

## REVIEW ARTICLE

## MECHANISMS OF DISEASE

## Systemic Lupus Erythematosus

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**T**O 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.<sup>1</sup> 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<sup>2</sup> to a 15-year survival rate of 80% today.<sup>3</sup> 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.<sup>4</sup> Later, myocardial infarction and stroke become important causes of death.<sup>4</sup> This bimodal pattern of mortality in lupus was recognized more than 30 years ago.<sup>5</sup>

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<sup>6</sup> 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 ( $P=0.01$ ).<sup>7</sup> However, trials of hormonal treatments for lupus, such as dehydroepiandrosterone, have been disappointing.<sup>8</sup> 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.<sup>9</sup> 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

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**Table 1. Susceptibility Loci with Confirmed Linkage to Systemic Lupus Erythematosus.\***

Cytogenetic Location	Candidate Genes with the Loci	Immune Response
1q23	<i>CRP</i> <i>FCGR2A</i> <i>FCGR2B</i> <i>FCGR3A</i> <i>FCGR3B</i>	Innate Innate Adaptive Adaptive Adaptive
1q25–31		
1q41–42	<i>PARP</i> <i>TLR5</i>	Apoptosis Innate
2q35–37	<i>PDCD1</i>	Adaptive
4p16–15.2		
6p11–21	MHC class II: <i>DRB1</i> MHC class III: <i>TNF-<math>\alpha</math></i> <i>C2</i> , <i>C4</i>	Adaptive Adaptive Innate
12q24		
16q12–13	<i>OAZ</i>	Adaptive

\* *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- $\alpha$*  tumor necrosis factor  $\alpha$ .

with lupus — much higher proportions than those in the control group.<sup>10</sup> 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.<sup>11,12</sup>

The concordance rate for lupus is 25% among monozygotic twins and approximately 2% among dizygotic twins<sup>13</sup>; 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.<sup>14,15</sup> Eight susceptibility loci that have been identified in these studies are listed in Table 1.

Genes of the major histocompatibility complex (MHC), particularly *HLA-A1*, *B8*, and *DR3*, have been linked to lupus.<sup>16</sup> 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.<sup>17</sup> Family studies have identified genes that are more likely to occur in patients with lupus than in their healthy relatives.<sup>14</sup> 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).<sup>18</sup>

Wakeland and colleagues<sup>14</sup> have identified genetic loci that promote lupus in mice.<sup>19</sup> 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.<sup>14</sup> 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.<sup>14</sup>

#### 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.<sup>20</sup> 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.<sup>21</sup> 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.<sup>22</sup> Levels of anti-double-stranded DNA antibodies in serum tend to reflect disease activity,<sup>23</sup> 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.<sup>24</sup>

In a study of renal-biopsy specimens obtained from patients with lupus at autopsy,<sup>25</sup> 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- $\alpha$ -actinin antibodies (see below).

Although anti-double-stranded DNA antibodies are the most extensively studied autoantibodies in lupus, others play a role in clinical manifesta-

tions, 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.<sup>41,43</sup> 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.<sup>27</sup> NMDA is an excitatory amino acid released by neurons. Kowal and colleagues showed that in patients with lupus, the serum with antibodies against DNA and NMDA receptors caused cognitive impairment and hippocampal

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

Antigen Specificity	Prevalence† %	Main Clinical Effects	Source of Evidence		
			Clinical Studies	Studies of Tissues from Patients with Lupus	Animal Models
Anti-double-stranded DNA	70–80	Kidney disease, skin disease	ter Borg et al., <sup>23</sup> Bootsma et al., <sup>31</sup> Tseng et al. <sup>32</sup>	Koffler et al. <sup>20</sup>	Ravirajan et al., <sup>33</sup> Ehrenstein et al., <sup>34</sup> Madaio et al. <sup>35</sup>
Nucleosomes	60–90	Kidney disease, skin disease	Amoura et al. <sup>26</sup>	Grootscholten et al., <sup>36</sup> Kalaaji et al., <sup>37</sup> Kalaaji et al. <sup>38</sup>	Kramers et al., <sup>39</sup> van Bruggen et al. <sup>40</sup>
Ro	30–40	Skin disease, kidney disease, fetal heart problems	Buyon and Clancy, <sup>41</sup> Sontheimer et al. <sup>42</sup>	Mannik et al., <sup>25</sup> Clancy et al., <sup>43</sup> Maddison and Reichlin <sup>44</sup>	
La	15–20	Fetal heart problems	Buyon and Clancy <sup>41</sup>	Mannik et al. <sup>25</sup>	
Sm	10–30	Kidney disease	McCarty et al. <sup>45</sup>	Mannik et al. <sup>25</sup>	
NMDA receptor	33–50	Brain disease	Yoshio et al., <sup>46</sup> Lapteva et al. <sup>47</sup>	Kowal et al. <sup>27</sup>	Kowal et al. <sup>27</sup>
Phospholipids	20–30	Thrombosis, pregnancy loss	Alarcón-Segovia et al. <sup>48</sup>		Girardi et al., <sup>49</sup> Pierangeli et al. <sup>50</sup>
$\alpha$ -Actinin	20	Kidney disease	Mason et al., <sup>51</sup> Becker-Merok et al. <sup>28</sup>		Mostoslavsky et al., <sup>52</sup> Deocharan et al. <sup>53</sup>
C1q	40–50	Kidney disease	Siegert et al. <sup>29</sup>	Mannik et al. <sup>25</sup>	

\* NMDA denotes *N*-methyl-D-aspartate.

