Immunopathogenesis of systemic lupus erythematosus

Gayatri Mittal, Lesley Mason & David Isenberg†

†Author for correspondence
Centre for Rheumatology Research, Division of Medicine, Room 331, 3rd Floor, Windeyer Building 46 Cleveland Street London, W1T 4JF, UK
Tel.: +44 207 679 9252; Fax: +44 207 679 9143; d.isenberg@ucl.ac.uk

There has been a substantial improvement in mortality and morbidity in patients with systemic lupus erythematosus (SLE) over the past 50 years. This change results from earlier diagnosis (with the aid of clinically useful biomarkers), development of disease monitoring and damage assessment methods, more effective pharmacotherapy, early recognition of side effects and efficient adjunctive therapies, including dialysis and renal transplant. Gene expression profiling and proteomic approaches may give insight into the etiology of SLE. Recent advances in the understanding of the various immunological defects in SLE have led to an era of therapeutic trials of agents, targeted at blocking effector mechanisms of either surface antigens, costimulatory molecules or cytokines.

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease with diverse clinical features. The musculoskeletal and skin manifestations are most common with frequent involvement of the kidneys, heart, lungs and CNS. The patients have a variable prognosis that depends upon the severity and type of organ involvement. The prognosis is most favorable in those having skin or musculoskeletal manifestations only where renal or CNS involvement pose the greatest risk to survival. Studies of inception cohorts of lupus patients followed since 1980 have shown a striking improvement in survival. The current 5-year survival rate of up to 97% compares favorably with that of 51% in the 1950s [1]. This improvement in short-term survival is attributed to the cumulative effect of a multiplicity of factors, including earlier diagnosis, widely available diagnostic tests and effective pharmacotherapy. However, the long-term prognosis has not changed much recently. This notion is confirmed by the results of a recent multicenter international cohort study of 9547 SLE patients demonstrating decreased risk of deaths from lupus activity-related factors but no decrease in deaths from circulatory disease [2]. A standardized mortality ratio of 2.4 (confidence interval: 2.3–2.5) in SLE is consistent with a higher mortality than in the general population. Since lupus predominantly affects women of child-bearing age, the estimated 87% survival rate at 15 years still leaves a one in seven chance of an individual dying early. Indeed, more than a third of deaths due to lupus have been reported to occur in people aged 15–44 years. The mortality pattern in SLE follows a bimodal curve, those having very active disease dying within 5 years of the disease onset whereas later deaths occur due to sepsis, malignancy and cardiovascular disease. Premature coronary artery disease is increasingly recognized as a cause of mortality. Besides the traditional risk factors, lupus-specific factors such as chronic nephritis, treatment with glucocorticoids, low levels of complement component (C3) and elevated levels of anti-DNA antibodies have been implicated in playing a role in the acceleration of coronary artery disease. Poor prognostic factors for survival in SLE include Black race, male sex, older age at presentation, low socioeconomic status, uncontrolled hypertension, renal disease, overall high disease activity and a concomitant antiphospholipid antibody syndrome [3].

SLE patients are not only at risk of higher mortality but also significant morbidity as a consequence of active disease and drug side effects. The risk of disease flares, profound fatigue, increased susceptibility to infections and declining renal function has remained unchanged over time. Cognitive dysfunction, joint deformities, avascular necrosis and osteoporosis have emerged as being particularly important in patients with long-standing disease. In patients who survive for over 10 years the management is directed not only at preventing death, but also at reducing the morbidity.

Continued progress in the field of SLE has led to the development and validation of outcome measures of disease activity and damage. The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Systemic Lupus Activity Measure, European Consensus Lupus Activity Measure and British Isles Lupus Assessment Group (BILAG) are the disease activity indices designed in an attempt to accurately monitor disease activity. Each, except BILAG, is a global score

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future medicine part of fsg

index. BILAG shows which organ/system is active 'at-a-glance' and is based on the principle of the physician's intention to treat. The Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage index (SDI) estimates organ damage and has been shown to be a useful prognostic indicator in SLE. Generic tools for assessment of health-related quality of life, such as short form-36, have been performed for SLE patients. These three elements, specifically, activity, damage and health status, now form the core assessments in new therapeutic trials and are being increasingly used in daily practice for the purpose of therapeutic judgements and prognostication.

