CHAPTER 15

Systemic Lupus Erythematosus
B. Epidemiology, Pathology, and Pathogenesis

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- Systemic lupus erythematosus (SLE) is primarily a disease of young women, though it can be seen in both pediatric and older patients where the sex ratio is more balanced.
- The pathologic findings of SLE occur throughout the body and are manifested by inflammation, blood vessel abnormalities that encompass bland vasculopathy and vasculitis, and immune-complex deposition.
- Autoantibodies can occur in the absence of clinical lupus, but pathogenic autoantibodies are important contributors to tissue damage in the kidney as well as in other involved organs.

EPIDEMIOLOGY

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease with diverse clinical manifestations in association with autoantibodies to components of the cell nucleus. SLE primarily is a disease of young women, with a peak incidence between the ages of 15 and 40 and a female:male ratio of 6 to 10:1. The age at onset, however, can range from infancy to advanced age; in both pediatric- and older-onset patients, the female:male ratio is approximately 2:1. In a general outpatient population, SLE affects approximately one in 2000 individuals, although the prevalence varies with race, ethnicity, and socioeconomic status (1).

Like other autoimmune diseases, SLE can display familial aggregation, with a higher frequency among first-degree relatives of patients. The disease occurs concordantly in approximately 25% to 50% of monozygotic twins and 5% of dizygotic twins. Moreover, in extended families, SLE may occur with other autoimmune conditions, such as hemolytic anemia, thyroiditis, and idiopathic thrombocytopenia purpura. Despite the influence of heredity, most cases of SLE appear sporadic.

IMMUNOPATHOLOGY

The pathologic findings of SLE occur throughout the body and are manifested by inflammation, blood vessel abnormalities that encompass bland vasculopathy and vasculitis, and immune-complex deposition. The best-characterized pathology involves the kidney, which displays increases in mesangial cells and mesangial matrix, inflammation, cellular proliferation, basement membrane abnormalities, and immune-complex deposition. These deposits are comprised of IgM, IgG, and IgA, as well as complement components. On electron microscopy, the deposits can be seen in the mesangium and the subendothelial and subepithelial sides of the glomerular basement membrane (Figure 15B-1). Renal pathology is classified according to two systems to provide information for clinical staging (see Chapter 15A; 2,3). With either system, lupus nephritis exhibits marked variability, differing in severity and pattern among patients, as illustrated in Figure 15B-2.

Skin lesions in SLE demonstrate inflammation and degeneration at the dermal–epidermal junction, and the basal or germinal layer is the primary site of injury. In these lesions, granular deposits of IgG and complement...
components occur in a bandlike pattern as observed by immunofluorescence microscopy. Necrotizing vasculitis also may cause skin lesions. Other organ systems affected by SLE usually display nonspecific inflammation or vessel abnormalities, although pathologic findings sometimes are minimal. For example, despite the severity of central nervous system (CNS) involvement, the typical findings are cortical microinfarcts and a bland vasculopathy with degenerative or proliferative changes; inflammation and necrosis indicative of vasculitis are found only rarely.

The heart may show nonspecific foci of inflammation in the pericardium, myocardium, and endocardium, even in the absence of clinically significant manifestations. Verrucous endocarditis, known as Libman–Sacks endocarditis, is a classic pathologic finding of SLE and is manifested by vegetations, most frequently at the mitral valve. These vegetations consist of accumulations of immune complexes, inflammatory cells, fibrin, and necrotic debris.

Occlusive vasculopathy with venous and arterial thrombosis is a common pathologic finding in SLE. Although coagulation can result from inflammation, autoantibodies also may trigger thrombotic events. These autoantibodies represent a spectrum of specificities designated as antiphospholipid antibodies, antiparadriolipin antibodies, or lupus anticoagulants (4). Although some of these antibodies bind lipid antigens, others are directed to the serum protein beta_2-glycoprotein 1, a protein that can form complexes with lipids. Vessel abnormalities in SLE may also result from increases in endothelial cell adhesiveness by a mechanism analogous to the Schwartzman reaction triggered by Gram-negative bacteria.

