EXHIBIT 13

"Epidemiology and Pathogenesis of Systemic Lupus Erythematosus"

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EPIDEMIOLOGY — The reported prevalence of systemic lupus erythematosus (SLE) in the population is 20 to 150 cases per 100,000 [1-3]. In women, prevalence rates vary from 164 (white) to 406 (African American) per 100,000 [2]. Due to improved detection of mild disease, the incidence nearly tripled in the last 40 years of the 20th century [4]. Estimated incidence rates are 1 to 25 per 100,000 in North America, South America, Europe and Asia [3,5-7].

Geographic and racial distribution — Both geography and race affect the prevalence of SLE and of frequency and severity of clinical and laboratory manifestations:

- The disease appears to be more common in urban than rural areas [2,8].
- The prevalence of SLE is higher among Asians, Afro-Americans, Afro-Caribbeans, and Hispanic Americans compared with Americans of European decent in the United States, and among Asian Indians compared with Caucasians in Great Britain [6,9,10]. In comparison, SLE occurs infrequently in Blacks in Africa [11].
- In New Zealand, the prevalence and mortality of SLE are higher in Polynesians than in Caucasians [12].
- Photosensitivity and discoid skin lesions may be more frequent clinical manifestations in patients with Northern European than those with Southern European ancestry; the former group is, however, less likely to have anti-cardiolipin and anti-dsDNA antibodies [13].

Gender — The increased frequency of SLE among women has been attributed in part to an estrogen hormonal effect (see 'Hormonal factors' below) [14,15]. An estrogen effect is suggested by a number of observations including the female-to-male ratio of SLE in different age groups:

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- In "older" individuals, especially post-menopausal women, the ratio is approximately 8:1 [16].

In support of the potential role of estrogens in predisposing to SLE, the Nurse's Health study showed that women with early menarche, or treated with estrogen-containing regimens, such as oral contraceptives or postmenopausal hormone replacement therapies, have a significantly increased risk for SLE (hazard ratios of 1.5 to 2.1 [15,17]).

Factors related to the X chromosome may also be important in predisposing women to SLE. At least three predisposing genes are located on X chromosomes (IRAK1, MECP2, TLR7) [18]. There is also evidence for a gene dose effect, since the prevalence of XXY (Klinefelter's syndrome) is increased 14-fold in men with SLE when compared with the general population of men, whereas XO (Turner's syndrome) is underrepresented in women [19].

Other possibilities for female predisposition include: X-inactivation, imprinting, X or Y chromosome genetic modulators, differential methylation of DNA and acetylation of histones bound to DNA, intrauterine influences, chronobiologic differences, pregnancy, and menstruation [20,21].

Age at onset — Sixty-five percent of patients with SLE have disease onset between the ages of 16 and 55 [22]. Of the remaining cases, 20 percent present before age 16 [23], and 15 percent after age 55 [24]. Median ages at diagnosis for white females range from 37 to 50 years, in white males from 50 to 59, in black females from 15 to 44 and in black males from 45 to 64 [6].

Factors affecting disease outcome — Different epidemiologic subgroups (eg, race/ethnicity, gender, and age of onset) tend to have varying degrees of disease activity and may thus affect disease outcome:

- Blacks and Mexican Hispanics in the United States have a poorer renal prognosis than Caucasians, a finding not entirely independent of socioeconomic status [25]. Blacks are more likely to have anti-Sm, anti-RNP, discoid skin lesions, proteinuria, psychosis, and serositis [25-27]. Blacks with lupus nephritis are also less likely to respond to cyclophosphamide treatment than Whites [28].

- The clinical status is poorer in those with less education [25,29]; this effect may reflect poor compliance [30]. Clinical status is also poorer in those with lower socioeconomic status and with inadequate access to medical care [31].

UpToDate 19.3

Epidemiology and pathogenesis of systemic lupus erythematosus

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hypertension, and vasculitis than women [34]. In contrast, Raynaud phenomenon, photosensitivity, and mucosal ulceration are less frequent manifestations in men than women. Most, but not all studies suggest that men have a higher one-year mortality rate [34-39].

- SLE in children tends to be symptomatically more severe than in adults, with a high incidence of malar rashes, nephritis, pericarditis, hepatosplenomegaly, and hematologic abnormalities [23,35].