The availability of biomarkers such as serum autoantibodies has helped in making an early diagnosis of SLE possible. A rising anti-dsDNA antibody and a falling C3 are the best predictors of a flare but are not perfect. An analysis of more conventional biomarkers, observed in our own cohort of 435 lupus patients is shown in **Table 1**. Other biomarkers such as antibodies to C1q and nucleosomes, complement breakdown products, soluble T-cell activation products, cell-surface markers of immunological activation and serum levels of various cytokines and adhesion molecules, have been investigated as potentially useful indicators of disease activity. Confirmation of their usefulness is awaited. Gene-expression profiling and proteomic approaches may eventually provide additional indices of disease activity. Increased interferon (IFN)-α-inducible gene expression is associated with disease activity, disease severity, low complement levels, presence of various autoantibodies and a higher SDI score [4]. Moreover, on the basis of levels of gene expression, IFN scores have been derived, which may prove to be useful biomarkers of therapy of lupus nephritis [5]. The glomerular proteome array promises to be a powerful analytical tool for uncovering novel autoantibody disease associations. Using a multiplex glomerular proteomic microarray bearing approximately 30 antigens known to be expressed in glomerular milieu, five distinct clusters of immunoglobulin (Ig)G autoantibody and two clusters of IgM autoantibody reactivity were identified in lupus sera. Two of the IgG clusters were associated with disease activity while IgM polyreactivity was associated with reduced severity of the disease [6].

Table 1. Prevalence of serological abnormalities in systemic lupus erythematosus clinic at University College Hospital, London, 1978–2006 (n = 435).

Autoantibody	Percentage
Antinuclear antibodies	96
Antidouble stranded DNA	70
Anti-Sm	14
Anti-RNP	28
Anti-Ro	38
Anti-La	14
Decreased C3	46
Rhematoid factor	27
Anticardiolipin (G)	25
Anti-cardiolipin (M)	10
Lupus anticoagulant	16
Coombs'	24
Antithyroglobulin	13
Antithyroid microsomes	14

RNP: Ribonucleoprotein.
Antinuclear antibodies/RF ≥ 1:80.

Etiology of SLE

The etiology of SLE is multifactorial. A combination of immunological, genetic, hormonal and environmental factors is thought to play a role.

Immune abnormalities

SLE is characterized by a loss of self tolerance, with both T and B cells critical to its development. The nature of the triggering antigen remains to be established. The etiology of various demonstrable immune defects remains unclear. Some of the immune abnormalities that have been described in SLE are discussed below.

T lymphocytes

T lymphocytopenia, a hallmark of SLE, results from an anti-T-cell antibody-dependent decrease in cells predominantly bearing the $CD4^+/CD45R^+$ phenotype (**Table 2**). Defects in Fas/Fas ligand (L)-mediated pathways result in acceleration of $CD4^+$ T-cell apoptosis [7]. $CD8^+$ T cells in lupus behave aberrantly by providing help rather than suppression of B cells. Nucleosome-specific self-reactive T cells have been described in lupus patients. These appear in lupus sera before anti-DNA antibodies. It is loss of peripheral rather than central tolerance mechanisms that results in the production of autoreactive T cells. In SLE, naturally occurring regulatory T cells (Tregs) are found to be diminished [8]. Another characteristic T-cell abnormality in lupus is the presence of $CD4^-$ $CD8^-$ (double-negative), nonclass II restricted

T cells expressing γδ T-cell receptor chains. These double-negative T cells help B cells to make pathogenic anti-DNA antibodies.

Abnormalities of the costimulatory pathways of T- and B-cell interactions involving CD28/B7 (CD80, CD86)/cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) or CD40 ligand (CD154)/CD40 have been documented in SLE. In their interaction through costimulaotry molecules with activated T cells, hyperactive B cells produce pathogenic antibodies. Increased plasma levels of soluble CD80, CD86, CD28 and CTLA-4 (CD152) were detected in a study of 79 SLE patients [9]. CTLA-Ig, an antagonist of the CD28/B7 interaction, has been shown to be effective in several murine models of lupus; trials in lupus patients are awaited to assess the efficacy in humans. Inducible costimulator (ICOS) is the third member of the CD28/CTLA-4 family and is involved in the proliferation and activation of T cells. It has been suggested that ICOS is involved in abnormal T-cell activation in SLE, and that blockade of the interaction between ICOS and its receptor may have therapeutic value in the treatment of this disease [10]. It has been established that T and B cells hyperexpress CD154 (CD40 ligand) in lupus. CD40 binding to CD154 is perhaps the most important costimulatory signal on B cells inducing activation, proliferation and class switching. Blocking the T-cell–B-cell interaction using anti-CD154 monoclonal antibody, however, was found to be no more effective than placebo in a randomized, controlled trial [11]. Another well-designed study of anti-CD154, which focused on lupus nephritis, showed improvement in serology and hematuria but was halted due to unexpected vascular complications [12].