† Prevalence data were obtained from a number of sources, including Amoura et al.,<sup>26</sup> Kowal et al.,<sup>27</sup> Becker-Merok et al.,<sup>28</sup> Siegert et al.,<sup>29</sup> and Ehrenstein and Isenberg.<sup>30</sup>

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.<sup>27</sup>

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.<sup>42</sup> 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.<sup>36</sup>

Autoantibody-mediated destruction of red cells and platelets is important in the hemolytic anemia and thrombocytopenia that can occur in patients with lupus.<sup>54</sup> Pujol et al.<sup>55</sup> 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.<sup>55</sup>

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#### TISSUE DAMAGE BY AUTOANTIBODIES IN LUPUS

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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.<sup>56</sup> These immune complexes activate complement, which initiates the glomerulonephritis. This series of events has been demonstrated in animal models.<sup>39,40</sup> Furthermore, IgG antibodies have been shown, by means of electron microscopy, to colocalize with extracellular chromatin in lupus nephritis in humans and mice.<sup>37,38</sup> Also relevant is the detection of anti-nucleosome antibodies in the blood and inflamed tissues of patients with lupus.<sup>26,36</sup>

The second model proposes that anti-double-stranded DNA, anti-nucleosome antibodies, or

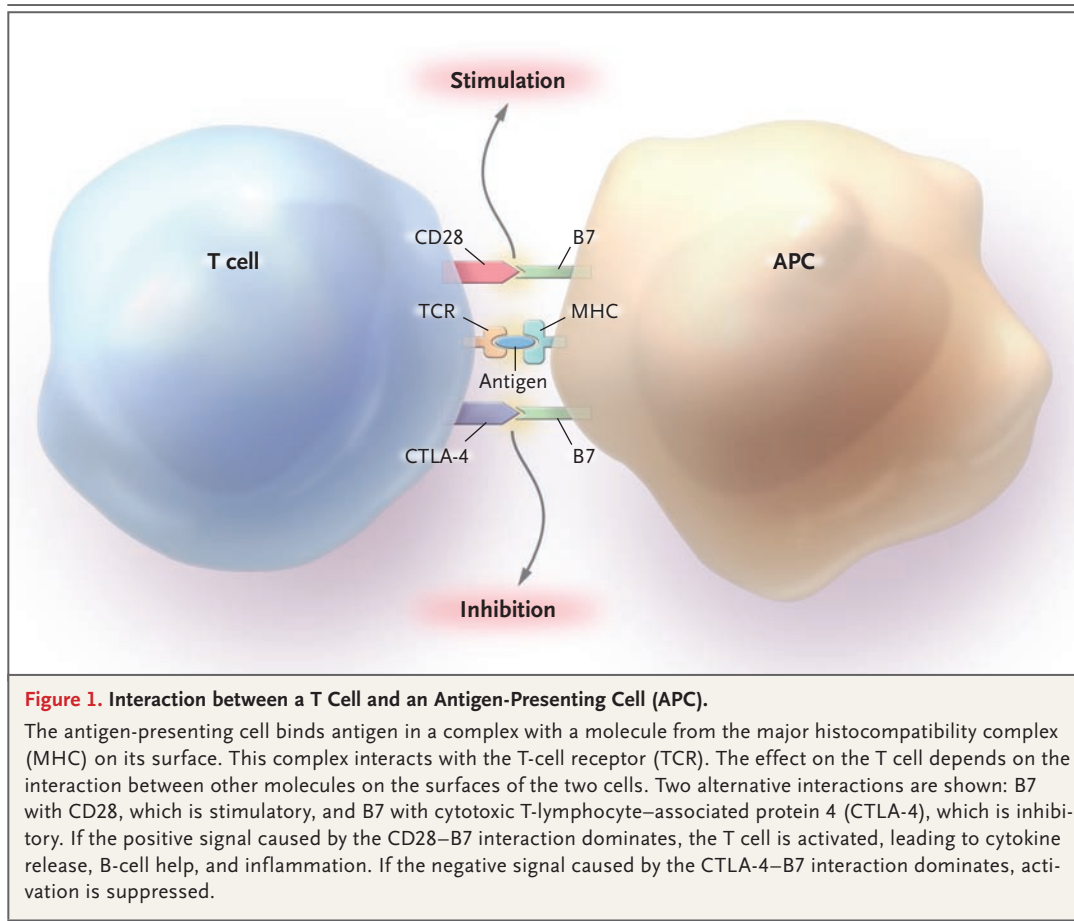
both cross-react with proteins in the kidney; thus, they have a direct pathogenic effect on renal cells. This is an example of polyreactivity, whereby the same antibody can bind to antigens with different structures because they have similar surface shapes (so-called shared epitopes) or areas of similar charge. Among possible target antigens in the kidney, attention is currently focused on  $\alpha$ -actinin. This protein is critical for maintaining the function of renal podocytes, which are constituents of the glomerular filtration barrier.<sup>57</sup> Two studies have shown that mouse monoclonal anti-DNA antibodies that cross-reacted with  $\alpha$ -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  $\alpha$ -actinin were nonpathogenic.<sup>52,53</sup> Pathogenicity was judged according to whether the antibodies caused proteinuria and histologic changes of glomerulonephritis after passive transfer into recipient mice.<sup>52,58</sup> Although anti- $\alpha$ -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.<sup>28,51</sup> The detection of anti- $\alpha$ -actinin antibodies has not been reported in specimens obtained from renal biopsies in patients with lupus.