Lupus tends to be milder in the elderly, who often have a presentation more similar to that of drug-induced lupus. Clinical features of lupus in older patients include the following [35,40-42]:

- A lower ratio of affected women to men than for younger patients
- Lower incidence of malar rash, photosensitivity, purpura, alopecia, Raynaud phenomenon, renal, central nervous system, and hematologic involvement,
- Lower prevalence of anti-La, anti-Sm, and anti-RNP antibodies and of hypocomplementemia
- Greater prevalence of sicca symptoms, serositis, pulmonary involvement, and musculoskeletal manifestations
- Greater prevalence of rheumatoid factor

ETIOLOGY — The etiology of SLE remains unknown and is clearly multifactorial. Many observations suggest a role for genetic, hormonal, immunologic, and environmental factors.

Genetic factors — The following observations are compatible with a genetic role in the pathogenesis of SLE [43-45]:

- There is a high concordance rate (14 to 57 percent) of SLE in monozygotic twins [46,47].

- Five to 12 percent of relatives of patients with SLE have the disease [48], and there is an increased frequency of anti-C1q and anti-cardiolipin antibodies and C3 and C4 abnormalities in relatives [49].

- Twenty-seven percent of 195 children of mothers with lupus had a positive test for anti-nuclear antibodies [50].

Genome-wide association studies (GWAS) have identified 30 to 40 gene loci with polymorphisms (or, rarely, mutations) that predispose to SLE [18,51-53]. The gene polymorphisms that increase risk for SLE can be understood best if SLE is considered to be caused initially by pathogenic autoantibodies and immune complexes (IC) that consist of nucleic acid derived from dead and

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deoxyribonucleic acid (DNA).

- Activation of adaptive immunity - T cells and B cells may be activated by interaction with self-antigens on or released by apoptotic cells.

Genetic factors that confer the highest hazard ratios (HR) of 5 to 25 are deficiencies of the complement components C1q (required to clear apoptotic cells), C4A and B, C2, or the presence of a mutated TREX1 gene (encodes the three prime repair endonuclease1 enzyme that degrades DNA). Each of these is relatively rare in the population.

The most common genetic predisposition is found at the major histocompatibility locus (MHC). The MHC contains genes for antigen presenting molecules (class I human leukocyte antigens [HLA-A, -B, and -C] and class II HLA molecules [HLA-DR, -DQ, and DP]). (See "Human leukocyte antigens (HLA): A roadmap".) The MHC also contains genes for some complement components, cytokines, and heat shock protein.

Predisposing loci, which include HLA-DR2 and HLA-DR3, are associated with HR of approximately 2, but the region is complex and involves multiple genes across the entire 120-gene region in multiple ethnic groups [54,55]. Within HLA-DRB1 loci, HLA-DRB1*0301 and HLA-DRB1*1501 predispose to SLE whereas HLA-DRB1*1401 reduces risk.

Other genes with predisposing variants involve some associated with innate immunity (IRF5, Stat4, IRAK1, TNFAIP3, SPP1), most of which are associated with interferon alpha (IFNa) pathways. Overexpression of IFNa-induced genes is found in the peripheral blood cells of approximately 60 percent of patients with SLE [56]. Some of the lupus-predisposing polymorphisms in STAT4, PTPN22 and IRF5 are associated with high levels of or increased sensitivity to IFN-a [56-58]. Furthermore, STAT4 and IRF5 may have additive effects [59].

Still other predisposing genes involve lymphocyte signaling (PTPN22, OX40L, PD-1, BANK-1, LYN, BLK), each of which plays a role in activation or suppression of T cell or B cell activation or survival. Other genes influence clearance of immune complexes (complement components C1q, C4 and C2 mentioned above, FcgammaRIIA, RIIA and RIIIB, CRP, and integrin alpha M [ITGAM]). The HR for predisposing HLA-DR/DQ is approximately 2.4, and is increased in patients homozygous for predisposing alleles, indicating a gene dose effect. HR for other genes varies from 1.2 to 2.3, with additional reports of significant, but relatively low HR-conferring, genes occurring at a rapid pace. In some cases, the genetic component is found in promoter regions (eg, IL-10), or is

UpToDate 19.3

Epidemiology and pathogenesis of systemic lupus erythematosus

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RELATED TOPICS

of susceptibility genes, or presence of susceptibility genes plus the absence of protective genes (such as TLR5 polymorphism or loss-of-function PTPN22 variant) are required to "achieve" enough genetic susceptibility to permit disease development [63,64].

