Although the term “lupus erythematosus” was introduced by 19th-century physicians to describe skin lesions, it took almost 100 years to realize that the disease is systemic and spares no organ and that it is caused by an aberrant autoimmune response. The clinical heterogeneity of the disease forced the establishment of 11 criteria (Table 1), with 4 needed for the formal diagnosis of systemic lupus erythematosus (SLE). The involvement of vital organs and tissues such as the brain, blood, and the kidney in most patients, the vast majority of whom are women of childbearing age, impels efforts to develop diagnostic tools and effective therapeutics (Fig. 1). The prevalence ranges from 20 to 150 cases per 100,000 population, with the highest prevalence reported in Brazil, and appears to be increasing as the disease is recognized more readily and survival increases. In the United States, people of African, Hispanic, or Asian ancestry, as compared with those of other racial or ethnic groups, tend to have an increased prevalence of SLE and greater involvement of vital organs. The 10-year survival rate is about 70%.

The diverse clinical manifestations of SLE present a challenge to the clinician. Several mechanisms lead to a loss of self-tolerance and organ dysfunction. This article summarizes the genetic, epigenetic, environmental, hormonal, and immunoregulatory factors that contribute to the expression of tissue injury and clinical manifestations and also describes efforts to develop rational treatments for the disease.

**Influences on SLE**

**Genetic Influences**

Genetic factors confer a predisposition to the development of SLE. Although in rare cases SLE may be associated with the deficiency of a single gene (e.g., the complement components C1q and C4), the more disease commonly results from the combined effect of variants in a large number of genes. Lack of C4 has been linked to decreased elimination of self-reactive B cells (compromising negative selection), whereas lack of C1q leads to deficient elimination of necrotic (waste) material. Each allele contributes only minimally, and the cumulative effect of several genes is necessary to substantially increase the risk of SLE.

Most single-nucleotide polymorphisms (SNPs) associated with SLE fall within non-coding DNA regions of immune response–related genes. Some genes have been associated with several autoimmune diseases (e.g., STAT4 and PTPN22 with rheumatoid arthritis and diabetes); others appear to increase the risk of SLE specifically (Fig. 2). Certain SNPs linked to SLE have been identified for genes whose products may contribute to abnormal T-cell function in SLE (CD3-ζ and PP2Ac10). A recent large-scale replication study confirmed some of these associations and identified TNIP1, PRDM1, JAZF1, UHRF1BP1, and IL10 as risk loci for SLE. Although these findings are promising, the loci identified so far can account for only about 15% of the heritability of SLE. In addition, an altered copy number of certain genes, such as C4, FCGR3B, and TLR7, has been linked to disease expression.
ENVIRONMENTAL INFLUENCES

Epigenetic changes such as DNA hypomethylation have been attributed to medications known to cause SLE. Smoking and exposure to ultraviolet light have been implicated in epidemiologic studies. The possibility that viruses may trigger SLE has been considered during the past 40 years. The faster seroconversion to Epstein–Barr virus (EBV) infection and higher viral load in patients with SLE than in normal subjects, the molecular similarity between EBV nuclear antigen 1 and the common lupus autoantigen Ro, and the inability of CD8+ T cells to control EBV-infected B cells suggest that viruses may contribute to the expression of lupus.

FEMALE HORMONES AND SEX

Hormones contribute through unknown mechanisms to the increased prevalence of SLE among women. The X chromosome may contribute independently from hormones because in castrated female and male mice that have been genetically manipulated to express XX, XO (female), XY, or XXY (male) combinations, the presence of two X chromosomes increases the severity of SLE. Among the genes known to contribute to the pathogenesis of SLE is CD40, which is located on chromosome X. Pregnancy may aggravate SLE, and although it is not clear whether rising levels of estradiol or progesterone play a role, a link between pregnancy outcome and the status of the disease at conception has been noted; in fact, the levels of these hormones are lower during the second and third trimesters in patients with SLE than in healthy pregnant women. Treatment with dehydroepiandrosterone has shown some clinical benefit. Pregnancy in patients with SLE presents a clinical challenge that requires the involvement of relevant specialists.