Other pathologic findings prominent in SLE have an uncertain relationship to inflammation. Patients, including women without the usual risk factors for cardiovascular disease, frequently develop accelerated atherosclerosis and have an increased risk of stroke and myocardial infarction. It is unclear whether these lesions result from corticosteroid-induced metabolic abnormalities, hypertension, or vascular changes caused by a chronic burden of inflammation. Similarly, osteonecrosis, as well as neurodegeneration in people with chronic severe disease, may arise from vasculopathy, drug side effects, or persistent immunologic insults.
IMMUNOPATHOGENESIS OF ANTINUCLEAR ANTIBODIES

The central immunologic disturbance in SLE is autoantibody production. These antibodies are directed to a host of self-molecules found in the nucleus, cytoplasm, or surface of cells. In addition, SLE sera contain antibodies to such soluble molecules as IgG and coagulation factors. Because of the wide range of its antigenic targets, SLE is classified as a disease of generalized autoimmunity.

Among autoantibodies found in patient sera, those directed against components of the cell nucleus (anti-nuclear antibodies, or ANA) are the most characteristic of SLE and are found in more than 95% of patients (5). These antibodies bind DNA, RNA, nuclear proteins, and protein/nucleic acid complexes (Table 15B-1). As a group, the molecules targeted by ANA are highly conserved among species, serve important cellular functions, and exist inside cells as part of complexes (e.g., nucleosomes). Furthermore, these molecules, depending upon context (e.g., presence in immune complexes), display intrinsic immunological activity. This activity results from stimulation of the innate immune system via receptors known as the Toll-like receptors (TLR). The TLRs can recognize a diverse array of foreign and self-molecules, with DNA, single-stranded RNA and double-stranded RNA all TLR ligands (6).

Antibodies to certain nuclear antigens (e.g., DNA and histones) frequently occur together, a phenomenon known as linkage. Linkage suggests that a complex, rather than the individual components, serves as the target of autoreactivity, as well as its driving antigen. Among ANA specificities in SLE, two appear unique to this disease. Antibodies to double-stranded (ds) DNA and a nuclear antigen called Sm are essentially found only in people with SLE, and are included as serologic criteria in the classification of SLE (see Appendix I). Although both anti-DNA and anti-Sm are serologic markers, they differ in their pattern of expression and clinical associations. Whereas anti-DNA levels can fluctuate markedly over time, anti-Sm levels remain more constant. The anti-Sm and anti-DNA responses also differ in the nature of their target antigens. The Sm antigen is designated an snRNP (small nuclear ribonucleoprotein) and consists of uridine-rich RNA molecules complexed with proteins. In contrast to anti-DNA antibodies, which react to a nucleic acid determinant, anti-Sm antibodies target snRNP proteins and not RNA.

Perhaps the most remarkable feature of the anti-DNA response is its association with immunopathologic events in SLE, especially glomerulonephritis. This role has been established by correlating anti-DNA serum levels with disease activity, isolating anti-DNA in enriched form from glomerular eluates of patients with active nephritis, and inducing nephritis by administering anti-DNA antibodies to normal animals. The relationship between levels of anti-DNA and active renal disease is not invariable; some patients with active nephritis may lack serum anti-DNA, and others with high levels of anti-DNA are clinically discordant and escape nephritis (7).

The occurrence of nephritis without anti-DNA may be explained by the pathogenicity of other autoantibody specificities (e.g., anti-Ro or anti-Sm). The converse situation of clinical quiescence despite serologic

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<td>U1RNP</td>
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<tr>
<td>SSA/Ro</td>
<td>60- and 52-KDa proteins, complexed with Y1-Y5 RNAs</td>
<td>Unknown</td>
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<td>SSB/La</td>
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Abbreviations: ss, double-stranded; ss, single-stranded; snRNP, small nuclear ribonucleoprotein.
activity suggests that only some anti-DNA provoke glomerulonephritis. Antibodies with this property are denoted as pathogenic or nephritogenic. Features promoting pathogenicity may include isotype, charge, ability to fix complement, and capacity to bind glomerular preparations (7). In this regard, anti-DNA antibodies appear to be a subset of pathogenic antibodies that bind to nucleosomes, the likely form of DNA in the circulation as well as in immune deposits. Unless the full range of antinucleosomal antibodies is assessed, the presence of nephritogenic antibodies may be missed.

