

Aetiology and pathology of SYSTEMIC LUPUS ERYTHEMATOSUS

By C. SILVA, M D, and D. A. ISENBERG, M D, FRCP

Systemic lupus erythematosus is the subject of this month's special feature. In this article, the authors discuss the aetiology and pathology of the disease

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease characterised by widespread inflammation affecting virtually every organ or system in the body. The disease is associated with the deposition of autoantibodies and immune complexes, leading to tissue damage.

It has a multifactorial aetiology and affects mainly women during the childbearing years. The various factors include genetic, hormonal and environmental components. As in any autoimmune condition, it is believed that the presence of susceptibility

genes in a predisposed individual can be triggered by an initial stimulus (probably environmental) which enables a certain critical threshold to be attained, leading to the development of clinical features. This pathway incorporates the perturbation of the immune response involving polyclonal B cell activation and excessive T cell help.

The precise immune disturbances leading to the development of SLE remain unknown, although various clues have been provided by studies of animal models.¹ Current research involves attempts to understand the process of production of pathogenic autoantibodies and the roles played by cytokines, adhesion molecules and apoptosis.

The understanding of SLE immunopathology is essential to improving how patients are treated. The treatment

methods are non-specific and prone to causing serious side effects. An overview of the factors involved in the aetiopathogenesis of SLE is presented below.

GENETIC FACTORS

The higher rate of the disease seen in monozygotic twins (25 per cent) compared with dizygotic twins (3 per cent), the increased frequency of lupus and other immunological disorders in relatives of lupus patients compared with healthy controls, and the higher prevalence of SLE in certain ethnic groups, leads to the suggestion that genetic factors play a role in the pathogenesis of SLE.

Recent studies have shown that there is a complex genetic trait to the susceptibility of this disorder, with contributions from the

Dr Silva is research fellow and Professor Isenberg is professor of rheumatology at the Centre for Rheumatology, Department of Medicine, University College, London

major histocompatibility complex (MHC) genes and many other genes, which regulate apoptosis (see below), cytokines, immunoglobulin production and antigen presentation. Genetic complexity in polygenic diseases is mostly related to the low penetrance of each contributing gene, that is, to the increase in probability of disease expression given a particular allele.²

The ethnic background in SLE shows a bias, with more Afro-Caribbeans (1:250) being affected than Orientals (1:1000) and Caucasians (1:4300). The black race is an independent risk factor for developing SLE. African-Americans and Afro-Caribbeans living in the United States and the United Kingdom have the greatest risk of developing SLE. They also develop the disease earlier in life, and have an increased frequency and severity of renal pathology. Also of note and not satisfactorily explained, is the fact that SLE is rare in native Africans.³ A study in Birmingham demonstrated major differences in the incidence and prevalence rates of SLE in the UK depending on ethnic group. The observed prevalence in females was 206:100,000 among Afro-Caribbeans, 91:100,000 among Asians and 36:100,000 among Caucasians. These results were irrespective of place of birth.⁴

MHC

The association between certain class II MHC complex genes and SLE has been known for a long time. Human leucocyte antigen (HLA)-specific associations have been shown to increase the risk for SLE, and the expression of antibodies and clinical subtypes.^{2,5} The presence of HLA-DR2 and HLA-DR3 confers a two- to three-fold increase in risk in Caucasians, while in African-Americans it is the presence of HLA-DR2 and HLA-DR7.

The contribution of class II MHC genes in SLE is predominantly at the level of production of specific antibodies, as shown in Table 1.

Other MHC-associated genes linked with susceptibility to SLE include the C4 null allele, and the polymorphic region of the class III gene encoding for tumour necrosis factor- α (TNF α), but to date, the studies have been inconclusive in determining strong disease susceptibility.

NON-MHC ALLELES

Complement is a substance that is normally present in serum and is destructive to some bacteria and other cells which have been sensitised by specific complement-fixing antibodies. Deficiencies in the components of the classical pathway of complement (C1q, C1r, C1s, C2 or C4) are major predisposing factors for SLE. The most powerful disease susceptibility factor for lupus-like disease in humans is the

homozygous deficiency in Clq, and more than 90 per cent of individuals with this condition are affected.