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#### THE ROLE OF T CELLS

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Autoantibodies can occur in healthy people without causing harm, and they may play a protective role.<sup>59</sup> 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.<sup>33,34,60</sup> 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



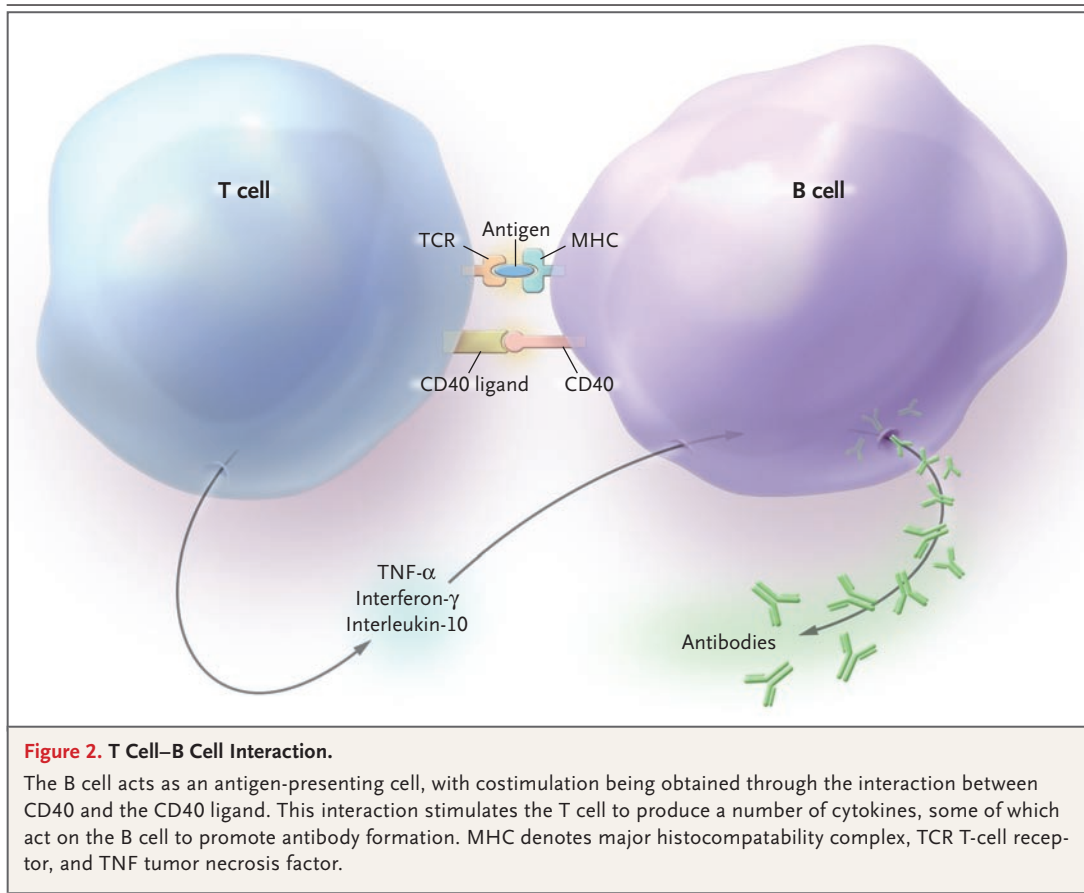
occur only in B lymphocytes that are being stimulated by T lymphocytes as well as by antigen. This process is known as T-lymphocyte help.

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<sup>61</sup> and cytotoxic T-lymphocyte-associated protein 4 IgG1 (CTLA-4–Ig),<sup>62</sup> a molecule

that blocks the CD28–B7 interaction, are potential treatments for lupus. The prospects for these treatments are reviewed elsewhere.<sup>63</sup>

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,<sup>64</sup> and promoting a change in the molecular sequence of the secreted antibody so that it binds more strongly to the driving antigen.<sup>65</sup> 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.<sup>33,34,60,66</sup> 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.<sup>67</sup>

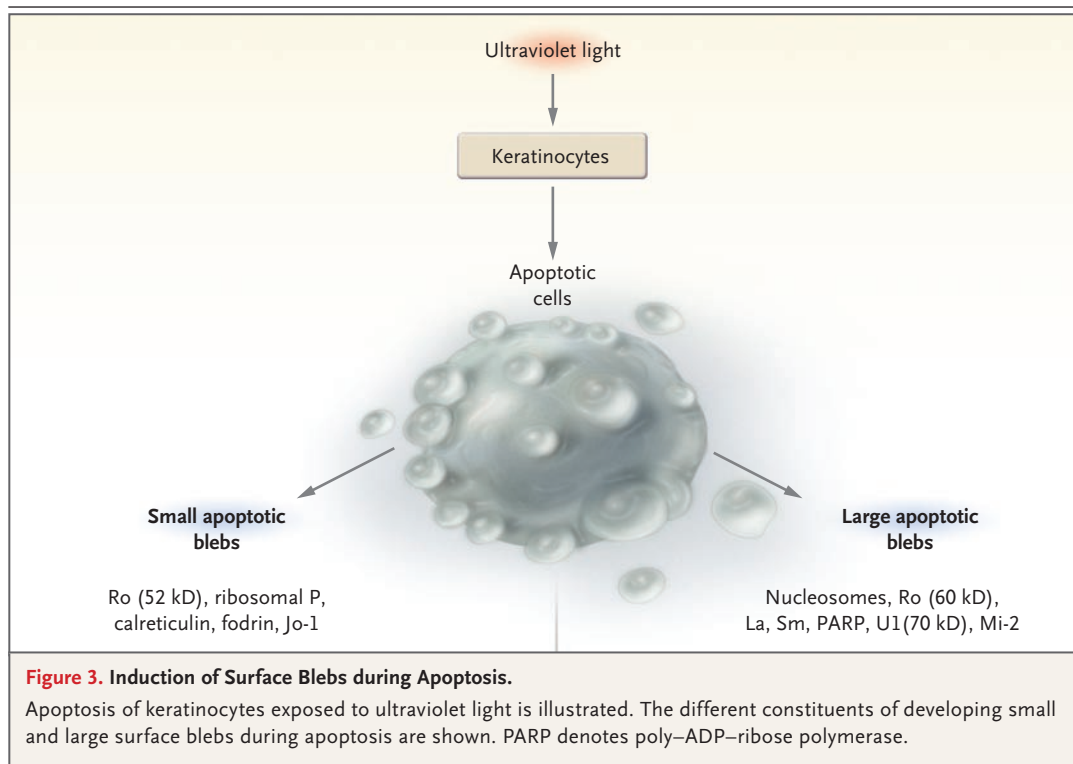
Histones constitute the protein core of a nucleosome, around which the DNA winds. Lu and colleagues<sup>68</sup> showed that the histone-derived peptides H2B<sub>10-33</sub>, H4<sub>16-39</sub>, H4<sub>71-94</sub>, H3<sub>91-105</sub>, H2A<sub>34-48</sub>, and H4<sub>49-63</sub> stimulated T cells from 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.<sup>26,39,40,56</sup>