In addition to genome-encoded susceptibility genes, epigenetic modifications are likely to be important in pathogenesis of SLE. These include hypomethylation of DNA [65], which influences transcription into protein. The influence of microRNAs (miRNA) on transcription of several SLE-predisposing genes has also been identified [66,67]. The hypomethylation likely affects specific genes.

Some of the single-nucleotide polymorphisms (SNPs) in SLE risk genes predispose to particular clinical subsets of SLE. As examples:

- The SNP in the third intron of STAT4 (which predisposes to both rheumatoid arthritis and to SLE in several ethnic groups) increases risk for anti-DNA antibodies, nephritis and the antiphospholipid syndrome [68-71].
- SNPs associated with LYN decrease risk for SLE susceptibility and for hematologic manifestations in European-American cohorts [72].
- A CRP-A allele is associated with SLE nephritis but is inversely correlated with arthritis [73].
- The polymorphism of FcgammaRIIa associated with low binding of immune complexes predisposes to lupus nephritis [73-75].
- A coding variant of the ITGAM gene is associated with the development of renal disease, discoid rash and "immunological manifestations" in patients with systemic lupus erythematosus with European ancestry [76].

Stratification by disease phenotypes may be of benefit in genetic analyses of molecular pathogenesis. A GWAS of SLE patients stratified by ancestry and extremes of phenotype in serology and serum IFNa, and using a multi-step screening approach, identified several loci of particular interest; each of these demonstrated a strong association with increased serum IFNa and with a particular serologic profile [77]. These included LRRC20 and PPM1H (both with anti-La), LPAR1 (with anti-Ro and –Sm), ANKS1A (with anti-Ro and anti-dsDNA), and VSIG2 (with anti-RNP, but lacking anti-Sm). Additionally, SNPs in both PTPRM and LRRC20 were associated with increased serum IFNa independent of serologic profile. The findings demonstrate heterogeneity in SLE molecular

UpToDate 19.3

Epidemiology and pathogenesis of systemic lupus erythematosus

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production of certain autoantibodies (eg, anti-ds DNA [19p13.2]), or to increased risk for end stage renal disease [44,78].

Hormonal factors — Substantial evidence of the immunoregulatory function of estradiol, testosterone, progesterone, DHEA, and pituitary hormones, including prolactin, has supported the hypothesis that they modulate the incidence and severity of SLE [79,80]. As examples:

- The use of estrogen-containing contraceptive agents is associated with a 50 percent increase in risk of developing SLE; while either early onset of menarche (age ≤10 years) or administration of estrogen to postmenopausal women doubles their risk [15].
- Treatment of women with clinically stable SLE with oral contraceptives for one year does not increase disease flares [81,82]. However, treatment of postmenopausal women with hormone replacement may increase flares, although evidence is mixed [17,83].
- SLE has been observed in some males with Klinefelter's syndrome [16]. This may be due to hormonal effects, including the lack of adequate androgenic hormones, other effects related to the presence in these patients of two X chromosomes, or both of these factors; the precise cause has not been determined.
- Altered sex hormone levels may predispose to the development of SLE or result from the autoimmune process. However, it is important to emphasize that hormone levels remain within the physiologic range [79]. In women, plasma levels of the following hormones are decreased: testosterone, progesterone, and dehydroepiandrosterone (DHEA), while estradiol and prolactin are increased. In men there are limited data that suggest that DHEA is probably decreased and prolactin increased, while testosterone and estradiol are unchanged.
- Breastfeeding may decrease risk of developing SLE [15,84], although evidence is mixed. It is clear that neither breastfeeding nor the duration of breastfeeding increase risk of developing SLE.
- The finding that nulliparous women are at higher risk of SLE than are women who have given birth at least once may suggest a role for hormonal influences, but the observed difference could also arise as a result of the higher rates of spontaneous abortions, missed abortions, and stillbirths in women with SLE [85].

UpToDate 19.3

Epidemiology and pathogenesis of systemic lupus erythematosus

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hybrid mice is more severe, has an earlier onset in females, and is ameliorated by oophorectomy, or treatment with male hormones [86]. Other strains of mice with a lupus-like disease, such as MRL/Fas-/- do not have as marked gender differences [87]. BXSB mice have lupus-like disease primarily in males, probably due to translocation of the gene encoding TLR7 from the X to the Y chromosome with resultant increased gene copies in males. In XX females, the locus is probably silenced on the inactive X, but in XY males the Y loci also encode TLR7, thus increasing expression with increased autoantibody formation to RNA-containing self antigens (which activate innate immunity via TLR7) [88,89]. Thus, the effect may not be hormonal in this instance, but related to genetic contributions on the X and Y chromosomes [87].

