Mechanisms of Disease

Systemic Lupus Erythematosus

Anisur Rahman, Ph.D., and David A. Isenberg, M.D.

To the clinician, systemic lupus erythematosus is important because it is a potentially fatal disease that is easily confused with many other disorders. To the immunologist, lupus is intriguing because all the key components of the immune system are involved in the underlying mechanisms of the disease. This review describes these mechanisms and shows how knowledge of the pathogenesis of lupus facilitates its treatment.

The prevalence of lupus ranges from approximately 40 cases per 100,000 persons among Northern Europeans to more than 200 per 100,000 persons among blacks. In the United States, the number of patients with lupus exceeds 250,000. The life expectancy of such patients has improved from an approximate 4-year survival rate of 50% in the 1950s to a 15-year survival rate of 80% today. Even so, a patient in whom lupus is diagnosed at 20 years of age still has a 1 in 6 chance of dying by 35 years of age, most often from lupus or infection. Later, myocardial infarction and stroke become important causes of death. This bimodal pattern of mortality in lupus was recognized more than 30 years ago.

The diverse presentations of lupus range from rash and arthritis through anemia and thrombocytopenia to serositis, nephritis, seizures, and psychosis. Lupus should be part of the differential diagnosis in virtually any patient presenting with one of these clinical problems, especially in female patients between 15 and 50 years of age.

Genetic and Epidemiologic Factors

Since 90% of patients with lupus are female, an important role for female hormones seems likely, but a protective role for male hormones or an effect of genes on the X chromosome is also possible. In a blinded, randomized, controlled trial, menopausal women with lupus who received hormone-replacement therapy containing conjugated estrogens and progesterone had a risk of a mild-to-moderate disease flare that was 1.34 times the risk among women who received placebo (P = 0.01). However, trials of hormonal treatments for lupus, such as dehydroepiandrosterone, have been disappointing. It is unclear how sex hormones could promote lupus.

Many drugs cause a variant of lupus called drug-induced lupus. The best known of these drugs are procainamide, hydralazine, and quinidine. Patients with drug-induced lupus usually present with skin and joint manifestations; renal and neurologic features are very rare. An antecedent viral-like illness may occur at the onset of lupus or immediately before a flare. Identifying a particular causative virus has proved challenging. Epstein–Barr virus (EBV) may be important, since a temporal association between the onset of lupus and the occurrence of EBV infection has been reported. A case–control study involving children and young adults showed that anti-EBV antibodies were present in 99% and EBV DNA was present in 100% of patients.
with lupus — much higher proportions than those in the control group.10 Ultraviolet radiation is the most obvious environmental factor linked to lupus. A photosensitive rash is a criterion of the American College of Rheumatology for the classification of the disease.11,12

The concordance rate for lupus is 25% among monozygotic twins and approximately 2% among dizygotic twins13; these rates indicate that a genetic contribution is important, but it is not sufficient to cause the disease. Many genes that probably contribute to lupus have been identified by means of whole-genome scans from families in which multiple members have lupus.14,15 Eight susceptibility loci that have been identified in these studies are listed in Table 1.

<table>
<thead>
<tr>
<th>Cytogenetic Location</th>
<th>Candidate Genes with the Loci</th>
<th>Immune Response</th>
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<tbody>
<tr>
<td>1q25–31</td>
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<tr>
<td>1q41–42</td>
<td>PARP, TLR5</td>
<td>Apoptosis, Innate</td>
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<tr>
<td>2q35–37</td>
<td>PDCD1</td>
<td>Adaptive</td>
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<tr>
<td>4p16–15.2</td>
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<tr>
<td>6p11–21</td>
<td>MHC class II: DRB1, MHC class III: TNF-α, C2, C4</td>
<td>Adaptive, Adaptive, Innate</td>
</tr>
<tr>
<td>12q24</td>
<td>OAZ</td>
<td>Adaptive</td>
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<tr>
<td>16q12–13</td>
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* CRP denotes C-reactive protein, FCGR IgG Fc receptor, MHC major histocompatibility complex, OAZ OLF1/EBF-associated zinc finger protein, PARP poly–ADP–ribose polymerase, PDCD1 programmed cell death 1, TLR5 toll-like receptor 5, and TNF-α tumor necrosis factor α.