Abnormalities in biochemical pathways as a consequence of primary T-cell signaling defects, for example as shown in **Table 2**, have been implicated as some of the mechanisms by which dysfunctional effector T cells contribute to the pathogenesis of lupus.

B lymphocytes

A central role for B cells in the pathogenesis of SLE has more recently gained prominence (**Table 3**). Altered development and function of B cells may play a prominent role. The most marked defect in SLE is the increase in numbers of activated B lymphocytes, resulting in the production of excessive autoantibodies. Checkpoint abnormalities in the development of the mature naive B-cell repertoire have been shown to result in persistent autoantibody production in SLE [13]. For example, the autoreactive B cells escape phagocytosis in germinal centers in lymph nodes, after which possible defects in apoptosis and/or complement deficiency lead to their prolonged survival. Autoreactive B cells through the expression of aberrant FasL are able to kill Fas positive immunoregulatory T lymphocytes and thus escape from the immune tolerance system [14].

Both antibody-dependent and -independent mechanisms of B cells are important in SLE. Suggested autoantibody-independent B-cell functions include antigen presentation, T-cell activation and polarization, and dendritic cell (DC) modulation. CD20 is a B-cell specific cell surface molecule of uncertain function. Rituximab, an anti-CD20 chimeric monoclonal antibody that specifically depletes B cells, has emerged as a promising therapy. Rituximab resulted in a marked and rapid improvement in global disease activity in 80 out

Table 2. T-cell abnormalities in systemic lupus erythematosus.

Cell type	Abnormality	Effects
$CD4^+/CD45R^+$	Reduced number	Reduced $CD8^+$ suppressor function
$CD8^+$	Aberrant function	Help to B cells than suppression
NK cells	Aberrant function	Help to B cells than suppression
Double negative T cells	Increased number	Help B cells for production of IgG
B7–2	Increased expression	Active disease
CD40 ligand	Increased expression	Increased B-cell activation
T-cell signaling	Impaired phosphorylation Reduced cyclic AMP Increased free intracytoplasmic calcium	Impaired apoptosis Reduced interleukin-2 production Reduced gene methylation leads to homing of T cells

Ig: Immunoglobulin; NK: Natural killer.

Table 3. B-cell abnormalities in systemic lupus erythematosus.

Cell type	Abnormality	Effects
B cells	Increased number of hyperactive B cells	Self-reactive IgG antibodies
B cells	Increased number of hyper-affinity B cells	High-affinity autoantibodies
B cells	Function as APCs	T-cell activation
B-cell signaling	Reduced FcγRIIB expression Reduced expression of Lyn protein Increased Expression of BLys	B-cell activation B-cell proliferation, increased anti-dsDNA, increased interleukin-10 Increased SLE activity, Increased anti-dsDNA
$CD1^+$ B cells	Early expansion	Lipid antigen presentation to T cells

APC: Antigen-presenting cell; BLys: B-lymphocyte stimulator; FcgRIIB: Fc receptor RIIB; Ig: Immunoglobulin; Lyn: lck/yes-related novel; SLE: Systemic lupus erythematosus.

of 100 patients with severe, refractory SLE [15]. Open, uncontrolled studies of rituximab (with or without cyclophosphamide) have shown favorable responses in a diverse array of disease manifestations in SLE [16,17]. Sfikakis and colleagues showed that clinical remission of lupus nephritis in their patients was associated with decreased T-helper cell activation; the findings favoring an antibody-independent role of B cells in disease promotion. Good tolerability of rituximab is reported with rare serious side effects. Moreover, repeat B-cell depletion by rituximab in case of relapse has been found to be safe and effective [18]. However, the efficacy and role of humanized anti-CD20 are still to be defined. Monoclonal antibody against CD22, another specific B-cell molecule, downregulates B-cell activity through negative signaling and also moderately depletes B cells. Treatment with epratuzumab (a humanized anti-CD 22) in an open-label trial of 14 patients with mild to moderate active lupus resulted in rapid and durable clinical benefit [19]. Synthetic molecules that bind to and crosslink autoantibodies, but do not contain T-cell epitopes, have the potential to be tolerogens. The first B-cell tolerogen (LJP 394), directed at anti-dsDNA responses, significantly decreased titers of high-affinity anti-dsDNA antibodies in human trials but overall had no clinically beneficial effect [20].