In addition to their direct role in nephritis, antibodies to DNA may promote immune system disturbances that potentiate inflammation systemically as well in the kidney. Thus, immune complexes containing DNA can promote the expression of interferon alpha (IFN-alpha) by a specialized population of dendritic cells known as plasmacytoid dendritic cells. This response requires the presence of both antibody and DNA in an immune complex and depends upon Fc receptors. While the basis of this response is not well understood, stimulation may involve the TLRs as well as other non-TLR signaling systems that respond to internalized nucleic acids. Antibodies to other nuclear antigens, including RNP complexes, can also stimulate this response, raising the possibility that immune complexes, in addition promoting organ damage, can contribute to the overall disturbance in the immune system in patients (8).

In addition to anti-DNA, other autoantibodies may have a clinical impact because of effects on organ-specific manifestations. Associations of other autoantibodies with disease events include antibodies to ribosomal P proteins (anti-P) with neuropsychiatric disease and hepatitis; antibodies to Ro with neonatal lupus and subacute cutaneous lupus; antibodies to phospholipids with vascular thrombosis, thrombocytopenia, and recurrent abortion; and antibodies to blood cells with cytopenias.

The contribution of ANAs to clinical events in SLE has been difficult to understand because the intracellular location of the target antigens should protect them from antibody interactions. The location of these antigens may not be fixed, however, and some antigens may translocate to the membrane and become accessible to antibody attack either during development or during apoptosis. Thus, during cardiac development, a molecule bound by anti-Ro appears on the surface of myocytes and, in the presence of complement, lead to local inflammation and damage to the conducting system (9).

Because of the impact of kidney disease on morbidity and mortality, nephritis has been the clinical event in SLE most intensively studied mechanistically. Clinical observations strongly suggest that SLE renal disease results from the deposition of immune complexes containing anti-DNA, because active nephritis is marked by elevated anti-DNA levels with a depression of total hemolytic complement. Because anti-DNA shows preferential renal deposition, these findings suggest that DNA/anti-DNA immune complexes are a major pathogenic species. DNA in these complexes likely is in the form of nucleosomes, suggesting that antibodies to other components of this structure may participate in immune-complex formation.

Although immune complexes may provoke renal injury in SLE, the amounts of such complexes in the serum appear limited. This finding has suggested that complexes may form in situ, rather than within the circulation. According to this mechanism, immune complexes assemble in the kidney on DNA or other nucleosomal components adherent to the glomerular basement membrane. Another mechanism for nephritis in SLE is the direct interaction of autoantibodies with glomerular antigens. Many anti-DNA antibodies are polyspecific and interact with molecules other than DNA. The binding of anti-DNA to these molecules could activate complement and inciting inflammation.

The pathogenesis of other SLE manifestations is less well understood, although immune-complex deposition at relevant tissue sites generally has been considered a likely mechanism. Indeed, the frequent association of depressed complement levels and signs of vasculitis with active SLE suggests that immune complexes are important agents for initiating or exacerbating organ damage. These considerations do not exclude the possibility that tissue injury results from either cell-mediated cytotoxicity or direct antibody attack on target tissues. Consistent with the operation of such a mechanism, a cross-reactive population of antibodies to the NMDA receptor may CNS disturbances by inducing excitotoxic damage (10).

**DETERMINANTS OF DISEASE SUSCEPTIBILITY**

Studies of patients suggest that SLE is caused by genetically determined immune abnormalities that can be triggered by exogenous or endogenous factors. Although the predisposition to disease is hereditary, it is likely multigenic and involves different sets of genes in different individuals (see Chapter 5). Analysis of genetic susceptibility has been based primarily on the search for gene polymorphisms occurring with greater frequency in people with SLE than in control populations. The study of genetic factors predisposing to SLE also has involved genomewide scans of siblings with SLE or multiplex families. Although this approach has led to the identification of chromosomal regions that contain genes potentially relevant to pathogenesis, the identities of these genes are not yet known definitively. Fur-
thermore, the regions associated with disease may differ depending upon racial and ethnic group (11).