Regulatory T cells in humans and mice sup-

press 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.<sup>69,70</sup> 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.<sup>70</sup> 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 H4<sub>71-94</sub>.<sup>71</sup>

#### 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

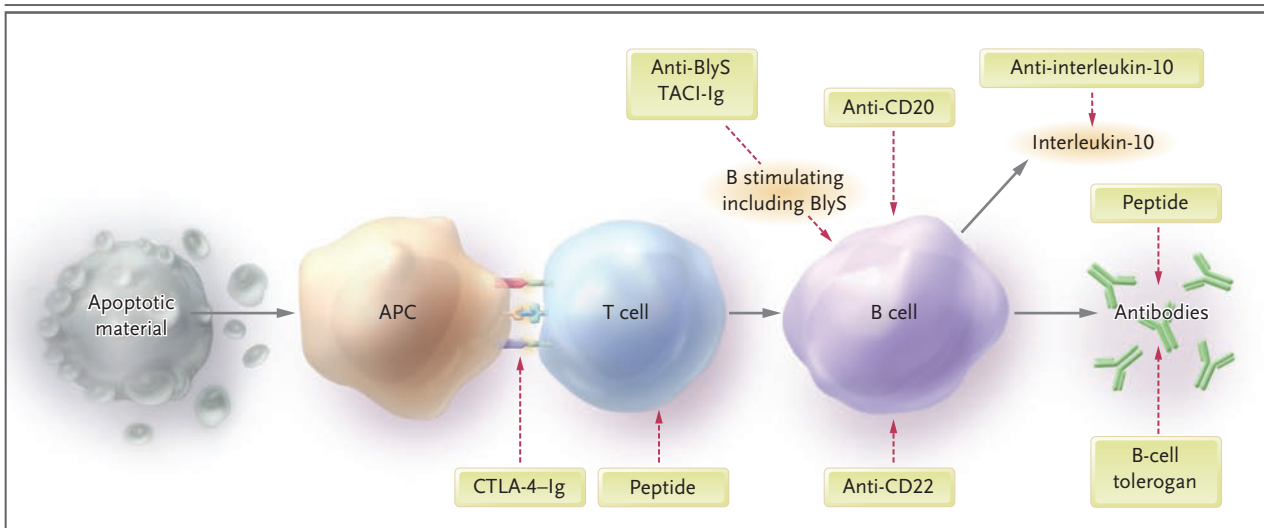


the surface of these blebs (Fig. 3), and they may trigger an immune response. These exposed antigens include nucleosomes, Ro 62, Ro 50, La, and anionic phospholipids.<sup>72</sup> Antibodies to these antigens occur commonly in patients with lupus.

The removal of apoptotic debris is abnormal in patients with lupus.<sup>73</sup> 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.<sup>74</sup> 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.<sup>17</sup> In C1q knockout mice, a lupuslike renal disease develops; kidney-biopsy specimens from mice with this condition reveal multiple apoptotic fragments.<sup>75</sup> 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.<sup>76</sup>

#### CYTOKINES IN LUPUS

The role of tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) in lupus is controversial. This cytokine may be protective in patients with lupus, since giving TNF- $\alpha$  to lupus-prone NZB/W F1 mice delayed the development of lupus.<sup>77</sup> 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- $\alpha$  antibodies, anti-double-stranded DNA antibodies developed,<sup>78</sup> and lupus developed in a few of these patients.<sup>79</sup> One group has shown that the balance between TNF- $\alpha$  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- $\alpha$  activity is associated with increased disease activity in lupus.<sup>80</sup> By contrast, the level of TNF- $\alpha$  messenger RNA was high in kidney-biopsy specimens from patients with lupus nephritis.<sup>81</sup> Aringer et al. reported that giving the anti-TNF- $\alpha$  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.<sup>82</sup>



**Figure 4. Targeted Therapeutic Approaches in Systemic Lupus Erythematosus.**

This simplified diagram, which is based on our increased understanding of the immunologic events thought to occur in lupus, indicates the targets of current therapeutic interventions. APC denotes antigen-presenting cell, BlyS B-lymphocyte stimulator, CTLA-4-Ig cytotoxic T-lymphocyte-associated protein 4 IgG1, and TACI-Ig transmembrane activator and CAML interactor immunoglobulin (CAML denotes calcium modulator and cyclophilin ligand).