Activated nuclear factor-κB and mitogen-activated protein kinase signaling pathways in peripheral B cells of SLE patients suggest a role of signaling abnormalities in the pathogenesis [21]. Defects in Fc receptor (FcγR)IIB signaling, decreased expression of the protein tyrosine kinase lck/yes-related novel (Lyn) and increased serum levels of B-lymphocyte stimulator (BLyS) have been linked to abnormal B-cell signaling in active lupus. Mackay and colleagues have demonstrated an impaired expression of FcγRIIB, a negative regulator of memory B cell in SLE [22]. Altered expression of Lyn protein, a key negative regulator of B cell-receptor signaling, was associated with heightened spontaneous B-cell proliferation, anti-dsDNA autoantibodies and increased interleukin (IL)-10 production in SLE [23]. Accumulating evidence suggests that BLyS or B-cell activating factor (BAFF) is indispensable for proliferation, differentiation and survival of B cells. Increased levels of BAFF correlate with SLEDAI scores and anti-dsDNA antibodies [24]. Preliminary data on the treatment of SLE with belimumab, a fully human monoclonal antibody that specifically binds to BLyS or BAFF, are now available. Belimumab was well tolerated and significantly reduced disease activity in serologically active patients [25].

Accessory cells

A crucial role of antigen-presenting cells (APCs) has been suggested in SLE. Plasmacytoid DCs, which are natural IFN-α producing cells, are thought to play a pivotal etiopathogenic role in SLE. SLE patients have a reduced number of DC [26]. Monocyte-derived DCs in SLE were shown to exhibit a significantly reduced upregulation of major histocompatibiliy complex (MHC) class II molecules that correlated with disease activity [27]. In SLE, the number of apoptotic neutrophils is increased and monocyte/macrophage clearance of apoptotic cells is impaired. Abnormalities of the surface receptors for the Fc of IgG (FcγR) appear to contribute to the defective immune-complex clearance in SLE.

Autoantibodies

SLE is the autoimmune disease with the largest number of detectable autoantibodies. These autoantibodies, although predominantly targeting intracellular nucleoprotein particles, are

directed against a wide range of antigens, including cytoplasmic antigens, cell membrane antigens, phospholipid-associated antigens, blood cells, endothelial cells, nervous system antigens, plasma proteins, matrix proteins and miscellaneous antigens. The autoantibody frequencies, clinical associations and correlation with disease activity are described for more than 100 autoantibodies [28]. Detectable levels of antinuclear antibodies (ANAs) in serum are found years before clinical manifestations of SLE [29]. Development of the ANA has been linked to apoptosis. Ultraviolet light induces apoptosis in human keratinocytes, resulting in blebs of nuclear and cytoplasmic autoantigens on the cell surface. A failure to remove these apoptotic cells efficiently has led to a theory that lupus is a disease of waste disposal.

Antibodies against dsDNA are found in 70% of lupus sera and have been eluted from affected kidney and skin samples. High anti-DNA titers are virtually confined to SLE. Anti-DNA antibodies that can bind nucleosomes appear to be particularly pathogenic. Antinucleosome IgG antibodies appear earlier than dsDNA antibodies and may prove to be a more sensitive diagnostic marker of SLE [30]. High-affinity IgG anti-dsDNA antibodies are believed to be the major culprits in the pathogenesis of lupus nephritis and appear to deposit preferentially in the kidney through the mechanism of planted antigen. It is proposed that the circulating, noncomplexed, cationic anti-DNA antibodies bind to collagen Type IV and the heparin sulphate glycosaminoglycan component of glomerular basement membrane or to α actinin, an important structural renal protein [31].

Table 4. Complement abnormalities in systemic lupus erythematosus.

Complement	Abnormality	Effects
C1q	Greatly decreased	Severe SLE (glomerulonephritis and skin)
C2	Greatly decreased	Mild lupus (skin and joint)
C4	Greatly decreased	Mild lupus (skin and joint)
MBP	Defective allele	Decreased complement activation resulting in SLE in several ethnic groups
CR1	Decreased expression on red and white blood cells	Greatly decreased binding and transportation of ICs Correlates with activity
CR2	Decreased expression on T cells	Active lupus
CR2	Decreased expression on B cells	Highly activated B cells

CR: Complement receptor; IC: Immune complex; MBP: Mannose-binding protein; SLE: Systemic lupus erythematosus.