EPIGENETIC REGULATION OF GENE EXPRESSION

DNA accessibility to transcription factors, and thus gene expression, is regulated by DNA methylation and histone modifications (acetylation and methylation). Hydralazine and procainamide inhibit DNA methylation and can induce manifestations of lupus in healthy persons. The regulatory regions of some genes known to be involved in the pathogenesis of the disease (ITGAL, CD40LG, CD70, and PPP2CA) have been reported to be hypomethylated in SLE. Recruitment of histone deacetylase 1 to the IL2 promoter suppresses its expression.

Table 1. American College of Rheumatology Criteria for the Diagnosis of Systemic Lupus Erythematosus (SLE).*

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Malar rash</td>
<td>A rash on the cheeks and nose, often in the shape of a butterfly</td>
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<tr>
<td>Discoid rash</td>
<td>A rash that appears as red, raised, disk-shaped patches</td>
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<tr>
<td>Photosensitivity</td>
<td>A reaction to sunlight that causes a rash to appear or get worse</td>
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<tr>
<td>Oral ulcers</td>
<td>Sores in the mouth</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Joint pain and swelling of two or more joints</td>
</tr>
<tr>
<td>Serositis</td>
<td>Inflammation of the lining around the lungs (pleuritis) or inflammation of the lining around the heart that causes chest pain, which is worse with deep breathing (pericarditis)</td>
</tr>
<tr>
<td>Kidney disorder</td>
<td>Persistent protein or cellular casts in the urine</td>
</tr>
<tr>
<td>Neurologic disorder</td>
<td>Seizures or psychosis</td>
</tr>
<tr>
<td>Blood disorder</td>
<td>Anemia (low red-cell count), leukopenia (low white-cell count), lymphopenia (low level of specific white cells), or thrombocytopenia (low platelet count)</td>
</tr>
<tr>
<td>Immunologic disorder</td>
<td>Positive test for anti–double-stranded DNA, anti-Sm, or antiphospholipid antibodies</td>
</tr>
<tr>
<td>Abnormal antinuclear antibodies</td>
<td>Positive antinuclear-antibody test</td>
</tr>
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</table>

* Four of the 11 criteria are needed for the formal diagnosis of SLE.

Trichostatin A, an inhibitor of histone deacetylase, normalizes the function of T cells from patients with SLE, and treatment of lupus-prone mice results in disease improvement.

IMMUNE CELLS AND CYTOKINES

Antigen receptor–mediated activation is altered in T and B cells from patients with SLE, and early signaling events are amplified. The T-cell receptor–CD3 complex, which recognizes and binds antigen and autoantigen and sends activation signals to the interior of the cell, is “rewired” in T cells, with the CD3-ζ chain replaced by the FcR-y common chain. In relaying the signal intracellularly, the spleen tyrosine kinase (Syk) is used rather than the canonical 70-kD ζ-associated protein (ZAP-70). Lipid rafts, cholesterol-rich scaffolds that contain signaling proteins on the surface membrane of cells, are present in aggregates that are metabolically active, and their inhibition in lupus-prone mice results in a change in disease expression (Fig. 3). Deficient production of interleukin-2 has been attributed to the binding of the transcriptional re-
The expression of the adhesion molecule CD44 is abnormally increased in T cells from patients with SLE.\textsuperscript{34} In addition, such cells migrate at increased rates in response to the chemokine CXCL12, most likely because they express more CXCR4 receptors than T cells from healthy subjects, which enables them to migrate into inflamed organs.\textsuperscript{34,35} The expression of CD44 variant 3 and CD44 variant 6 is increased in T cells from patients with SLE, and these cells infiltrate the kidneys in such patients.\textsuperscript{27}

In active SLE, a marked disease activity–dependent reduction in the number of naïve B cells is observed, and the number of plasma cells is increased in the peripheral blood.\textsuperscript{36} All B-cell subclasses (B1 and B2 cells in both the follicular and marginal zones) contribute to the production of autoantibodies. B cells are central to the expression of the disease. In addition to producing autoantibodies, which mediate tissue damage (as described below), B cells process and present antigen and autoantigen to T cells and contribute to disease expression (at least in lupus-prone mice), even independently of their ability to produce antibodies.\textsuperscript{37}