Serum levels of interleukin-10 are consistently high in patients with lupus, and they correlate with the activity of the disease.<sup>83</sup> 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.<sup>84</sup>

Serum levels of interferon- $\alpha$  are also elevated in patients with active lupus,<sup>85</sup> 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.<sup>86</sup> In studies of lupus-prone NZB/W F1 mice, nephritis developed 15 to 20 weeks earlier in mice continuously exposed to interferon- $\alpha$  from a young age than in control mice not subject to this exposure.<sup>87</sup> 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.<sup>88</sup> 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<sup>31,32</sup> have shown that a strategy of increasing doses of corticosteroids in response to a specified increase in levels of anti-double-stranded



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.<sup>31</sup> Rituximab<sup>89</sup> and abetimus sodium<sup>90</sup> 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.<sup>91</sup>

Several case series suggest that rituximab is helpful in treating lupus.<sup>89,92</sup> The use of a monoclonal anti-CD22 antibody (which also targets B cells)<sup>93</sup> 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.<sup>88,94</sup> 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.<sup>90</sup>

Anti-CD40 ligand<sup>61</sup> and CTLA-4-Ig<sup>62</sup> 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.<sup>95</sup> Trials of anti-TNF- $\alpha$  antibody<sup>82</sup> and anti-interleukin-10 antibody<sup>84</sup> are described above.

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#### SUMMARY

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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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#### REFERENCES

1. Johnson AE, Gordon C, Palmer RG, Bacon PA. The prevalence and incidence of systemic lupus erythematosus in Birmingham, England: relationship to ethnicity and country of birth. *Arthritis Rheum* 1995;38:551-8.
2. Merrell M, Shulman LE. Determination of prognosis in chronic disease, illustrated by systemic lupus erythematosus. *J Chronic Dis* 1955;1:12-32.
3. Abu-Shakra M, Urowitz MB, Gladman DD, Gough J. Mortality studies in systemic lupus erythematosus: results from a single center. II. Predictor variables for mortality. *J Rheumatol* 1995;22:1265-70.
4. Gladman DD, Urowitz MB. Prognosis, mortality and morbidity in systemic lupus erythematosus. In: Wallace DJ, Hahn BH, eds. *Dubois' lupus erythematosus*. 7th ed. Philadelphia: Lippincott Williams & Wilkins, 2007:1333-53.
5. Urowitz MB, Bookman AA, Koehler BE, Gordon DA, Smythe HA, Ogryzlo MA. The bimodal mortality pattern of systemic lupus erythematosus. *Am J Med* 1976;60:221-5.
6. Mason LJ, Isenberg D. The pathogenesis of systemic lupus erythematosus. In: Davidson AM, Cameron JS, Grunfeld JP, et al., eds. *Oxford textbook of clinical nephrology*. Oxford, England: Oxford University Press, 2005:809-29.
7. Buyon JP, Petri MA, Kim MY, et al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. *Ann Intern Med* 2005;142:953-62.
8. Chang DM, Lan JL, Lin HY, Luo SF. Dehydroepiandrosterone treatment of women with mild-to-moderate systemic lupus erythematosus: a multicenter randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002;46:2924-7.
9. Rubin R. Drug induced lupus. In: Wallace DJ, Hahn BH, eds. *Dubois' lupus erythematosus*. 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2002:885-916.
10. James JA, Kaufman KM, Farris AD, Taylor-Albert E, Lehman TJ, Harley JB. An increased prevalence of Epstein-Barr virus infection in young patients suggests a possible etiology for systemic lupus erythematosus. *J Clin Invest* 1997;100:3019-26.
11. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271-7.
12. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.
13. Sullivan KE. Genetics of systemic lupus erythematosus: clinical implications. *Rheum Dis Clin North Am* 2000;26:229-56.
14. Wakeland EK, Liu K, Graham RR, Behrens TW. Delineating the genetic basis of systemic lupus erythematosus. *Immunity* 2001;15:397-408.
15. Namjou B, Kelly JA, Harley JB. The genetics of lupus. In: Tsokos GC, Gordon C, Smolen JS, eds. *Systemic lupus erythematosus*. Philadelphia: Mosby Elsevier, 2007:74-80.
16. Walport MJ, Black CM, Batchelor JR. The immunogenetics of SLE. *Clin Rheum Dis* 1982;8:3-21.
17. Walport MJ. Complement and systemic lupus erythematosus. *Arthritis Res* 2002;4:Suppl 3:S279-S293.
18. Sigurdsson S, Nordmark G, Göring HH, et al. Polymorphisms in the tyrosine kinase 2 and interferon regulatory factor 5 genes are associated with systemic lupus erythematosus. *Am J Hum Genet* 2005;76:528-37.
19. Morel L, Croker BP, Blenman KR, et al. Genetic reconstitution of systemic lupus