Complement

Inherited complement deficiencies are rare but occur with increased frequency in SLE (**Table 4**). Deficiency of C1q leads to lupus-like illness in 95% of cases, C4 in 57% and C2 in 10%. Homozygous C4A deficiency occurs in 10–15% of Caucasian lupus patients despite being rare in the healthy population. Partial C4A deficiency occurs in 50–80% of SLE patients, but only 10–20% of controls. Patients with homozygous C1q deficiency suffer from a particularly severe form of SLE with glomerulonephritis and skin manifestations, whereas complete C2 or C4 deficiencies are associated with mild lupus, limited to skin and joints. Several studies have demonstrated a link between anti-C1q antibodies (anti-C1q) and lupus nephritis [32]. Monitoring anti-C1q antibody titers in SLE patients could be important for predicting renal flares. Mannose-binding lectin (MBL), an acute-phase protein, facilitates complement opsonisation and activation. A recent meta-analysis showed that dysfunctional alleles of MBL result in reduced levels of serum MBL incurring increased risk of SLE [33]. The mechanisms that unite early complement deficiencies to pathogenesis of SLE are not entirely clear. Complement deficiencies interfere with the processing and clearing of immune complexes, clearance of apoptotic cells and help autoreactive B cells escape from negative selection. The levels of complement receptors 1 and 2 are also found to be altered in SLE (**Table 4**).

Cytokines

The aberrant cellular effector mechanisms seen in SLE are closely connected to the interaction of cells with their extracellular environment, which critically involves the cellular messengers, cytokines (**Table 5**). However, experiments and potential treatments that target a particular cytokine in isolation may not provide meaningful data since the cytokine network is inter-related and cytokines compensate for each other. The following is a simplified summary of the major findings in this area.

Interferon-α

It is now well accepted that IFN-α plays a critical role in the pathogenesis and perpetuation of SLE. Raised serum levels of IFN-α correlate with serological and clinical manifestations [34]. Enhanced production of IFN-α by DCs is dependent on Toll-like receptors [35].

Interleukin-10

IL-10 is a potent stimulator of B-cell proliferation and differentiation. Serum titers of IL-10 correlate positively with anti-dsDNA antibody titer and disease activity.

Interleukin-6

Via an autocrine route IL-6 is involved in maintaining B-cell hyperactivity. Unlike healthy controls, IL-6 receptors are constitutively expressed on B cells from lupus patients. Patients with lupus nephritis have an increased ratio of IL-6/soluble IL-6 receptor compared with controls. IL-6 protein and mRNA found in kidney biopsies from these patients indicate a local production.

Tumor necrosis factor-α

A genetic predisposition towards a strong tumor necrosis factor (TNF)-α response is protective against developing lupus nephritis. The ratio of TNF-α to its soluble receptor is significantly lower in SLE, suggesting a relative deficiency of active TNF-α in this disease. Treatment of rheumatoid arthritis patients with infliximab, a TNF receptor blocker, was associated with the development of anti-DNA antibodies in 16% of patients. Furthermore, 0.2% of those patients developed a lupus-like syndrome, with resolution of symptoms at treatment suspension [36]. Interestingly, treatment of six SLE patients with infliximab in a preliminary open-label study improved arthritis and proteinuria, albeit with a concomitant increase in circulating titers of anti-dsDNA antibody [37].

Interleukin-1

Accessory cells in lupus seem to produce insufficient amounts of IL-1 to provide the necessary activation signal for T cells. It is therefore likely that the actual defect exists either at the level of the IL-1 receptor on T cells or at a distal point in the biochemical pathway.

Table 5. Cytokine abnormalities in systemic lupus erythematosus.

Cytokine	Defect	Effects
IL-10	Increased serum levels	Decreased B7–1 expression leading to reduced APC function Decreased Th1 cells leading to impaired cell-mediated immunity Increased B-cell activation Acceleration of disease
IL-6	Increase in serum and CSF Increased mRNA in PBMCs Localized in nephritic kidneys	
IL-6 receptor	Increased expression on B cells	Increased antibody production
TNF-α	Decreased TNF-α/sTNFR ratio	Lupus nephritis
IFN-α	Increased serum levels Increased expression of type I IFN-inducible genes	Activation of immature dendritic cells Facilitation of B/T cell autoimmunity
IFN-γ	Functional defects, levels normal	Impairment of macrophage and NK cell-mediated cytotoxicity
IL-1	Decreased production	
IL-1 receptor	Decreased	Decreased T-cell responsiveness
IL-4	Increased secretion from antigen-primed T cells	
IL-12	Decreased	Especially in glomerulonephritis
IL-16	Increased	Correlates with disease activity
IL-17, IL-18	Increased	
TGF-β	Decreased	Impaired suppression of IgG production Associated with lupus nephritis