Compromise of tolerance checkpoints, along with other factors, may lead to increased production of autoantibodies.\textsuperscript{38} The number of DNA-binding B cells (recognized with a peptide that looks in structure like DNA) is increased in antigen-exposed and antigen-unexposed B cells and correlates with disease activity.\textsuperscript{39} Increased signaling of B-cell receptors\textsuperscript{40} may be facilitated by limited Fc type II receptor–mediated suppression.\textsuperscript{41} Germline variants of sialic acid acetyleraserase, an enzyme that limits signaling of B-lymphocyte antigen receptors, are linked to SLE and other autoimmune diseases; these variants have reduced activity and thus may contribute to increased B-cell signaling.\textsuperscript{42} A variant of protein tyrosine phosphatase, nonreceptor type 22, that is associated with increased phosphatase activity is linked to autoimmunity,\textsuperscript{43} and it has been proposed that by suppressing the signaling of B-cell receptors, the variant limits negative selection of autoreactive lymphocytes.

Antibody responses overall are lower than normal after immunization of patients with SLE.
against tetanus toxoid or hemophilus influenza, but the majority of patients have protective responses. Low responses are associated with SLE itself and with immunosuppressive drug treatment. Patients with SLE should always be vaccinated (but only with killed vaccines) to gain all possible protection against infections.

Interferon-α, CD40 ligand, free nucleosomes, and autoantibody–DNA complexes cause differentiation and activation of normal dendritic cells and stimulate their cytokine production. Dendritic cells may promote or suppress the immune response. Plasmacytoid dendritic cells secrete large amounts of type I interferon (interferon-α) on viral

Figure 2. Chromosome Loci and Genes Associated with SLE.
The approximate locations on the chromosomes of the genes associated with SLE are depicted. The genes are divided into six categories according to the main known function of the gene. Each category is represented by a different color on the 22 autosomal chromosomes and 2 sex chromosomes. An additional category (gray) includes genes that do not belong in these functional groups. Chromosome loci with orange bars on both sides indicate large SLE-associated loci. IFN denotes interferon.
In SLE, the T-cell receptor (TCR) is “rewired” (Panel A). The place and function of the CD3-ζ chain are taken by the FcR-γ chain, which uses spleen tyrosine kinase (Syk) to relay the signal that is initiated after the binding of antigen or autoantigen. Lipid rafts (Panels B and C), cholesterol-rich domains in which the TCR and important signal molecules converge, are aggregated and further contribute to abnormal signaling and, at least in mice, to disease expression. CD44 (Panel D), an adhesion molecule that facilitates homing of T cells to inflamed tissues (e.g., in the skin and kidney), is overexpressed in the T cells of patients with SLE and is associated with its signaling partner, ERM (ezrin, radixin, and moesin), with phosphorylation by Rho kinase (ROCK). Increased calcium concentrations after cross-linking of the TCR promote the translocation of calcium/calmodulin-dependent protein kinase IV (CaMK4) to the nucleus, where it facilitates the binding of the transcriptional repressor cyclic AMP response-element modulator α (CREM-α) to the promoter of interleukin-2 and suppresses its expression. In contrast, binding of CREM-α to the promoter of interleukin-17 enhances its activity. P denotes phosphate group PO₄.
infection because of the activation of toll-like receptors 7 and 9, and these cells are probably the main source of interferon-α in patients with SLE. Interferon-inducible genes are up-regulated in the majority of patients with SLE as compared with normal controls or patients with other rheumatic diseases.\(^{50,51}\) The number of plasmacytoid dendritic cells is reduced in the peripheral blood, but they extensively infiltrate skin and renal lesions in patients with SLE.\(^{51}\)