- erythematosus immunopathology with polycongenic murine strains. *Proc Natl Acad Sci U S A* 2000;97:6670-5.
20. Koffler D, Schur PH, Kunkel HG. Immunological studies concerning the nephritis of systemic lupus erythematosus. *J Exp Med* 1967;126:607-24.
21. Isenberg DA, Manson JJ, Ehrenstein MR, Rahman A. Fifty years of anti-dsDNA antibodies: are we approaching journey's end? *Rheumatology (Oxford)* 2007;46:1052-6.
22. Isenberg DA, Shoenfeld Y, Walport M, et al. Detection of cross-reactive anti-DNA antibody idiotypes in the serum of systemic lupus erythematosus patients and of their relatives. *Arthritis Rheum* 1985;28:999-1007.
23. ter Borg EJ, Horst G, Hummel EJ, Limburg PC, Kallenberg CG. Measurement of increases in anti-double-stranded DNA antibody levels as a predictor of disease exacerbation in systemic lupus erythematosus: a long-term, prospective study. *Arthritis Rheum* 1990;33:634-43.
24. Ng KP, Manson JJ, Rahman A, Isenberg DA. Association of antinucleosome antibodies with disease flare in serologically active clinically quiescent patients with systemic lupus erythematosus. *Arthritis Rheum* 2006;55:900-4.
25. Mannik M, Merrill CE, Stamps LD, Wener MH. Multiple autoantibodies form the glomerular immune deposits in patients with systemic lupus erythematosus. *J Rheumatol* 2003;30:1495-504.
26. Amoura Z, Koutouzov S, Chabre H, et al. Presence of antinucleosome autoantibodies in a restricted set of connective tissue diseases: antinucleosome antibodies of the IgG3 subclass are markers of renal pathogenicity in systemic lupus erythematosus. *Arthritis Rheum* 2000;43:76-84.
27. Kowal C, Degiorgio LA, Lee JY, et al. Human lupus autoantibodies against NMDA receptors mediate cognitive impairment. *Proc Natl Acad Sci U S A* 2006;103:19854-9.
28. Becker-Merok A, Kalaaji M, Haugbro K, et al. Alpha-actinin-binding antibodies in relation to systemic lupus erythematosus and lupus nephritis. *Arthritis Res Ther* 2006;8:R162.
29. Siegert CE, Daha MR, Swaak AJ, van der Voort EA, Breedveld FC. The relationship between serum titers of autoantibodies to C1q and age in the general population and in patients with systemic lupus erythematosus. *Clin Immunol Immunopathol* 1993;67:204-9.
30. Ehrenstein M, Isenberg DA. Systemic lupus erythematosus in adults — clinical features and aetiopathogenesis. In: Isenberg DA, Maddison PJ, Woo P, Klars D, Breedveld FC, eds. *Oxford textbook of rheumatology*. 3rd ed. Oxford, England: Oxford University Press, 2004:819-41.
31. Bootsma H, Spronk P, Derksen R, et al. Prevention of relapses in systemic lupus erythematosus. *Lancet* 1995;345:1595-9. [Erratum, *Lancet* 1995;346:516.]
32. Tseng CE, Buyon JP, Kim M, et al. The effect of moderate-dose corticosteroids in preventing severe flares in patients with serologically active, but clinically stable, systemic lupus erythematosus: findings of a prospective, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2006;54:3623-32.
33. Ravirajan CT, Rahman MA, Papadaki L, et al. Genetic, structural and functional properties of an IgG DNA-binding monoclonal antibody from a lupus patient with nephritis. *Eur J Immunol* 1998;28:339-50. [Erratum, *Eur J Immunol* 1999;29:3052.]
34. Ehrenstein MR, Katz DR, Griffiths MH, et al. Human IgG anti-DNA antibodies deposit in kidneys and induce proteinuria in SCID mice. *Kidney Int* 1995;48:705-11.
35. Madaio MP, Carlson J, Cataldo J, Ucci A, Migliorini P, Pankewycz O. Murine monoclonal anti-DNA antibodies bind directly to glomerular antigens and form immune deposits. *J Immunol* 1987;138:2883-9.
36. Grootsholten C, van Bruggen MC, van der Pijl JW, et al. Deposition of nucleosomal antigens (histones and DNA) in the epidermal basement membrane in human lupus nephritis. *Arthritis Rheum* 2003;48:1355-62.