APC: Antigen-presenting cell; CSF: Cerebrospinal fluid; IFN: Interferon; Ig: Immunoglobulin; IL: Interleukin; NK: Natural killer; PBMC: Peripheral blood mononuclear cell; sTNFR: Soluble TNF receptor; TGF: Transforming growth factor; Th: T helper; TNF: Tumor necrosis factor.

Table 6. Abnormalities of adhesion molecules in systemic lupus erythematosus.

Adhesion molecule	Defect	Effects
E-selectin, VCAM-1, ICAM-1	Increased expression on dermal vessel endothelial cells	Correlates with cutaneous activity
sE-selectin, sVCAM-1, sICAM-1	Increased serum levels	Active lupus
ICAM-1, VLA-3	Increased glomerular expression	RPGN
E-selectin	Increased expression on glomerular and tubular epithelium	RPGN
VCAM-1	Increased expression on endothelium of interstitial vessels	RPGN
ICAM-1, VCAM-1	Increased expression in kidneys	Nephritis in MRL-lpr/lpr mice
LFA-1, VLA-4	Increased expression on peripheral lymphocytes	SLE with vasculitis
ICAM-1	Increased expression in keratinocytes on ultraviolet irradiation	Photosensitive lupus

ICAM: Intracellular adhesion molecule; LFA: Lymphocyte function-associated antigen; RPGN: Rapidly progressive glomerulonephritis; sICAM: Soluble ICAM; SLE: Systemic lupus erythematosus; VCAM: Vascular cell-adhesion molecule; VLA: Very-late antigen.

Interleukin-2

IL-2 generation is reduced in SLE and has a profound effect on T-cell responses. A defect of IL-2 functional activity remains a possibility. *In vitro* studies have indicated that $CD4^+$ subset in lupus expresses low-affinity IL-2 receptors. There is no alteration of IL-2 receptors on the $CD8^+$ T-cell subset in lupus; the $CD8^+$ cells fail to respond owing to lack of signal from $CD4^+$ cells.

Cell adhesion molecules

Adhesion molecules, classified into selectin, integrin and Ig supergene family groups, mediate the interaction between lymphocytes and vascular endothelial cells during homing and local retention of cells in the extracellular matrix. They are also involved in the interaction between APCs and T cells to ensure effective T-cell help or cytotoxic T-cell function. Some of the defects of adhesion molecules described in lupus patients are listed in **Table 6.**

Genetic factors

Lupus is inherited as a polygenic trait with added contributions from environment and random variance. The importance of genetic predisposition in SLE is evident from a higher concordance rate in monozygotic twins (25%) than in dizygotic twins (3%), increased frequency of lupus and immunological abnormalities in relatives of lupus patients and a preference for Black race. Afro–Caribbeans (1 per 250) are more frequently affected than Orientals (1 per 1000) who, in turn, are more frequently affected than Caucasians (1 per 4300). Linkage analysis studies have identified eight chromosomal regions; 1q23, 1q25–31, 1q41–42, 2q35–37, 4p16–15.2, 6p11–21, 12p24 and 16q12, exhibiting significant linkage to SLE. The pathogenicity of SLE may be influenced by inheritance of genes expressing complement mannose binding protein polymorphism, T- and B-cell receptor gene usage, expression of phagocyte Fcγ receptor alleles, polymorphisms of various cytokines and cytokine receptors, intracellular signaling molecules, gender, race and tissue type (human leukocyte antigen [HLA]). Abnormalities in receptor editing, somatic hypermutation, and positive and negative selection of the Ig variable region chain gene have been implicated in the fundamental alteration of the composition of the peripheral B-cell repertoire, resulting in autoimmunity in SLE [38]. Homozygous C1q deficiency is the strongest disease susceptibility gene for the development of SLE that has been characterized in humans. A single nucleotide polymorphism of program cell death 1 gene, within 2q35–37 locus, has been linked to SLE susceptibility [39]. Lupus genetics, however, is not dominated by the powerful effect of a single locus. No particular gene is necessary or sufficient for disease expression. Instead, each specific aspect of diverse SLE phenotypes is mostly controlled separately by a different set of susceptibility loci. A substantial number of genes (>10) are expected to be identified to contribute to lupus [40]. It has been demonstrated that HLA haplotypes are genetic risk factors for SLE in several ethnic populations. Interestingly, DR/DQ alleles show stronger association with the autoantibody profiles observed in SLE than with disease expression itself.