When compared with peripheral blood cells of men, those from women produce significantly higher IFN-alpha (but not TNF-alpha) after TLR-7 stimulation, but not after TLR-9 stimulation [90].

Since upregulation of genes controlled by IFN-alpha is characteristic of some SLE patients, particularly during active disease [91], this may be an important difference accounting for increased susceptibility of females to SLE.

The etiologic role of hormones in SLE may be related to their effects on immune responsiveness. Estrogen stimulates thymocytes, CD8+ and CD4+ T cells, B cells, macrophages, the release of certain cytokines (eg, interleukin-1), and the expression of both HLA and endothelial cell adhesion molecules (VCAM, ICAM) [92]. Estrogen also causes increased macrophage proto-oncogene expression and enhanced adhesion of peripheral mononuclear cells to endothelium [92]. Another potentially important effect of estradiol may be its ability to reduce apoptosis in self-reactive B cells, thus promoting selective maturation of autoreactive B cells with high affinity for anti-DNA [93]. Consequently, women are predisposed to make autoantibodies that eventually lead to clinically apparent SLE. In comparison, androgens tend to be immunosuppressive [94]. Serum levels of DHEA, an intermediate compound in testosterone synthesis, are low in nearly all patients with SLE. This may be mediated by impaired IL-2 production in SLE patients [95].

Progesterone and prolactin also affect immune activity [96,97]. Progesterone downregulates T cell proliferation and increases the number of CD8 cells [96], while lupus flares have been associated with hyperprolactinemia [98]. In addition, both progesterone and high levels of estrogen promote a Th2 response, which favors autoantibody production [16].

There is an increased incidence of thyroid disease in patients with SLE. In one study of 41 patients with SLE, for example, the

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exist among those with SLE. Patients appear to have an abnormal reaction to stress characterized by a heightened response to human corticotropin releasing hormone (hCRH) [101]. However, non-hormonal factors may play a role in the excess of lupus in females [102].

Immune abnormalities — There are numerous immune defects in patients with SLE. However, the etiology of these abnormalities remains unclear; we do not know which defects are primary, and which are secondarily induced. In certain cases these immune defects are episodic, and some correlate with disease activity.

SLE is primarily a disease with abnormalities in immune regulation [103-105]. These abnormalities are thought to be secondary to a loss of self tolerance; thus, affected patients (either before or during disease evolution) are no longer totally tolerant to all of their self-antigens, and consequently develop an autoimmune response [106,107].

The mediators of SLE are autoantibodies and immune complexes they form with antigens; the autoantibodies may be present for years before the first symptom of disease appears [108]. Self-antigens that are recognized are presented primarily on cell surfaces, particularly by cells that are activated or undergoing apoptosis, where intracellular antigens access cell surfaces where they can be recognized by the immune system [109,110]. To form immune complexes, antigens have to leave, versus be "released from", cells.

Phagocytosis and clearing of immune complexes, of apoptotic cells, and of necrotic cell-derived material are defective in SLE, allowing persistence of antigen and immune complexes [111]. B cells/plasma cells that make autoantibodies are more persistently activated and driven to maturation by B cell activating factor (BAFF, also known as B lymphocyte stimulator, BLyS) and by persistently activated T helper cells making B-supporting cytokines such as IL-6 and IL-10. BAFF (BLyS), serum levels of which are elevated in some patients with SLE, promotes formation and survival of memory B cells and plasmablasts. This increased autoantibody persistence is not downregulated appropriately by anti-idiotypic antibodies, or by CD4+CD25hi-Foxp3+ regulatory T cells, or by CD8+ suppressor T cells.

As mentioned earlier, some antibody/antigen complexes, particularly those containing DNA or RNA/proteins, activate the innate immune system via TLR-9 or TLR-7, respectively. Thus, dendritic cells are activated and release type 1 interferons and TNF-alpha, T cells release IFN-gamma, IL6, IL10, while NK and T cells fail to release adequate quantities of TGF-beta. These cytokine patterns favor continued autoantibody formation [112].

