interactions (reviewed in KH Costenbader et al: Autoimmune Rev 11:604, 2012) result in abnormal immune responses that generate pathogenic autoantibodies and immune complexes that deposit in tissue, activate complement, cause inflammation, and over time lead to irreversible organ damage (reviewed in GC Tsokos: N Engl J Med 365:2110, 2011; and BH Hahn, in DJ Wallace, BH Hahn [eds]: *Dubois' Lupus Erythematosus and Related Syndromes*, 8th ed. New York, Elsevier, 2013). Ag, antigen; C1q, complement system; C3, complement component; CNS, central nervous system; DC, dendritic cell; EBV, Epstein-Barr virus; HLA, human leukocyte antigen; FcR, immunoglobulin Fc-binding receptor; IL, interleukin; MCP, monocyte chemotactic protein; PTPN, phosphotyrosine phosphatase; UV, ultraviolet.

IFNs is a genetic "signature" in peripheral blood cells of 50–60% of SLE patients. Decreased production of other cytokines also contributes to SLE: lupus T and natural killer (NK) cells fail to produce enough IL-2 and transforming growth factor beta (TGF-β) to induce and sustain regulatory CD4+ and CD8+ T cells. The result of these abnormalities is sustained production of autoantibodies (referred to in Fig. 378-1 and described in Table 378-1) and immune complexes; pathogenic subsets bind target tissues, with activation of complement, leading to release of cytokines, chemokines, vasoactive peptides, oxidants, and proteolytic enzymes. This results in activation of multiple tissue cells (endothelial cells, tissue-fixed macrophages, mesangial cells, podocytes, renal tubular epithelial cells) and influx into target tissues of T and B cells, monocyte/macrophages, and dendritic cells. In the setting of chronic inflammation, accumulation of growth factors and products of chronic oxidation contribute to irreversible tissue damage, including fibrosis/sclerosis in glomeruli, arteries, lungs, and other tissues.

SLE is a multigenic disease. Rare single-gene defects confer high hazard ratios (HRs) for SLE (5 to 25), including homozygous deficiencies of early components of complement (C1q,r,s; C2; C4) and a mutation in *TREX1* on the X chromosome. In most genetically susceptible individuals, normal alleles of multiple genes each contribute a small amount to abnormal immune/inflammation/tissue damage responses; if enough predisposing variations are present, disease results. Approximately 45 predisposing genes (examples listed in Fig. 378-1) have been identified in recent genome-wide association studies in different racial groups. Individually, they confer an HR for SLE of 1.5–3 and account for approximately 18% of disease susceptibility, suggesting that environmental exposures and epigenetics play major roles. Predisposing, antigen-presenting human leukocyte antigen (HLA) molecules are most commonly found, in multiple ethnic groups (HLA DRB1 *0301 and *1501, as well as multiple genes across the major histocompatibility complex (MHC) 120-gene region). Other genetic factors in whites include innate immunity pathway gene polymorphisms, especially associated with IFN-α (*STAT4, IRF5, IRAK1, TNFAIP3, PTPN22*), genes in lymphocyte signaling pathways (*PTPN22, PDCD-1, Ox40L, BANK-1, LYN, BLK*), genes that affect clearance of apoptotic cells or immune complexes (*C1q, FCRGIIA, FCRGIIIA, CRP, ITGAM*), genes that influence neutrophil adherence (*ITGAM*), and genes that influence DNA repair (*TREX-1*). Some polymorphisms influence clinical manifestations; such as single nucleotide polymorphisms (SNPs) of *STAT4* that associate with severe disease, anti-DNA, nephritis, and antiphospholipid syndrome, and an allele of *FCGRIIA* encoding a receptor that binds immune complexes poorly and predisposes to nephritis. Some gene effects are in promoter regions (e.g., IL-10), and others are conferred by copy numbers (e.g., C4A). In addition to genome-encoded susceptibility and protective genes, the influence of certain microRNAs (miRNAs) on gene transcription, as well as post-transcriptional epigenetic modification of DNA (which is hypomethylated in T cells of SLE patients), probably play major roles in disease susceptibility.

Some gene polymorphisms contribute to several autoimmune diseases, such as *STAT4* and *CTLA4*. All of these gene polymorphisms/transcription/epigenetic combinations influence immune responses to the external and internal environment; when such responses are too high and/or too prolonged and/or inadequately regulated, autoimmune disease results.

Female sex is permissive for SLE with evidence for hormone effects, genes on the X chromosome, and epigenetic differences between genders playing a role. Females of many mammalian species make higher antibody responses than males. Women exposed to