37. Kalaaji M, Fenton KA, Mortensen ES, et al. Glomerular apoptotic nucleosomes are central target structures for nephritogenic antibodies in human SLE nephritis. *Kidney Int* 2007;71:664-72.
38. Kalaaji M, Mortensen E, Jørgensen L, Olsen R, Rekvig OP. Nephritogenic lupus antibodies recognize glomerular basement membrane-associated chromatin fragments released from apoptotic intraglomerular cells. *Am J Pathol* 2006;168:1779-92.
39. Kramers C, Hylkema MN, van Bruggen MC, et al. Anti-nucleosome antibodies complexed to nucleosomal antigens show anti-DNA reactivity and bind to rat glomerular basement membrane in vivo. *J Clin Invest* 1994;94:568-77.
40. van Bruggen MC, Walgreen B, Rijke TP, et al. Antigen specificity of anti-nuclear antibodies complexed to nucleosomes determines glomerular basement membrane binding in vivo. *Eur J Immunol* 1997;27:1564-9.
41. Buyon JP, Clancy RM. Maternal autoantibodies and congenital heart block: mediators, markers, and therapeutic approach. *Semin Arthritis Rheum* 2003;33:140-54.
42. Sontheimer RD, Maddison PJ, Reichlin M, Jordon RE, Stastny P, Gilliam JN. Serologic and HLA associations in subacute cutaneous lupus erythematosus, a clinical subset of lupus erythematosus. *Ann Intern Med* 1982;97:664-71.
43. Clancy RM, Kapur RP, Molad Y, Askanase AD, Buyon JP. Immunohistologic evidence supports apoptosis, IgG deposition, and novel macrophage/fibroblast crosstalk in the pathologic cascade leading to congenital heart block. *Arthritis Rheum* 2004;50:173-82.
44. Maddison PJ, Reichlin M. Deposition of antibodies to a soluble cytoplasmic antigen in the kidneys of patients with systemic lupus erythematosus. *Arthritis Rheum* 1979;22:858-63.
45. McCarty GA, Harley JB, Reichlin M. A distinctive autoantibody profile in black female patients with lupus nephritis. *Arthritis Rheum* 1993;36:1560-5.
46. Yoshio T, Onda K, Nara H, Minota S. Association of IgG anti-NR2 glutamate receptor antibodies in cerebrospinal fluid with neuropsychiatric systemic lupus erythematosus. *Arthritis Rheum* 2006;54:675-8.
47. Lapteva L, Nowak M, Yarboro CH, et al. Anti-N-methyl-D-aspartate receptor antibodies, cognitive dysfunction, and depression in systemic lupus erythematosus. *Arthritis Rheum* 2006;54:2505-14.
48. Alarcón-Segovia D, Delezé M, Oria CV, et al. Antiphospholipid antibodies and the antiphospholipid syndrome in systemic lupus erythematosus: a prospective analysis of 500 consecutive patients. *Medicine (Baltimore)* 1989;68:353-65.
49. Girardi G, Redecha P, Salmon JE. Heparin prevents antiphospholipid antibody-induced fetal loss by inhibiting complement activation. *Nat Med* 2004;10:1222-6.
50. Pierangeli SS, Liu X, Espinola R, et al. Functional analyses of patient-derived IgG monoclonal anticardiolipin antibodies using in vivo thrombosis and in vivo microcirculation models. *Thromb Haemost* 2000;84:388-95.
51. Mason LJ, Ravirajan CT, Rahman A, Putterman C, Isenberg DA. Is alpha-actinin a target for pathogenic anti-DNA antibodies in lupus nephritis? *Arthritis Rheum* 2004;50:866-70.
52. Mostoslavsky G, Fischel R, Yachimovich N, et al. Lupus anti-DNA autoantibodies cross-react with a glomerular structural protein: a case for tissue injury by molecular mimicry. *Eur J Immunol* 2001;31:1221-7.
53. Deocharan B, Qing X, Lichauro J, Putterman C. Alpha-actinin is a cross-reactive renal target for pathogenic anti-DNA antibodies. *J Immunol* 2002;168:3072-8.
54. Quismorio FP. Other serologic abnormalities in systemic lupus erythematosus. In: Wallace DJ, Hahn BH, eds. *Dubois' lupus erythematosus*. 7th ed. Philadelphia: Lippincott Williams & Wilkins, 2007:527-50.
55. Pujol M, Ribera A, Vilardell M, Ordi J, Feliu E. High prevalence of platelet autoantibodies in patients with systemic lupus erythematosus. *Br J Haematol* 1995;89:137-41.
56. Berden JH, Licht R, van Bruggen MC,