UpToDate 19.3

Epidemiology and pathogenesis of systemic lupus erythematosus

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The following are some of the immune abnormalities that have been described in SLE which relate to the vicious cycle described in the preceding discussion:

- An increase in circulating plasma cells (the producers of autoantibodies) and of a subset of memory B cells, is associated with disease activity in SLE [113,114].
- A decrease in cytotoxic T cells and in functions of suppressor T cells (which would normally downregulate immune responses) [107,115]
- Impaired generation of polyclonal T cell cytolytic activity [116]
- An increase in helper (CD4+) T cells and helper function by both CD4+ and CD8+ T cells [117,118]
- Polyclonal activation of B cells and abnormal B cell receptor signaling [119,120]
- Defects in B cell tolerance, perhaps related to defects in apoptosis and/or complement deficiency, lead to prolonged lives of B cells [107,121-123].
- Increased BAFF (BLyS) expression may promote autoimmunity. B cells have three receptors for BAFF: BAFFR, BCMA, and TACI [124]. BAFF, which is produced primarily by neutrophils and monocyte/macrophages, increases survival of B2 cells after their transitional T1 phase (which means the B cells have survived several deleting and anergizing tolerance mechanisms), as well as survival of resting memory B cells and plasmablasts. Stimulation by BAFF is particularly important for the survival of T-dependent B cells, the source of many autoantibodies. (See "Normal B and T lymphocyte development".)

  Increased BAFF (BLyS) production is promoted by increased TLR activation and increased type 1 and 2 interferons; in turn, BAFF promotes increased TLR activation. Thus, BAFF can contribute to sustained autoantibody production by several mechanisms. Clinical trials have demonstrated that belimumab, a monoclonal antibody to BAFF, may be beneficial for the treatment of patients with SLE, for whom its use has been approved by the FDA [125,126]. A proliferation-inducing ligand (APRIL), made primarily by dendritic cells, binds a transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI) and an additional B cell receptor, B cell maturation antigen (BCMA). In some conditions, APRIL promotes B cell survival and in others can

UpToDate 19.3

Epidemiology and pathogenesis of systemic lupus erythematosus

Find Patient Print

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hyperphosphorylation of cytosolic protein substrates, decreased nuclear factor kB, and abnormal voltage-gated potassium (Kv1.3) channels are implicated in facilitating excessive calcium entry into T cells [120,127,128]. These changes probably account for the decreased IL-2 production of lupus T cells, which might contribute to inability to generate adequate numbers of functioning regulatory T cells.

- Increased fetal microchimerism [129] providing "foreign" antigens to the immune system.

- Elevated circulating levels of interferon alpha and increased expression of interferon alpha-inducible RNA transcripts by mononuclear cells, especially in patients with active disease [130-135]. The elevated levels of interferon alpha and increased expression of alpha-interferon inducible transcripts may be due in part to the presence of predisposing genetic factors affecting interferon expression [136]. A similar increase in interferon alpha-inducible transcripts occurs in synovial tissue [137]. Patients with the SLE-risk enhancing PTPN22 C1858T allele are more likely to have elevated circulating INF-alpha, which may contribute to inflammation [58].

- Elevated levels of circulating TNF-alpha correlate with active disease, and TNF is expressed in renal tissue in lupus nephritis [138].

- Among patients with SLE treated with antimalarials, a genotype associated with low TNF and high IL-10 levels correlated with higher serum concentrations of IFN-alpha, while those with high TNF-alpha and low IL-10 levels had increased numbers of regulatory T cells [138]. The relative contributions of IFN and TNF to various aspects of SLE activity are poorly understood.

- Abnormally high levels of erythrocyte C4-derived activation fragments (C4d) and low levels of erythrocyte complement receptor (CR1) [139]

- Abnormal toll-like receptor (TLR)-7 signaling in response to RNA and TLR-9 signaling in response to DNA [140,141] and increased expression of TLR-9 on peripheral blood B cells and plasma cells and dendritic cells [140,142-146]. This means that B cells can be activated to secrete autoantibody by the innate immune system, independent of T cell help.

- Stimulation of TLR7 or TLR9 reduces the immunosuppressive activity of glucocorticoids, suggesting that nucleic acid containing immune complexes that induce TLR signaling may

UpToDate 19.3

Epidemiology and pathogenesis of systemic lupus erythematosus

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(SLEDAI) scores [144].

- Increased serum levels of HMGB1 (high mobility group box chromosomal protein 1) in patients with SLE is associated with disease activity [148]. Whether this is specific for SLE is as yet not clear; antibodies to HMG have been noted in patients with juvenile idiopathic arthritis [149]. (See "Miscellaneous antinuclear antibodies".)