Hormonal factors

SLE occurs nine-times more often in females than in males, suggesting the importance of hormonal factors in disease pathogenesis.

Women with SLE have an abnormal estrogen metabolism, which results in an excess of 16-α-hydroxyestrone and estrol metabolites. The role of sex hormones may be related to their effects on immune responsiveness. Estrogen stimulates thymocytes, T cells, B cells, macrophages, the release of certain cytokines (e.g., IL-1), the expression of adhesion molecules and increased macrophage proto-oncogene expression, while progesterone downregulates T-cell proliferation and increases the number of CD8 cells, hence promoting autoimmunity. However, Copper and colleagues found little evidence for an association between estrogen- or prolactin-related exposures and an increased risk of lupus in a population-based case control study [41].

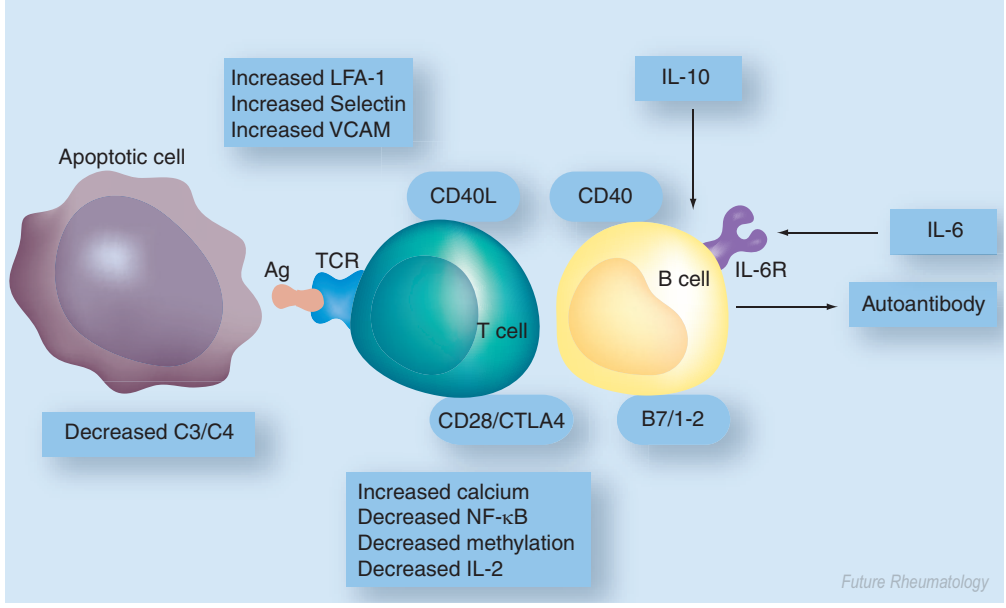
Environmental factors

Apart from the role of ultraviolet irradiation already described, a common, but unproven, hypothesis is that SLE is triggered by infectious agents, including viruses. Molecular mimicry of human endogenous retroviruses and Epstein–Barr virus nuclear antigen-1 to Sm and nribonucleoprotein leading to the generation of cross-reactive antibodies has been proposed as a potential mechanism for developing SLE [42,43].

Silica exposure has been associated with increased risk of SLE [44]. A case-controlled, population-based study from Sweden reports an increased risk of SLE with a number of factors including history of hypertension, drug allergy, a type I/II sun-reactive skin type, family history of SLE, smoking and blood transfusions [45]. Alcohol consumption has been associated with either an increased or decreased risk of SLE [45,46]. Procainamide or hydralazine, which are now rarely used, frequently caused a lupus-like condition (drug-induced lupus), which resolved once the drug was discontinued. Nowadays, a number of commonly used antihypertensive preparations, cholesterol-lowering agents and antibiotics, such as minocycline, cause drug-induced lupus in a small number of people who take them.

In conclusion, a simplified hypothetical model linking the complex interactions between various regulatory mechanisms and highlighting the role of the crucial pathogenic factors in SLE is shown in Figure 1. Apoptosis in SLE due to defects in macrophage-mediated clearance mechanisms (inherent or acquired) is associated with activation of DCs or the second-line effector scavenger cells. This, in turn, leads to necrosis of the apoptotic cells with a subsequent

Figure 1. Antigen-presenting cell, T- and B-cell interactions in the pathogenesis of lupus.