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**Tissue Injury in SLE**

Immune complexes are central players in the tissue injury in SLE. They are formed in large amounts as antinuclear antibodies bind to the abundant nuclear material in blood and tissues, and they are not cleared promptly because the Fc and complement receptors are numerically and functionally deficient.\(^{52}\) In addition to activating complement, immune complexes may alter the function of Fc receptors. Defective clearance of immune complexes is genetically associated with polymorphisms in the Fc receptor genes\(^{53}\) and the C3bi receptor gene (ITGAM).\(^{54}\)

In the kidney, immune complexes accumulate in the subendothelial and mesangial areas first, followed by deposition in the basement membrane and subepithelial areas (Fig. 4). Immune complexes containing cationic anti-DNA antibodies and antibodies against the collagen-like region of C1q have an increased propensity to accumulate in the kidney. Anti-DNA and anti-nucleosome antibodies contribute to lupus nephritis,\(^{55,56}\) and anti-chromatin–chromatin immune complexes are present in the mesangium of patients with lupus nephritis.\(^{58}\) In addition, immune complexes may accumulate in the skin and the central nervous system. Immune complexes may bind to receptors expressed by tissue-specific cells and alter their function, but more important, the complexes cause an influx of inflammatory cells by activating the complement cascade.

Although the spectrum of autoantibody specificities in SLE is extensive, only a few have been shown to contribute to disease-related tissue injury. Anti–blood-cell antibodies that activate complement and cause cytopenias are typical. Anti–T-cell (CD3 and T-cell receptor) antibodies suppress interleukin-2 production.\(^{59}\) Anti–Ro antibodies, which may alter the function of myocytes and cells of the conduction system, have been linked to neonatal lupus and specifically to congenital heart block. The presence of anti–Ro antibodies calls for special fetal monitoring (neonatal lupus develops in only 2% of fetuses of mothers who are positive for such antibodies) and treatment.\(^{60}\)

Some anti-DNA antibodies cross-react with N-methyl-D-aspartate receptors (NMDARs); these are widely distributed across the brain, with the highest density in the hippocampus and amygdala. Breach of the blood–brain barrier in animals enables these antibodies to bind to neuronal cells and destroy them. Anti-NMDAR antibodies in the cerebrospinal fluid and the brain in patients with SLE have been linked to neurocognitive defects.\(^{61}\) Proinflammatory cytokines that are present in the cerebrospinal fluid of patients with SLE (interleukin-6, interferon-α, and interleukin-1) compromise the blood–brain barrier. Mice born to mothers with anti-NMDAR antibodies have cognitive defects through mechanisms that have not been fully defined.\(^{62}\)

Some patients with SLE have antibodies against phospholipids and β2-glycoprotein 1. The presence of such antibodies is linked to thrombotic events and fetal loss in mice and is known as the antiphospholipid syndrome.\(^{63}\) Antiphospholipid antibodies interfere with the coagulation system (especially protein C) and the function of endothelial cells. These antibodies increase the expression of adhesion molecules on the surface of endothelial cells, induce the production of tissue factor, and thus promote the formation of thrombus.\(^{64}\)

Antiphospholipid antibodies also aggregate platelets. Fetal loss has been linked to the activation of complement by antiphospholipid antibodies that bind to placental trophoblast cells. Low doses of heparin (which has also been shown to inhibit complement activation) can reduce the risk of fetal loss in patients with the antiphospholipid syndrome.\(^{65}\)

Certain naturally occurring antibodies and autoantibodies (against DNA, phospholipids, histones, and ribonucleoprotein) may bind to ischemic tissues, activate complement, and cause damage. Such experimental findings may explain why some patients with SLE have disease flares after they experience a stressful event.\(^{66}\)