These changes promote the production of antinuclear antibodies (ANA, see below) [150]. In addition, certain strains of mice (ie, those with the lpr mutation) have a genetic defect in apoptosis, resulting in abnormal programmed cell death that allows the development of autoreactivity and the dramatic increase in an aberrant lymphoid population. Humans with a comparable mutation (ie, autoimmune lymphoproliferative syndrome) display abnormal lymphoproliferation in association with cytopenias and autoimmunity. In humans with lupus, abnormalities in extent of apoptosis or the clearance of apoptotic cells may also occur, although studies on human lupus primarily involve analysis of peripheral blood cells in which immune activation can lead to cell death. (See "Apoptosis and autoimmune disease", section on 'Autoimmune lymphoproliferative syndrome'.)

In addition, mice with lupus and possibly humans have a (genetic) defect in apoptosis, resulting in abnormal programmed cell death [109,110,151,152]. Apoptotic cells, often with nuclear antigens expressed on their surface in blebs, and cell fragments are also poorly cleared in SLE [153]. C1q and antiphospholipid antibodies enhance opsonization and clearance [154-157]; thus, depressed levels of C1q and C4 may impair phagocytosis and delay clearance [158,159]. The act of phagocytosis results in a stimulation of the immune response to autoantigens derived from the apoptotic cells [160,161]. In addition, protein cleavage by caspases and granzyme B may promote the antigenicity of the contents of apoptotic cells [110].

As noted above, Toll-like-receptors (TLR)-7 and TLR-9 may play a role in promoting autoimmunity. Lupus-prone mice deficient in TLR 9 have an abnormal immune response to microbial CpG DNA and have an inhibition of anti-dsDNA and anti-chromatin antibodies but still develop nephritis [162]. In this context, it is interesting that procainamide (which is one of the causes of drug-induced lupus) blocks CpG methylation and antimalarial drugs used to treat some manifestations of SLE (eg, hydroxychloroquine) may block TLR 7 and 9 signaling. TLR 7 and 9 are involved in the interferon alpha response [163], and immune complexes containing DNA/autoantibody activate dendritic cells through cooperation of CD32 and TLR-9 [145]; similarly RNA-containing self antigens can

UpToDate 19.3

Epidemiology and pathogenesis of systemic lupus erythematosus

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RELATED TOPICS

abnormal cellular breakdown, and ends with the production of autoantibodies. As cells break down abnormally, certain (especially nuclear and cryptic self peptides [164]) antigens are processed (perhaps abnormally [165,166]) into peptides by antigen-presenting cells (APCs) such as macrophages, B lymphocytes, and dendritic cells [106,167]. Alternatively, microorganisms may be broken down within APCs into "mimicry peptides" that have sufficient structural similarity with immunodominant self peptides [168].

With either mechanism, a peptide-MHC complex forms and stimulates the activation and clonal expansion of CD4+ autoreactive T cells [168]. These cells, via release of cytokines (eg, interleukin-4, interleukin-6 and interleukin-10) [106,169], cause autoreactive B cells to become activated, proliferate, and differentiate into antibody-producing cells that make an excess of antibodies to many nuclear antigens [106,167]. At the same time, activation of the innate immune system with release of IL-1, TNFa, type 1 interferons, BAFF (BLyS) and APRIL promotes inflammation and survival of autoreactive B cells. Thus, a specific immune profile develops that is characterized by the development of elevated levels of antinuclear antibodies, especially to DNA, Sm, RNP, Ro, La, nucleosomes, and other nuclear antigens [106,170,171].

Antinuclear antibodies are made to antigens from active sites on molecules involved in essential cellular functions (such as RNA splicing) [172]. With continued pressure over time from self-antigens, the immune response switches, via somatic hypermutation, from low affinity, highly cross-reactive IgM antibodies, to high affinity IgG antibodies, and then finally to antibodies directed toward more limited epitopes on self-antigens [173]. Unique idiotypes of antibodies may then stimulate autoreactive T cells to expand, thereby helping unique clones of B cells to expand [174]. The final result is the production of more specific antinuclear antibodies with unique idiotypes [175]. These antinuclear antibodies may precede clinical manifestations by years [108,176].

Not all autoantibodies cause disease. In fact, all normal individuals make autoantibodies, although in small quantities. The variability in clinical disease that exists among different patients may therefore reflect the variability in the quality and quantity of the immune response, including regulatory networks.

Environmental factors — The environment probably has a role in the etiology of SLE via its effects on the immune system.