- Tax WJ. Role of nucleosomes for induction and glomerular binding of autoantibodies in lupus nephritis. *Curr Opin Nephrol Hypertens* 1999;8:299-306.
57. Michaud JL, Lemieux LI, Dubé M, Vanderhyden BC, Robertson SJ, Kennedy CR. Focal and segmental glomerulosclerosis in mice with podocyte-specific expression of mutant alpha-actinin-4. *J Am Soc Nephrol* 2003;14:1200-11.
58. Katz JB, Limpanasithikul W, Diamond B. Mutational analysis of an autoantibody: differential binding and pathogenicity. *J Exp Med* 1994;180:925-32.
59. Avrameas S. Natural autoantibodies: from 'horror autotoxicus' to 'gnothis sea-ton.' *Immunol Today* 1991;12:154-9.
60. Okamura M, Kanayama Y, Amastu K, et al. Significance of enzyme linked immunosorbent assay (ELISA) for antibodies to double stranded and single stranded DNA in patients with lupus nephritis: correlation with severity of renal histology. *Ann Rheum Dis* 1993;52:14-20.
61. Sidiropoulos PI, Boumpas DT. Lessons learned from anti-CD40L treatment in systemic lupus erythematosus patients. *Lupus* 2004;13:391-7.
62. Davidson A, Diamond B, Wofsy D, Daikh D. Block and tackle: CTLA4Ig takes on lupus. *Lupus* 2005;14:197-203.
63. Isenberg D, Rahman A. Systemic lupus erythematosus — 2005 annus mirabilis? *Nat Clin Pract Rheumatol* 2006;2:145-52.
64. Coffman RL, Lebman DA, Rothman P. Mechanism and regulation of immunoglobulin isotype switching. *Adv Immunol* 1993;54:229-70.
65. Shlomchik MJ, Marshak-Rothstein A, Wolfowicz CB, Rothstein TL, Weigert MG. The role of clonal selection and somatic mutation in autoimmunity. *Nature* 1987;328:805-11.
66. Rahman A. Autoantibodies, lupus and the science of sabotage. *Rheumatology (Oxford)* 2004;43:1326-36.
67. Dörner T, Lipsky PE. Immunoglobulin variable-region gene usage in systemic autoimmune diseases. *Arthritis Rheum* 2001;44:2715-27.
68. Lu L, Kaliyaperumal A, Boumpas DT, Datta SK. Major peptide autoepitopes for nucleosome-specific T cells of human lupus. *J Clin Invest* 1999;104:345-55.
69. Mudd PA, Teague BN, Farris AD. Regulatory T cells and systemic lupus erythematosus. *Scand J Immunol* 2006;64:211-8.
70. Valencia X, Yarboro C, Illei G, Lipsky PE. Deficient CD4+CD25(high) T regulatory cell function in patients with active systemic lupus erythematosus. *J Immunol* 2007;178:2579-88.
71. Kang H-K, Michaels MA, Berner BR, Datta SK. Very low-dose tolerance with nucleosomal peptides controls lupus and induces potent regulatory T-cell subsets. *J Immunol* 2005;174:3247-55.
72. Casciola-Rosen LA, Anhalt G, Rosen A. Autoantigens targeted in systemic lupus erythematosus are clustered in two populations of surface structures on apoptotic keratinocytes. *J Exp Med* 1994;179:1317-30.
73. Munoz LE, Gaipil US, Franz S, et al. SLE — a disease of clearance deficiency? *Rheumatology (Oxford)* 2005;44:1101-7.
74. Herrmann M, Voll RE, Zoller OM, Hagenhofer M, Ponner BB, Kalden JR. Impaired phagocytosis of apoptotic cell material by monocyte-derived macrophages from patients with systemic lupus erythematosus. *Arthritis Rheum* 1998;41:1241-50.
75. Botto M, Dell'Agnola C, Bygrave AE, et al. Homozygous C1q deficiency causes glomerulonephritis associated with multiple apoptotic bodies. *Nat Genet* 1998;19:56-9.
76. Davies KA, Erlendsson K, Beynon HL, et al. Splenic uptake of immune complexes in man is complement-dependent. *J Immunol* 1993;151:3866-73.
77. Jacob CO, McDevitt HO. Tumour necrosis factor-alpha in murine autoimmune 'lupus' nephritis. *Nature* 1988;331:356-8.
78. Charles PJ, Smeenk RJ, De Jong J, Feldmann M, Maini RN. Assessment of antibodies to double-stranded DNA induced in rheumatoid arthritis patients following treatment with infliximab, a monoclonal antibody to tumor necrosis factor alpha: findings in open-label and randomized placebo-controlled trials. *Arthritis Rheum* 2000;43:2383-90.
79. Mohan AK, Edwards ET, Coté TR, Siegel JN, Braun MM. Drug-induced systemic lupus erythematosus and TNF-alpha blockers. *Lancet* 2002;360:646.
80. Gabay C, Cakir N, Moral F, et al. Circulating levels of tumor necrosis factor soluble receptors in systemic lupus erythematosus are significantly higher than in other rheumatic diseases and correlate with disease activity. *J Rheumatol* 1997;24:303-8.
81. Herrera-Esparza R, Barbosa-Cisneros O, Villalobos-Hurtado R, Avalos-Díaz E. Renal expression of IL-6 and TNFalpha genes in lupus nephritis. *Lupus* 1998;7:154-8.
82. Aringer M, Graninger WB, Steiner G, Smolen JS. Safety and efficacy of tumor necrosis factor alpha blockade in systemic lupus erythematosus: an open-label study. *Arthritis Rheum* 2004;50:3161-9.
83. Houssiau FA, Lefebvre C, Vanden Berghe M, Lambert M, Devogelaer JP, Renaud JC. Serum interleukin 10 titers in systemic lupus erythematosus reflect disease activity. *Lupus* 1995;4:393-5.
84. Llorente L, Richaud-Patin Y, García-Padilla C, et al. Clinical and biologic effects of anti-interleukin-10 monoclonal antibody administration in systemic lupus erythematosus. *Arthritis Rheum* 2000;43:1790-800.
85. Rönnblom L, Alm GV. Systemic lupus erythematosus and the type I interferon system. *Arthritis Res Ther* 2003;5:68-75.
86. Baechler EC, Batliwalla FM, Karypis G, et al. Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. *Proc Natl Acad Sci U S A* 2003;100:2610-5.
87. Mathian A, Weinberg A, Gallegos M, Bancheureau J, Koutouzov S. IFN-alpha induces early lethal lupus in preautoimmune (New Zealand Black x New Zealand White) F1 but not in BALB/c mice. *J Immunol* 2005;174:2499-506.
88. Stohl W, Metyas S, Tan SM, et al. B lymphocyte stimulator overexpression in patients with systemic lupus erythematosus: longitudinal observations. *Arthritis Rheum* 2003;48:3475-86.
89. Leandro MJ, Edwards JC, Cambridge G, Ehrenstein MR, Isenberg DA. An open study of B lymphocyte depletion in systemic lupus erythematosus. *Arthritis Rheum* 2002;46:2673-7.
90. Alarcón-Segovia D, Tumlin JA, Furie RA, et al. LJP 394 for the prevention of renal flare in patients with systemic lupus erythematosus: results from a randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2003;48:442-54.
91. Weisman MH, Bluestein HG, Berner CM, de Haan HA. Reduction in circulating dsDNA antibody titer after administration of LJP 394. *J Rheumatol* 1997;24:314-8.
92. Chambers SA, Isenberg D. Anti-B cell therapy (rituximab) in the treatment of autoimmune diseases. *Lupus* 2005;14:210-4.
93. Dörner T, Kaufmann J, Wegener WA, Teoh N, Goldenberg DM, Burmester GR. Initial clinical trial of epratuzumab (humanized anti-CD22 antibody) for immunotherapy of systemic lupus erythematosus. *Arthritis Res Ther* 2006;8:R74.
94. Baker KP, Edwards BM, Main SH, et al. Generation and characterization of LymphoStat-B, a human monoclonal antibody that antagonizes the bioactivities of B lymphocyte stimulator. *Arthritis Rheum* 2003;48:3253-65.
95. Merrill JT. BlyS antagonists and peptide tolerance induction. *Lupus* 2005;14:204-9.

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