Genes of the major histocompatibility complex (MHC), particularly HLA-A1, B8, and DR3, have been linked to lupus.16 The response of a T lymphocyte to an antigen is triggered when a receptor molecule on the surface of the T cell recognizes a complex formed by the antigen and an MHC peptide on the surface of an antigen-presenting cell. Different types of cells within the immune system, such as B cells, macrophages, and dendritic cells, can function as antigen-presenting cells. The MHC genotype determines which MHC molecules are available to the antigens that are present and thus how well the antigens can be recognized by T cells. For this reason, particular MHC genes are associated with a risk of an immune response to self-antigens and hence a risk of diseases such as lupus.

Null alleles that cause a deficiency of one of the early complement components — C1q, C2, or C4 — are a strong risk factor for lupus.17 Family studies have identified genes that are more likely to occur in patients with lupus than in their healthy relatives.14 Many of these genes encode components of the immune system. For example, a Scandinavian study identified strong linkage between lupus and single-nucleotide polymorphisms in two interferon-related genes (those encoding tyrosine kinase 2 and interferon regulatory factor 5).18

Wakeland and colleagues14 have identified genetic loci that promote lupus in mice.19 These loci, designated Sle 1, Sle 2, and Sle 3, contain genes that mediate the loss of immunologic tolerance to nuclear autoantigens, B-cell hyperactivity, and T-cell dysregulation, respectively.14 The Sle 1 cluster contains genes similar to those in regions 1q21–23 and 1q41 of human chromosome 1 that have been linked to lupus in humans.14

**Autoantibodies in Lupus**

The affected organs in lupus that have been studied most intensively are the kidneys and the skin. In both cases, there is inflammation and the deposition of antibodies and complement. In 1967, kidneys from patients with lupus nephritis were shown to contain antibodies that bound native, double-stranded DNA.20 These antibodies are autoantibodies; that is, they bind a normal constituent — in this case, double-stranded DNA — of the patient’s cells and tissues. The importance of anti–double-stranded DNA antibodies in the pathogenesis of lupus has been confirmed.21 Anti–double-stranded DNA antibodies are highly specific for lupus; they are present in 70% of patients with lupus but in less than 0.5% of healthy people or patients with other autoimmune diseases such as rheumatoid arthritis.22 Levels of anti–double-stranded DNA antibodies in serum tend to reflect disease activity,23 but not in all patients. Among patients who have both elevated levels of anti–double-stranded DNA autoantibodies and...
clinically quiescent disease, 80% have disease that becomes clinically active within 5 years after the detection of elevated levels of these antibodies.24

In a study of renal-biopsy specimens obtained from patients with lupus at autopsy,25 Mannik et al. detected IgG that bound to a number of non-DNA antigens, including Ro (a ribonucleoprotein complex), La (an RNA-binding protein), C1q (a subunit of the C1 complement component), and Sm (nuclear particles consisting of several different polypeptides). The detection of antibodies to these antigens in autopsy specimens does not prove that they play a role in the development of lupus nephritis. Rather than cause the inflammation, these autoantibodies may establish themselves in tissue only after the apoptosis of cells in inflamed kidney tissue exposes nuclear antigens. The strongest evidence concerning the mechanism of lupus nephritis relates to anti–double-stranded DNA, anti-nucleosome, and anti–α-actinin antibodies (see below).

Although anti–double-stranded DNA antibodies are the most extensively studied autoantibodies in lupus, others play a role in clinical manifestations, particularly in autoimmune hemolytic anemia, thrombocytopenia, skin disease, and neonatal lupus. Table 2 lists common autoantibodies in lupus and the evidence that they are pathogenic; some are described in more detail below.

The presence of anti-Ro antibodies, anti-La antibodies, or both in pregnancy confers a 1 to 2% risk of fetal heart block. Ro antigens are exposed on the surface of fetal (but not maternal) cardiac myocytes as the heart undergoes remodeling by apoptosis, and maternal anti-Ro antibodies that cross the placenta interact with these antigens. The maternal autoantibodies damage the conducting tissues of the fetal heart.41,42 The absence of an effect on the mother’s heart shows the importance of both the autoantibody and exposure of the antigen on cardiac tissue.