T cells infiltrate tissues, including the skin and the kidney, where they contribute to tissue damage. Peripheral-blood T cells from patients with
SLE express adhesion molecules such as CD44 that may enable T cells to home inappropriately to tissues when CD44 is associated with its signaling partner, pERM (phosphorylated ezrin, radixin, and moesin). CD44+pERM+ cells are found in the kidneys of patients with SLE.\textsuperscript{34} Many of these cells are CD3+CD4−CD8− and secrete interleukin-17, which contributes to inflammation, particularly through the recruitment of polymorphonuclear cells.\textsuperscript{32} Polymorphonuclear cells are readily recognized in renal-biopsy material from patients with lupus nephritis. B cells are also present, although it is not known whether these cells produce autoantibodies.\textsuperscript{65}
Tissue-specific cells contribute to disease expression, and their importance should not be underestimated. In the kidney, mesangial cells, interstitial cells, and podocytes acquire antigen-presenting properties and secrete proinflammatory cytokines when exposed to interferon-γ. Mesangial cells from lupus-prone mice produce α-actinin, which is targeted by anti-actinin antibodies and which strengthens the inflammatory response.66 Kallikrein production seems to mitigate murine and human lupus nephritis, and kallikrein-gene polymorphisms and promoter-gene SNPs are associated with the development of nephritis in patients with SLE.67

In the skin, keratinocytes that are exposed to ultraviolet light become apoptotic and release nuclear material, which is not cleared efficiently in patients with SLE. This nuclear material may further stimulate the immune system. The clearance of nuclear material generated by the death of keratinocytes and other cells is mediated by serum amyloid P, C-Mer kinase, IgM, C1q, and DNase; a genetic deficiency of any of them in mice or humans leads invariably to SLE.7,68 Patients with C1q deficiency, which is rare, are particularly photosensitive. The expression of additional organ-specific molecules is important in determining which organ or organs are damaged. Expression of tumor necrosis factor receptor 1 is needed for the expression of skin disease, whereas it provides protection against kidney inflammation.69

Atherosclerosis-attributed vascular events are significantly more frequent in patients with SLE than in matched healthy persons.70,71 Several factors contribute to this increased frequency, including antibodies to lipoproteins, oxidized lipoproteins, hypertension, and the metabolic syndrome.72 Endothelial cells may become injured because of immune complexes and inflammatory molecules.73 Subsequently, they express adhesion molecules to attract lymphocytes and monocytes, which adhere to and infiltrate the subendothelial space or become detached. Increased numbers of endothelial cells are found in the blood of patients with SLE.74

**GENE-EXPRESSIO N PATTE RNS IN SLE**

Peripheral-blood cells from children with SLE display a unique expression pattern of genes related to granulopoiesis and induced by interferon, and treatment with prednisone eliminates these characteristic gene-expression patterns.75 Nevertheless, more information is needed to establish the so-called interferon signature as a disease biomarker.96 The expression profile of transcription factors in CD8+ T cells correlates with clinical patterns of disease.76

**PROSPECTS FOR NEW THERAPEUTICS**

Patients with SLE are treated with nonsteroidal antiinflammatory drugs, antimalarial agents, glucocorticoids, and immunosuppressive drugs, including cyclophosphamide, azathioprine, methotrexate, and mycophenolate mofetil (Table 2). The choice of the drug is determined largely by the severity of the disease and the function of the involved organ.

In addition to having antiinflammatory effects, inhibitors of cyclooxygenase-2 have been claimed to promote the death of autoreactive T cells.77 The antimalarial agent hydroxychloroquine has therapeutic value and limited toxicity. It inhibits the function of toll-like receptors that contribute to autoimmunity.78 Cyclophosphamide pulses (intravenous infusions every month or bimonthly at lower doses) are effective in the treatment of lupus nephritis, although there are serious potential side effects, including bone marrow suppression, infections, and gonadal suppression.79 Mycophenolate mofetil has considerable therapeutic value with few side effects,80,81 but its long-term effects with respect to the preservation of kidney function are unproven.82

B-lymphocyte stimulator (BLyS) is a cytokine that is involved in the survival of B cells, germinal-center formation, and T-cell–dependent and T-cell–independent immunoglobulin-class switching. It binds to the surface of B cells and acts with the B-cell receptor in signal transduction.83 Studies in mice have shown a role of BLyS in the expression of lupus.84 Blockade of BLyS85 with an anti-BLyS antibody resulted in a small but significant beneficial clinical effect within the first year of treatment in patients with mild or moderate disease.85 This antibody (belimumab) is approved by the Food and Drug Administration for use in the treatment of lupus.