Ag: Antigen; CD40L: CD40 ligand; CTLA: Cytotoxic T-lymphocyte-associated antigen; IL: Interleukin; LFA: Lymphocyte function-associated antigen; NF-κB: Nuclear factor-κB; R: Receptor; TCR: T-cell receptor; VCAM: Vascular cell-adhesion molecule.

translocation of internal cellular antigens to the surface. In contrast to the normal state of health, self tolerance to these usually deep-seated autoantigens is circumvented by activated T and B cells in patients with SLE. Abnormalities in the function of costimulatory molecules, deficiency of complement, changes in cytokine profiles, activation of adhesion molecules and migration and homing of inflammatory cells exemplify this autoimmune process. The activated T cells provide help to autoreactive B cells, allowing the expansion of B-cell clones. These autoreactive B cells then bind and process any available multideterminant autoantigens and present novel self-peptides to further T cells. This whole process results in a positive feedback cycle of activation and expansion of the self-antigenic material to fuel the whole cascade.

Future perspective

An early diagnosis and risk stratification would help in identifying high-risk patients. Selection of therapeutic agent(s) would be guided by genetic testing so as to achieve maximum efficacy by targeting specific etiopathogenic mechanisms with the least side effects. Novel biomarkers would enable more accurate monitoring of disease. Genetic engineering would help aid the design and development of drugs with improved efficacy and a better safety profile. Patient input is expected to be increasingly incorporated in planning and designing of future research studies.

Executive summary

Striking improvements in the mortality rates in systemic lupus erythematosus over the last 50 years

- The present 5-, 10- and 15-year survival rates of 97, 92 and 87%, respectively, are a sharp contrast from the 5-year rate of 51% in the 1950s.
- This is due to a cumulative effect of early recognition, clinically useful diagnostic tests, advances in pharmacological and adjunctive therapies.

SLE-related morbidity is still a major challenge

- Disease- and therapy-related morbidities have a great impact on health-related quality of life.
- In patients surviving longer than 10 years, reducing morbidity is an integral part of the management.

Better clinical outcome measures for the assessment of disease activity & damage

- Validation of disease activity indices, such as Systemic Lupus Erythematosus Disease Activity Index, Systemic Lupus Activity Measure, European Consensus Lupus activity Measure and British Isles Lupus Assessment Group, have been designed in an attempt to accurately monitor disease activity.
- Organ damage should be assessed by the Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index.
- Usefulness of assessing health-related quality of life using short form-36 in SLE.

Role of biomarkers in predicting disease exacerbation

- Anti-double stranded DNA titers and complement levels, the biomarkers in current use are unable to predict flares in all patients.
- Extensive research is required to address the putative usefulness of numerous potential biomarkers.
- Gene expression profiling and proteomic approaches may mark a turning point.

Etiopathogenesis

- A complex interplay of several defects in T cells, B cells, autoantibodies, apoptosis, complement, cytokines, cell-adhesion molecules, genetic, hormonal and environmental factors.

Conclusion

- Short-term mortality in lupus has greatly improved but long-term survival with accompanied risk of significant morbidity still remain a major challenge.
- Better understanding of pathogenic mechanisms has opened the avenues for targeted therapies in lupus (e.g., B-cell depletion and modulation).

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Affiliations

- *Gayatri Mittal, Specialist Registrar of Rheumatology*
  University College Hospital, 235 Euston Road, London, NW1 2BU, UK
  Tel.: +1 845 155 5000 ext. 3710;
  Fax: +1 207 380 9278;
  gayatri.mittal@uclh.nhs.uk
- *Lesley Mason, Postdoctoral Fellow*
  Centre for Rheumatology Research, Division of Medicine, Windeyer Building, 46 Cleveland Street, London, W1T 4JF, UK
  Tel.: +44 207 679 9704;
  Fax: +44 207 679 9143;
  l.mason@ucl.ac.uk
- *David Isenberg, Professor, Academic Director of Rheumatology*
  Centre for Rheumatology Research, Division of Medicine, Room 331, 3rd Floor Windeyer Building, 46 Cleveland Street, London, W1T 4JF, UK
  Tel.: +44 207 679 9252;
  Fax: +44 207 679 9143;
  d.isenberg@ucl.ac.uk