Antibodies against the N-methyl-D-aspartate (NMDA) receptor may be important in central nervous system lupus.27 NMDA is an excitatory amino acid released by neurons. Kawal and colleagues showed that in patients with lupus, the serum with antibodies against DNA and NMDA receptors caused cognitive impairment and hippocampal

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**Table 2. Pathogenic Autoantibodies in Systemic Lupus Erythematosus.**

<table>
<thead>
<tr>
<th>Antigen Specificity</th>
<th>Prevalence†</th>
<th>Main Clinical Effects</th>
<th>Source of Evidence</th>
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<tbody>
<tr>
<td></td>
<td>%</td>
<td></td>
<td>Clinical Studies</td>
</tr>
<tr>
<td>Anti–double-stranded DNA</td>
<td>70–80</td>
<td>Kidney disease, skin disease</td>
<td>ter Borg et al.,23 Bootsma et al.,31 Tseng et al.32</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Koffler et al.20</td>
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<td></td>
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<td>Ravirajan et al.,33 Ehrenstein et al.,34 Madaio et al.35</td>
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<tr>
<td>Nucleosomes</td>
<td>60–90</td>
<td>Kidney disease, skin disease</td>
<td>Amoura et al.26 Grootscholten et al.,36 Kalaaji et al.,37 Kalaaji et al.38</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Kramer et al.,39 van Bruggen et al.40</td>
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<tr>
<td>Ro</td>
<td>30–40</td>
<td>Skin disease, kidney disease, fetal heart problems</td>
<td>Buyon and Clancy41 Sontheimer et al.42</td>
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<td></td>
<td></td>
<td></td>
<td>Mannik et al.25 Clancy et al.,43 Madison and Reichlin44</td>
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<tr>
<td>La</td>
<td>15–20</td>
<td>Fetal heart problems</td>
<td>Buyon and Clancy41</td>
</tr>
<tr>
<td>Sm</td>
<td>10–30</td>
<td>Kidney disease</td>
<td>McCarty et al.45</td>
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<td></td>
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<td></td>
<td>Mannik et al.25</td>
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<tr>
<td>NMDA receptor</td>
<td>33–50</td>
<td>Brain disease</td>
<td>Yoshio et al.46 Lapteva et al.47</td>
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<td></td>
<td></td>
<td></td>
<td>Kowal et al.27</td>
</tr>
<tr>
<td>Phospholipids</td>
<td>20–30</td>
<td>Thrombosis, pregnancy loss</td>
<td>Alarcón-Segovia et al.48</td>
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<td></td>
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<td></td>
<td>Girardi et al.49 Pierangeli et al.50</td>
</tr>
<tr>
<td>α-Actinin</td>
<td>20</td>
<td>Kidney disease</td>
<td>Mason et al.51 Becker-Merok et al.28</td>
</tr>
<tr>
<td>C1q</td>
<td>40–50</td>
<td>Kidney disease</td>
<td>Siegert et al.29</td>
</tr>
</tbody>
</table>

* NMDA denotes N-methyl-D-aspartate.

† Prevalence data were obtained from a number of sources, including Amoura et al.,26 Kowal et al.,27 Becker-Merok et al.,28 Siegert et al.,29 and Ehrenstein and Isenberg.30
damage when given intravenously to mice. They also showed that anti–NMDA-receptor antibodies are present in the brain tissue of patients with cerebral lupus.27

Both anti-Ro and anti-nucleosome antibodies may play a role in cutaneous lupus. Anti-Ro antibodies are associated with an increased risk of the development of a photosensitive rash.42 Anti-nucleosome antibodies have been detected in skin-biopsy specimens obtained from a minority of patients with active renal lupus, and these patients had no rash.36

Autoantibody-mediated destruction of red cells and platelets is important in the hemolytic anemia and thrombocytopenia that can occur in patients with lupus.54 Pujol et al.55 detected antiplatelet antibodies in the serum of 56 of 90 patients with lupus. A total of 29 of 90 patients had thrombocytopenia, and in these patients there was a strong correlation between thrombocytopenia and the presence of antiplatelet antibodies.55