- Viruses, for example, may stimulate specific cells in this immune network [106,177,178]. In addition, trypanosomiasis or mycobacterial infections may induce anti-DNA antibodies

UpToDate 19.3

Epidemiology and pathogenesis of systemic lupus erythematosus

Find Patient Print

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RELATED TOPICS

nuclear antigens [179,180]. In fact, studies in children with SLE suggest that EBV infection may be a triggering event resulting in clinical SLE [179]. Antibodies to these molecular mimicry molecules may contribute to the development of autoimmunity [181]. Endogenous retroviruses have also been postulated to trigger lupus through structural and functional molecular mimicry [182].

- Ultraviolet (UV) light may stimulate keratinocytes to express more snRNPs on their cell surface [183,184] and to secrete more IL-1, IL-3, IL-6, GM-CSF, and TNF-alpha, thereby stimulating B cells to make more antibody. In addition to the local effects in skin, UV light may also increase the degree of systemic autoimmunity by interfering with antigen processing by and activation of macrophages. UV light decreases T cell DNA methylation, which may lead to overexpression of LFA-1 (lymphocyte function-associated antigen-1) [185]. These T cells may then become autoreactive, resulting in autoantibody formation.

- Silica dust, found in cleaning powders, soil, pottery materials, cement, and cigarette smoke may increase the risk of developing SLE, especially in African American women [14,186-190].

- Allergies to medications, particularly to antibiotics, are reported more frequently in patients with newly diagnosed SLE than healthy controls [178].

- There is a slight, but significantly higher, prevalence of lupus in pet dogs of patients with SLE (3 cases among 59 pet dogs owned by 37 SLE patients, versus none among 187 dogs in non-SLE households) [191]. These observations suggest a possible common environmental factor for both human and dog systemic lupus.

- There is no apparent association between SLE and the use of hair dyes, occupational solvent exposure, the use of pesticides, or alcohol consumption [188,192].

- A meta-analysis of studies of alcohol use and SLE risk concluded that moderate alcohol consumption had a protective effect [193].

PATHOGENESIS OF CLINICAL MANIFESTATIONS — Although the exact etiology of SLE remains obscure, it is clear that many of the clinical manifestations of SLE are mediated directly or indirectly by antibody formation and the creation of immune complexes (IC). As an example, immune complex deposition and subsequent complement activation in the kidney is responsible for much of the

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Find Patient Print

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The pathogenic potential of IC varies, depending on the following:

- The characteristics of the antibody, such as its specificity, affinity, charge, and ability to activate complement or other mediator of inflammation. In the glomerulus, for example, different antibodies may bind to antigens at different sites in the glomerular capillary wall, leading to different histologic and clinical manifestations [194,195].

- The nature of the antigen, such as its size and charge. Smaller cationic antigens, for example, are more able to cross the glomerular basement membrane and be deposited in the subepithelial cell. The ensuing formation of IC should lead to membranous nephropathy rather than a proliferative glomerulonephritis. (See "Types of renal disease in systemic lupus erythematosus", section on 'Pathogenesis'.)

- The ability of the IC to be solubilized by complement and bound to the CR1 receptors on red blood cells (both systems may be defective in SLE).

- The rate at which the IC are cleared by immunoglobulin Fc receptors on monocytes/macrophages in the liver and spleen from the circulation may be genetically impaired in SLE [196].

Renal disease — Renal disease in SLE is likely due to the deposition or formation of immune complexes in the mesangium, subendothelial or subepithelial spaces.

Immune complexes (IC) in this disease consist of nuclear antigens (especially DNA), and high-affinity, complement-fixing IgG antinuclear antibodies [197] (especially IgG1 and IgG3 [198]), and antibodies to DNA [199]. These complexes either form in the circulation, where they are poorly cleared [200] or form in situ as free antibody binds to free antigen that has already deposited in the glomerulus or is an intrinsic glomerular antigen [201]. Histones have high affinity for the glomerular basement membrane (GBM) and may facilitate IC deposition [202]. Antibody reactivities in the serum that best correlate with active nephritis in human SLE are directed against DNA/chromatin or laminin/myosin/vimentin/heparan sulphate [203], suggesting the importance of these reactivities to pathogenesis.