Of genetic systems that could predispose to autoimmunity, the major histocompatibility complex (MHC) has been most intensively scrutinized for its contribution to human SLE. Using a variety of MHC gene markers, population-based studies indicate that the susceptibility to SLE, like many other autoimmune diseases in humans, involves class II gene polymorphisms. An association of human leukocyte antigen (HLA)-DR2 and HLA-DR3 (and various subspecificities) with SLE has been commonly observed, with these alleles producing a relative risk of disease that ranges approximately from 2 to 5. This analysis of MHC gene associations is complicated by the existence of extended HLA haplotypes in which class II genes are in linkage disequilibrium with other potential susceptibility genes. Because the MHC is rich in genes for immune-system elements, the association of disease with a class II marker does not denote a specific functional abnormality promoting pathogenesis.

Among other MHC gene systems, inherited complement deficiencies can influence disease susceptibility. Like class I and II molecules, complement components, in particular C4a and C4b, show striking genetic polymorphism, with a deficiency of C4a molecules (null alleles) a common occurrence in the population. As many as 80% of people with SLE have null alleles irrespective of ethnic background, with homozygous C4a deficiency conferring a high risk for SLE. Because C4a null alleles are part of an extended HLA haplotype with the markers HLA-B8 and HLA-DR3, the influence of these class I and class II alleles of disease susceptibility may reflect linkage disequilibrium with complement deficiency. SLE also is associated with inherited deficiency of Clq,Clr/s, and C2 (12).

An association of SLE with inherited complement deficiency may seem surprising because of the prominence of immune-complex deposition and complement consumption during disease. However, a decrease in complement activity could promote disease susceptibility by impairing the clearance of foreign antigen or apoptotic cells. Apoptosis, or programmed cell death, is a process of cell suicide that has become apparent in many normal and diseased tissues. In mice, these abnormalities result from mutations in proteins involved in apoptosis. Apoptosis plays a critical role in the development of the immune system, as well as in the establishment and maintenance of tolerance. The lpr mutation leads to the absence of Fas, a cell-surface molecule that triggers apoptosis in lymphocytes, and gld affects a molecule that interacts with Fas, the Fas ligand. These gene defects appear to operate in peripheral, in contrast to central, tolerance and allow the persistence of autoreactive cells. Among humans, while mutations of Fas can lead to lymphoproliferation and autoantibody production, clinical and serologic findings of SLE are uncommon, suggesting that in humans, as in the mouse, SLE requires more than one gene.

The interaction of genes in SLE also occurs in New Zealand mice. NZB/NZW F1 mice develop an SLE-like illness that results from genes contributed by both NZB and NZW parents. Among these genes, an interferon inducible gene called Ifi202 contributes powerfully to the development of autoimmunity, providing additional evidence between the link between the interferon system and SLE (8). In the NZM2410 model, extensive genetic studies have shown that genes that can promote as well as suppress autoimmunity. Individually, genes are illustrated by the features of mice in which C1q has been eliminated by genetic knockout techniques. C1q-deficient mice have elevated anti-DNA levels, glomerulonephritis, and increased apoptotic cells in the tissue (13). Impairment of other aspects of the clearance system (e.g., IgM and DNase) can also provoke immune system abnormalities, including the stimulation of interferon by dead and dying cells and their constituents.

### GENETICS OF MURINE SYSTEMIC LUPUS ERYTHEMATOSUS

Several strains of inbred mice with inherited lupuslike disease have been studied as models to elucidate the human disease. These mice mimic human SLE in ANA production, immune complex glomerulonephritis, lymphadenopathy, and abnormal B-cell and T-cell function. These strains differ in the expression of certain serologic and clinical findings (e.g., anti-Sm, hemolytic anemia, and arthritis), as well as in the occurrence of disease among males and females. Among various lupus strains described (NZB, NZB/NZW, MRL-lpr/lpr, BXSB, and C3H-gl/gld), the development of a full-blown lupus syndrome requires multiple unlinked genes (11).