**TISSUE DAMAGE BY AUTOANTIBODIES IN LUPUS**

Most studies of autoantibody-mediated tissue damage in patients with lupus have focused on the role of anti–double-stranded DNA antibodies in patients with lupus nephritis. There are two main theories; both stress that the binding of antibodies to double-stranded DNA itself is probably not the most critical determinant of tissue damage. Extracellular double-stranded DNA occurs mainly in the form of nucleosomes, which are fragments of chromatin that cells release when they undergo apoptosis. Berden and colleagues have proposed that pathogenic anti–double-stranded DNA autoantibodies in patients with lupus bind to nucleosomes that have entered the bloodstream; in turn, these antibody–nucleosome complexes settle in the renal glomerular basement membrane.56 These immune complexes activate complement, which initiates the glomerulonephritis. This series of events has been demonstrated in animal models.39,40 Furthermore, IgG antibodies have been shown, by means of electron microscopy, to colocalize with extracellular chromatin in lupus nephritis in humans and mice.37,38 Also relevant is the detection of anti-nucleosome antibodies in the blood and inflamed tissues of patients with lupus.26,36

The second model proposes that anti–double-stranded DNA, anti-nucleosome antibodies, or both cross-react with proteins in the kidney; thus, they have a direct pathogenic effect on renal cells. This is an example of polyreactivity, whereby the same antibody can bind to antigens with different structures because they have similar surface shapes (so-called shared epitopes) or areas of similar charge. Among possible target antigens in the kidney, attention is currently focused on α-actinin. This protein is critical for maintaining the function of renal podocytes, which are constituents of the glomerular filtration barrier.57 Two studies have shown that mouse monoclonal anti-DNA antibodies that cross-reacted with α-actinin (a protein that cross-links actin, a component of the cytoskeleton) were pathogenic, whereas monoclonal anti-DNA antibodies that did not cross-react with α-actinin were nonpathogenic.52,53 Pathogenicity was judged according to whether the antibodies caused proteinuria and histologic changes of glomerulonephritis after passive transfer into recipient mice.52,58 Although anti–α-actinin antibodies are not specific for lupus, these antibodies, when present in the serum of patients with lupus, can serve as a marker of renal involvement.28,51 The detection of anti–α-actinin antibodies has not been reported in specimens obtained from renal biopsies in patients with lupus.

**THE ROLE OF T CELLS**

Autoantibodies can occur in healthy people without causing harm, and they may play a protective role.59 Pathogenic autoantibodies in patients with lupus have particular properties that enable them to cause disease. Clinical investigations and studies in laboratory mice have shown that IgG antibodies with high-affinity binding to double-stranded DNA tend to be more strongly associated with tissue damage than IgM or lower-affinity IgG antibodies.33,34,60 Production of these high-affinity IgG antibodies is “driven” by antigen. The term “antigen-driven” refers to a process in which antigen binds immunoglobulin on the surface of B lymphocytes, thereby stimulating the cells to proliferate. The higher the affinity of the surface immunoglobulin for the antigen, the more strongly the cells are stimulated and the more they proliferate. In the presence of the stimulating antigen, there is a continuous selective pressure favoring B cells that display on their surface and secrete immunoglobulins with high affinity for that antigen. In general, this antigen-driven process can
occur only in B lymphocytes that are being stimulated by T lymphocytes as well as by antigen. This process is known as T-lymphocyte help.

The concept of T-lymphocyte help is critical in understanding the pathogenesis of lupus. Each T cell carries a surface-receptor molecule with the ability to interact best with one particular antigen when it is presented to the T-cell receptor in a complex with an MHC molecule on the surface of an antigen-presenting cell. Presentation of the antigen–MHC complex alone is not enough to stimulate the T cell. As shown in Figure 1, the antigen-presenting cell must also make a second molecular interaction with the T lymphocyte through costimulation. There are several different costimulatory molecular pairs, including the CD40–CD40 ligand and CD28–B7, which can generate the second signal required for T-cell activation. Agents that block costimulation can inhibit any immune response that depends on T-cell help. Since T-cell help is critical in lupus, both the anti-CD40 ligand and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), which blocks the CD28–B7 interaction, are potential treatments for lupus. The prospects for these treatments are reviewed elsewhere.

Figure 2 shows a B cell and a T cell interacting and stimulating each other. T-cell cytokines affect B cells by stimulating cell division, switching antibody production from IgM to IgG, and promoting a change in the molecular sequence of the secreted antibody so that it binds more strongly to the driving antigen. Thus, T-cell help makes possible the production of high-affinity IgG autoantibodies. These kinds of antibodies are closely linked to tissue damage in lupus.