Elevated levels of anti-DNA antibodies commonly precede development of clinical lupus nephritis. This was illustrated in a study of serum samples collected from military recruits. Among those who developed SLE and renal disease, 92 percent had positive anti-double stranded DNA antibodies present before diagnosis [176]. In addition, the combination of a rising level (titer) of anti-DNA and evidence of increased complement activation (eg,

UpToDate 19.3

Epidemiology and pathogenesis of systemic lupus erythematosus

Find Patient Print

TOPIC OUTLINE

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leukocytes and mononuclear cells. These cells phagocytose IC and release mediators (such as cytokines and activators of the clotting system) that perpetuate glomerular inflammation. With continuing IC deposition, chronic inflammation may ensue, ultimately leading to fibrinoid necrosis, scarring, and reduced renal function.

Although necessary, immune complex deposition and complement activation do not appear to be sufficient to initiate the development of chronic inflammation in lupus nephritis. As an example, the significance of the gamma chain of the immunoglobulin Fc receptor was assessed via its deletion in a strain of mice, the New Zealand Black/New Zealand White, in which severe nephritis normally develops spontaneously [205]. Nephritis was completely prevented in the gamma chain-deficient mice despite immune complex deposition and complement activation, thereby suggesting an uncoupling of activation of the immune system from ongoing complement activity [205].

In addition, in situ antibody deposition occurring in the subepithelial space in lupus membranous nephropathy is not associated with inflammation. In this setting, complement is activated at a site that is separated from circulating inflammatory cells by the GBM [206]. As a result, these patients develop epithelial cell injury and proteinuria but not active inflammation and glomerulonephritis.

Cell-surface antibodies — SLE patients make antibodies to a number of cell-surface antigens. Antibodies to a 66-kDa membrane antigen have been implicated in lupus nephritis, vasculitis and hypocomplementemia; to a 55-kDa antigen in thrombocytopenia; and to a 18-kDa protein in thrombocytopenia [207], and antibodies to neuronal cells in organic brain disease. (See "Neurologic manifestations of systemic lupus erythematosus".) Cell-surface antibodies also attach to red blood cells, white blood cells, and platelets. (See "Hematologic manifestations of systemic lupus erythematosus in adults".) In addition, antinuclear antibodies may interact with nuclear antigens expressed on cell surfaces, triggering cell injury and even death, either by activating complement and/or by cell penetration [208].

These complexes are cleared from the circulation, and may cause organ damage, through one of the following mechanisms:

- Fc receptors on macrophages of the reticuloendothelial system
- Complement-mediated cytotoxicity
- Antibody-dependent cellular cytotoxicity (ADCC) resulting in hemolytic anemia, leukopenia, and thrombocytopenia

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Antiphospholipid antibodies — Patients with SLE may form antibodies to a phospholipid-beta-2 glycoprotein I complex. Beta-2-glycoprotein I normally has an anticoagulant effect that is diminished by this antibody formation. This may explain why antiphospholipid antibodies are implicated in the etiology of the arterial and venous thromboses (causing strokes and thrombophlebitis), and in placental infarcts (causing miscarriages). (See "Pathogenesis of the antiphospholipid syndrome".)

Antiphospholipid antibodies, like antinuclear antibodies, may be present prior to the diagnosis of SLE. This was illustrated in a study of a cohort of 130 patients for whom stored serum samples that preceded the SLE diagnosis were available [102]. The presence of anticardiolipin antibodies was noted in 24 patients who later developed SLE, and in these patients, developed an average of three years prior to the diagnosis of SLE. Furthermore, the patients with anticardiolipin antibodies tended to develop more severe lupus than those without these antiphospholipid antibodies. Eleven patients with anticardiolipin antibodies developed thrombotic events prior to the diagnosis of SLE.

Skin lesions — Skin lesions are thought to be multifactorial in origin [209]. (See "Mucocutaneous manifestations of systemic lupus erythematosus".) In particular, exposure to UV light has a number of local effects in the skin:

- It damages DNA. The patient can then make antibodies to DNA, IC form, complement is activated, and a local inflammatory response ensues.
- It increases binding of anti-Ro, anti-La, and anti-RNP antibodies to UV-activated keratinocytes, which express those antigens in apoptotic blebs on the cell surface [210].
- It alters cellular membrane phospholipid metabolism. Portions of cell membranes may be rearranged so the usually cytoplasmic-facing surfaces (and potentially antigenic molecules) are on the extracellular surface.
- It increases IL-1 release from cutaneous keratinocytes and Langerhans cells.
- It increases apoptosis of keratinocytes in patients with SLE and healthy persons; but clearance of apoptotic cells by phagocytes is abnormal [211].

As noted above, in addition to the local effects in skin, UV light may also increase the degree of autoimmunity [185].

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detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient information: Systemic lupus erythematosus (SLE)")

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