Interleukin-6 promotes antibody production in humans and mice with lupus86 and is present in the urine of patients with lupus nephritis.87 A monoclonal antibody against the interleukin-6 receptor (tocilizumab) was judged to be promising in a phase 1 clinical trial. Complement activation
is profoundly increased in patients with SLE, and inhibition of C5 with an antibody (eculizumab), which has proved efficacious in the treatment of paroxysmal nocturnal hemoglobinuria, is being considered.88

The proinflammatory cytokines interleukin-17 and interleukin-23 are important in the pathogenesis of nephritis in lupus-prone mice. Given that interleukin-17–producing cells are found not only in the peripheral blood but also in the inflamed kidney in patients with SLE,32,33 blockade of interleukin-17, interleukin-23, or both may warrant evaluation.

B-cell depletion in the treatment of autoimmune and rheumatoid arthritis has shown some clinical efficacy. A chimeric anti-CD20 antibody (rituximab) has shown initial promise in small studies and case series involving patients with SLE,89-91 but a trial of rituximab in patients with moderate-to-severe SLE failed to reach its primary end points.92 Thus, the role, if any, of B-cell depletion in the treatment of SLE is unclear. Such treatment may not come to fruition until we understand the short-term and long-term immune effects of B-cell depletion. For example, increased production of BlyS after B-cell depletion may counteract the expected clinical benefit. Rituximab plus belimumab may be a rational combination to test.

One approach to reestablish B-cell tolerance in patients with SLE involves the use of a compound that carries four short DNA pieces meant to promote capping and internalization of surface immunoglobulin, rendering B cells unable to recognize DNA. However, a clinical trial showed that the use of this compound was ineffective.93 Restoration of T-cell tolerance with peptide components of putative autoantigens is being tested in clinical trials.94 Efforts to block the interaction between T and B cells have led to the use of a fusion molecule of cytotoxic T-lymphocyte–associated antigen 4 with immunoglobulin (abatacept), which in a phase 2 trial failed to meet set end points.95 Inducible co-stimulator, a regulatory molecule, and its ligand, B7-related peptide 1, represent another costimulatory pair, and disruption of the interaction with a human antibody is currently in a phase 1 trial. In addition, the costimulatory pair CD40–CD40 ligand is important in the production of autoantibodies, but the use of antibodies to disrupt the interaction had considerable side effects in clinical trials.27

In developing antibody-based biologic therapies for SLE, the mechanism of action should be considered carefully. For example, complement levels are low in patients with severe disease, and the Fc portion of the antibody may need to be engineered to facilitate maximal complement activation. Certain Fc-receptor variants that are often
found in patients with SLE do not allow sufficient binding of IgG subclasses, so the appropriate immunoglobulins may need to be selected or engineered.

Small-molecule inhibitors of kinases such as Syk and CaMK4 that are abnormally expressed in the immune cells of patients with SLE may present new therapeutic opportunities. Correction of the levels of these kinases in vitro in T cells from patients with SLE results in normalization of cell signaling and interleukin-2 production. Inhibitors of either kinase have been shown to prevent or suppress disease in lupus-prone mice. Inhibitors of the nuclear factor of activated T cells (NFAT), such as tacrolimus, may benefit patients with SLE, as should dipyriddamole, which along with its antiplatelet function inhibits calcineurin-mediated NFAT activity. The mammalian target of rapamycin (mTOR), which plays a role in several key metabolic pathways, is increased in T cells of patients with SLE, and treatment of cells with rapamycin (i.e., sirolimus) corrects the signaling process.

SLE is an autoimmune disease that predominantly affects women and typically has manifestations in multiple organs. Immune-system aberrations, as well as heritable, hormonal, and environmental factors, contribute to the expression of organ damage. Immune complexes, autoantibodies, and autoantibodies, dendritic cells, and local factors are all involved in clinical manifestations of SLE. Biologic therapies and small-molecule drugs that can correct the aberrant immune-cell function are being developed in the hope that they will be more effective and less toxic than current treatments.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.