The autoantigen-specific B cells and T cells that interact to produce injurious autoantibodies are absent in healthy people. Several mechanisms could account for the absence of such cells. These mechanisms include removal (deletion) of the autoreactive B cells, inactivation of the cells so that they remain in the body but are anergic, or a change in the light chain of the antibody expressed by an autoreactive B lymphocyte (so-called receptor editing) such that the antibody loses the
ability to bind autoantigen. The use of certain light-chain genes by populations of B cells from patients with lupus indeed differs from the light-chain repertoire in healthy people; this difference could be due to aberrant receptor editing.

Histones constitute the protein core of a nucleosome, around which the DNA winds. Lu and colleagues showed that the histone-derived peptides H2B10-33, H416-39, H471-94, H391-105, H2A34-48, and H449-63 stimulated T cells from patients with lupus (but not from healthy people) to produce cytokines, and very similar peptides also stimulated T cells from lupus-prone mice. The authors suggested that stimulation of these peptide-specific helper T cells would allow them to help B cells that also respond to antigenic epitopes derived from nucleosomes. Thus, the interaction between these B lymphocytes and T lymphocytes could lead to the production of high-affinity pathogenic autoantibodies. Nucleosomes carry both T-cell and B-cell epitopes, and anti-nucleosome antibodies are present and play a pathogenic role in patients with lupus.

Regulatory T cells in humans and mice suppress the activation of helper T cells and B cells. Some investigators have reported a reduction in the number or function — or both — of regulatory T cells in patients with lupus and in lupus-prone mice. Regulatory T cells from patients with active lupus have a reduced ability to suppress the proliferation of helper T cells, as compared with regulatory T cells from patients with inactive lupus or healthy controls. Kang et al. found that some of the immunogenic histone peptides they had previously identified promoted the development of regulatory T cells and delayed the development of nephritis in lupus-prone mice. The most potent effect was seen with peptide H471-94.

**Source of the Autoantigens in Lupus**

The obvious source of nucleosomes is the cellular debris released as a result of apoptosis. During apoptosis, blebs of cellular material form on the surface of the dying cell. Antigens that are normally buried within the cells are exposed on
the surface of these blebs (Fig. 3), and they may trigger an immune response. These exposed antigens include nucleosomes, Ro 62, Ro 50, La, and anionic phospholipids. Antibodies to these antigens occur commonly in patients with lupus.

The removal of apoptotic debris is abnormal in patients with lupus. In vitro, phagocytes from patients with lupus were shown to engulf far less apoptotic material than phagocytes from healthy people during a 7-day culture period. C1q plays a role in phagocytosis by binding to cell debris, which can then be engulfed by macrophages that have surface C1q receptors. Thus, a deficiency of complement may be an important reason for the poor “waste disposal” seen in lupus. Homozygous deficiencies of C1q, C2, and C4 are rare disorders, but the presence of any of these genetic conditions is a strong predisposing factor for lupus. In C1q knockout mice, a lupuslike renal disease develops; kidney-biopsy specimens from mice with this condition reveal multiple apoptotic fragments. Davies and colleagues reported reduced clearance of immune complexes through the spleen in a patient with C2 deficiency and lupus; this was corrected by restoring the C2 levels with the use of transfusions of fresh-frozen plasma.

**Figure 3. Induction of Surface Blebs during Apoptosis.**

Apoptosis of keratinocytes exposed to ultraviolet light is illustrated. The different constituents of developing small and large surface blebs during apoptosis are shown. PARP denotes poly–ADP–ribose polymerase.

**Cytokines in Lupus**

The role of tumor necrosis factor α (TNF-α) in lupus is controversial. This cytokine may be protective in patients with lupus, since giving TNF-α to lupus-prone NZB/W F1 mice delayed the development of lupus. The protective effect is specific to that mouse strain, and the mechanism is unknown. In some patients with rheumatoid arthritis who were treated with anti–TNF-α antibodies, anti–double-stranded DNA antibodies developed, and lupus developed in a few of these patients. One group has shown that the balance between TNF-α and the soluble inhibitors (TNF-soluble receptor 75kDa and TNF-soluble receptor 55kDa) is altered in favor of the inhibitors in active lupus; this provides support for the idea that low TNF-α activity is associated with increased disease activity in lupus. By contrast, the level of TNF-α messenger RNA was high in kidney-biopsy specimens from patients with lupus nephritis. Aringer et al. reported that giving the anti–TNF-α antibody agent infliximab to six patients with lupus led to resolution of joint swelling in three patients with arthritis and the reduction of urinary protein loss by 60% in four patients with renal lupus.
Serum levels of interleukin-10 are consistently high in patients with lupus, and they correlate with the activity of the disease. Interleukin-10 has a number of biologic effects, including stimulation of polyclonal populations of B lymphocytes. Blocking this cytokine could reduce the production of pathogenic autoantibodies. In an open trial of 20 mg of a mouse anti-interleukin-10 antibody administered daily in six patients for 21 days, skin and joint symptoms improved in all the patients, and this improvement was maintained at the 6-month follow-up assessment.