In mice, single mutant genes (lpr, gld, and Yaa) can promote anti-DNA production and abnormalities in the number and function of B and T cells. In lpr and gld mice, these abnormalities result from mutations in proteins involved in apoptosis. Apoptosis plays a critical role in the development of the immune system, as well as in the establishment and maintenance of tolerance. The lpr mutation leads to the absence of Fas, a cell-surface molecule that triggers apoptosis in lymphocytes, and gld affects a molecule that interacts with Fas, the Fas ligand. These gene defects appear to operate in peripheral, in contrast to central, tolerance and allow the persistence of autoreactive cells. Among humans, while mutations of Fas can lead to lymphoproliferation and autoantibody production, clinical and serologic findings of SLE are uncommon, suggesting that in humans, as in the mouse, SLE requires more than one gene.

As shown in in vitro and in vivo systems, the clearance of apoptotic cells, a process called **efferocytosis**, involves diverse cellular and humoral pathways, including the complement system. Clq, for example, binds to apoptotic cells, initiating complement’s role in clearance. In the absence of complement, apoptotic cells may persist and stimulate immune responses. The importance of complement deficiency to autoimmunity...
that promote autoimmunity (denoted sle1, sle2, sle3) lead to distinct immune disturbances, including expression of ANA. When these genes are co-expressed because of genetic crosses, the clinical and serologic features of SLE occur. Importantly, other genes can suppress the development of SLE in mice, indicating complexity in the genetic predisposition for disease (11).

Among lupus mice, New Zealand strains have an MHC-linked deficiency in the expression of the proinflammatory cytokine tumor necrosis factor alpha (TNF-alpha). This deficiency may be pathogenic because administration of TNF-alpha to mice with low endogenous production ameliorates disease. In humans, TNF blockers have not been extensively used to treat patients because of concerns that it can potentiate autoactivity; in small clinical trials, however, such therapy did not exacerbate disease (14). A role of TNF-alpha in the pathogenesis of autoimmunity is also suggested by the development of anti-DNA antibodies in patients with rheumatoid arthritis treated with TNF blockers, although the full development of SLE is very uncommon in this setting.

A variety of new SLE models have been created using molecular genetic techniques. These models reflect aberrant patterns of gene expression that occur in mice in which specific genes are eliminated by knockouts or enhanced by transgene expression. Studies of these mice suggest that a variety of genetic abnormalities may predispose to autoimmunity and genes regulating immune cell life span or signaling threshold may lead to autoantibody production. These genetic defects may affect the establishment of tolerance or the persistence of autoreactive cells.

**IMMUNE CELL DISTURBANCES**

Autoantibody production in SLE occurs in the setting of generalized immune cell abnormalities that involve the B cell, T cell, and monocyte lineages. These immune cell disturbances appear to promote B-cell hyperactivity, leading to hyperglobulinemia, increased numbers of antibody-producing cells, and heightened responses to many antigens, both self and foreign. Another consequence of B-cell and T-cell disturbance in SLE may be abnormal tolerance. In healthy individuals, anti-DNA precursors are tolerated by anergy or deletion; however, people with SLE or animals with SLE models may retain such precursors, which can be stimulated to generate high affinity autoantibody responses (15).

While these immune cell disturbances can affect multiple cell types and lineages, the appearance of an interferon signature is a prominent feature in peripheral blood cells of patients. As shown using microarray and related molecular techniques, peripheral blood cells of SLE patients demonstrate patterns of gene expression consistent with stimulation by IFN-alpha. Furthermore, this signature appears to be associated with antibodies to DNA or RNP antigens, consistent with stimulation of this cytokine by the nucleic acid components of immune complexes impacting on Toll-like receptors (TLR) or other receptors (see Chapter 4; 16,17). In view of the broad effects of the type I interferons on the immune system, a host of nonspecific functional abnormalities could result from the presence of high levels of this cytokine.