Serum levels of interferon-α are also elevated in patients with active lupus, and microarray studies showed that 13 genes regulated by interferon were up-regulated in peripheral-blood mononuclear cells from patients with lupus, as compared with similar cells from healthy controls. In studies of lupus-prone NZB/W F1 mice, nephritis developed 15 to 20 weeks earlier in mice continuously exposed to interferon-α from a young age than in control mice not subject to this exposure. Anti-interferon drugs may be the next anticytokine agents to be developed as treatments for patients with lupus.

The B-lymphocyte stimulator is a member of the TNF-ligand superfamily. It promotes the proliferation and survival of B lymphocytes. Circulating levels of B-lymphocyte stimulator are elevated in several other conditions, including rheumatoid arthritis and Sjögren’s syndrome, as well as in lupus. The overexpression of B-lymphocyte stimulator has been detected in both humans with lupus and lupus-prone mice. Stohl et al. reported elevated levels of soluble B-lymphocyte stimulator in serum and on peripheral-blood mononuclear cells in up to 50% of patients with active lupus. Levels of B-lymphocyte stimulators correlated with levels of anti–double-stranded DNA antibodies in serum and decreased in nine patients who were treated with high-dose corticosteroids. Elevated levels of B-lymphocyte stimulators may thus be associated with the increased activity of lupus in some patients, and the use of anti–B-lymphocyte stimulator agents may be a useful therapeutic approach.

**Implications for Treatment**

Figure 4 summarizes the pathogenesis of lupus and the targets of some new drugs that are currently being evaluated in clinical trials. If autoantibodies are the proximate agents of tissue damage in patients with lupus, then treatments aimed at reducing autoantibody levels could be effective. Two trials have shown that a strategy of increasing doses of corticosteroids in response to a specified increase in levels of anti–double-stranded DNA antibodies could reduce disease activity in patients with lupus.
DNA antibodies leads to lower mean levels of such antibodies and reduced frequency of severe flares of disease, but one study indicated that the side effects of corticosteroids were a problem.31 Rituximab and abetimus sodium have been used as specific methods of reducing levels of anti–double-stranded DNA. Rituximab is nonspecific; that is, it is an antibody against CD20, which is found on the surface of all mature B cells. Abetimus sodium is designed to deplete only B lymphocytes that produce anti–double-stranded DNA antibodies because its four surface oligonucleotides can engage surface anti–double-stranded DNA antibodies on those cells, but it has no epitopes to allow binding of helper T cells. The B cells therefore undergo apoptosis rather than proliferation, but it is not clear whether this depleting mechanism occurs in patients. Abetimus sodium may also work by forming complexes with anti–double-stranded DNA antibodies, which are then cleared from the circulation.91

Several case series suggest that rituximab is helpful in treating lupus.88,92 The use of a monoclonal anti-CD22 antibody (which also targets B cells)93 is being studied in a clinical trial, and the survival and proliferation of B cells can also be modulated with the use of anti-B-lymphocyte stimulator 28, 29. A large trial showed that abetimus sodium was not superior to placebo in an analysis of the primary outcome measure (time to renal flare) for the whole study group, but in post hoc analyses, the drug was superior to placebo in a subgroup analysis of patients who had serum antibodies with high affinity for the drug.90

Anti-CD40 ligand and CTLA-4–Ig directly target the interaction between T cells and antigen-presenting cells by inhibiting costimulation. Peptides derived from pathogenic anti-DNA antibodies may be useful in generating anti-idiotypic responses to autoantibodies and thus suppressing their pathogenic effects.95 Trials of anti–TNF-α antibody82 and anti–interleukin-10 antibody84 are described above.

SUMMARY

Pathogenic autoantibodies are the primary cause of tissue damage in patients with lupus. The production of these antibodies arises by means of complex mechanisms involving every key facet of the immune system. Many different elements of the system are potential targets for therapeutic drugs in patients with lupus.

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