Although nonspecific immune activation can provoke certain ANA responses, it does not appear to be the major mechanism for inducing pathogenic autoantibodies, especially anti-DNA. Levels of these antibodies far exceed the extent of hyperglobulinemia. In addition, anti-DNA antibodies have features indicative of in vivo antigen selection by a receptor-driven mechanism. These features include variable-region somatic mutations that increase DNA binding activity and specificity for dsDNA. The generation of such responses also may be affected by the composition of the pre-immune repertoire and the content of precursors that can be mutated under influence of self-antigen drive.

The ability of DNA to drive autoantibody production in SLE contrasts with the poor immunogenicity of mammalian DNA when administered to normal animals. This discrepancy suggests that SLE patients either have a unique capacity to respond to DNA or are exposed to DNA in a form with enhanced immunogenicity (e.g., surface blebs on apoptotic cells or nucleosomes). Although serologic profiles of people with SLE and mice with murine models of SLE point to nucleosomes as the driving antigen, bacterial or viral DNA may stimulate this response. Bacterial DNA, because of characteristic sequence motifs, can stimulate a TLR directly and has potent adjuvant properties. As a result, bacterial DNA is immunogenic and may be able to elicit anti-DNA autoantibodies in a genetically susceptible host (18).

The specificity of ANA directed to nuclear proteins supports the hypothesis that these responses are antigen driven, because these antibodies bind multiple independent determinants found in different regions of these proteins. The pattern of ANA binding minimizes the possibility that molecular mimicry is the exclusive etiology for autoimmunity in SLE. This type of cross-reactivity has been hypothesized for many different autoimmune diseases, and it has been suggested for SLE because of the sequence similarity between certain nuclear antigens and viral and bacterial proteins. However, if SLE autoantibodies resulted from molecular mimicry, they would be expected to bind self-antigen only at sites of homology with foreign antigen, rather than throughout the entire molecule. While self-antigen
can sustain ANA production, a cross-reactive response to a foreign antigen can initiate it. A role of infection in SLE is suggested by the finding that people with SLE are infected more commonly with Epstein–Barr virus than are control populations (19).

Studies analyzing the genetics of SLE and the pattern of ANA production both strongly suggest that T cells are critical to disease pathogenesis. In murine models of lupus, the depletion of helper T cells by monoclonal antibody treatment abrogates autoantibody production and clinical disease manifestations. The basis of T-cell help in autoantibody responses may differ, however, from conventional responses because of the nature of the antigens. Most SLE antigens exist as complexes, such as nucleosomes, containing multiple protein and nucleic acid species. Because these antigens may trigger B-cell activation by multivalent binding, T-cell help for autoimmune responses could be delivered by nonspecifically activated T cells. Alternatively, T-cell reactivity to these antigens could be elicited to only one protein on a complex, allowing a single helper T cell to collaborate with B cells for determinants.

**TRIGGERING EVENTS**

Although inheritance and the hormonal milieu may create a predisposition toward SLE, the initiation of disease and its temporal variation in intensity likely result from environmental and other exogenous factors. Among these potential influences are infectious agents, which could induce specific responses by molecular mimicry and perturb overall immunoregulation; stress, which can provoke neuroendocrine changes affecting immune cell function; diet, which can affect production of inflammatory mediators; toxins, including drugs, which could modify cellular responsiveness and the immunogenicity of self-antigens; and physical agents, including drugs, which could induce specific responses by molecular mimicry and its alternating periods of flare and remission.

Because many patients with SLE can show serological abnormalities years in advance of clinical disease manifestations (20), mechanistically, disease may develop sequentially, with one step leading to autoantibody expression, and another step leading to clinical manifestation. The second triggering event could lead, for example, to the release of self-antigen and allow the formation of immune complexes to drive cytokine production. The separation of these events could also explain the phenomenon of serologically active, clinical quiescent lupus and the occurrence of remission in some patients following a flare.

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