Complement proteins play a vital role in the processing and clearing of immune complexes. Complement deficiency may be important in mediating clearance of antigenic material from apoptosis and therefore promoting the formation of antibodies against intracellular antigens, particularly when the system is overloaded, for example after ultraviolet light (UV) exposure or during infection. Mannose-binding lectin (MBL) is a serum protein with characteristics very similar to those of Clq, which is associated with increased risk of infection. An association with homozygous MBL variant alleles was found in SLE patients with renal involvement (86 per cent) as well as an increase in hospitalisation because of complicated infection (71 per cent for homozygous versus 20 to 24 per cent for other patients). A weak association with MBL deficiency and predisposition for SLE was also observed.⁶

Polymorphisms in low affinity IgG (Fc γ) receptors, which are important to the clearance of immunocomplexes, have also been found.⁷

LINKAGE STUDIES

One of the approaches to understanding SLE genetics, aiming to identify the loci responsible for the development of the disease, has been the genome screen of SLE families. To date there have been three American studies with a total of 455 sibling-pair families (Minnesota cohort I and 2, Oklahoma and Stanford).⁸⁻¹¹ Data from the studies support the hypothesis that there is not a single locus that contributes to disease susceptibility in these families, but the goal is to eventually identify major genes predisposing to SLE.

AUTOANTIBODIES

The serological hallmark of SLE is the presence of circulating autoantibodies against a multiplicity of nuclear, cytoplasmic and plasma membrane antigens. These antibodies bind to a variety of macromolecules, including DNA, ribonucleic protein (RNP) and other proteins, as well as to complexes comprised of both protein and nucleic acid. They predominantly target intracellular nucleoprotein particles, with 94 per cent of patients having antinuclear antibodies (ANA). Approximately 60 per cent of these have antibodies against native double stranded DNA (dsDNA) as shown in Table 1. The presence of these antibodies in high titres is virtually confined to SLE, and represent markers of diagnostic and prognostic significance.

Over 50 per cent of patients also have antibodies to histones and denatured single

stranded DNA (ssDNA). There are many other antibodies that have been identified in the serum of patients with lupus. Some have linked unequivocally to the pathogenesis of SLE, though the anti-Smith (anti-Sm) antibody is a diagnostic marker.

Origin The origin of a wide range of autoantibodies in patients with SLE remains controversial. Anti-DNA antibodies have been the most studied because of their pathogenicity and almost invariable expression in animal models. Their origin is still a matter of debate, since mammalian DNA is poorly immunogenic.¹² The question of whether the antibodies to dsDNA present in patients with SLE are antigen-driven responses or derive from a pool of germline gene-encoded natural autoantibodies which have undergone mutation, is still under research.

Murine models of SLE have a background of polyclonal B cell activation but the autoantibodies from human SLE patients are thought to have probably arisen as the result of antigen-driven T cell response.

Epitope spreading is another hypothetical mechanism by which the generation of multiple autoantibodies could arise. This theory suggests that once immunological tolerance to one component of a particular antigen is "broken", the immune response can diversify, allowing the recognition of new epitopes within the complex. However, these results were not confirmed by other groups¹⁹ and the role of epitope spreading in human disease remains uncertain.

Pathogenic role Although the association of ANAs and SLE is very strong, their role in

Table 1: SLE antibodies*

Antibody	% of patients
ANA	94
Anti-Sm	9
Anti-RNP	21
Anti-Ro	32
Anti-La	12
Anti-dsDNA	60
Decreased C3	40
Rheumatoid factor (RF)	20
Anti-cardiolipin (IgG)	25
Anti-cardiolipin (IgM)	13
Lupus anticoagulant	14
Coombs	18
Anti-thyroglobulin	10
Anti-thyroid microsomes	13

ANA (antinuclear antibody) was considered positive if present to a titre of $\leq 1:80$; RF (rheumatoid factor) was also considered positive if present to a titre of $\leq 1:80$

*These data are based on 300 patients attending the University College/Middlesex hospital lupus clinic (1978 to 2000)

Table 2: Autoantibodies associated with clinical subsets of SLE

Antibody specificity	Clinical association
dsDNA	Renal, cardiovascular and respiratory disease
Ro	Sjögren's syndrome
La	1/20 lupus pregnancies result in neonatal lupus syndrome: congenital heart block/cutaneous erythematous photosensitivity (Ro)
Sm (Spliceosome)	SLE-specific Association with ethnic origin (5 to 10 per cent of Caucasians, up to 30 per cent of Afro-Caribbeans)
U1 RNP	Mild disease
RA33	Erosive arthritis (non-Caucasians)
Hsp 90	Cardiovascular or respiratory disease (30 per cent of patients)
Ribosome P	Link to lupus psychosis is controversial (15-35 per cent of patients)
Phospholipids and cardiolipin	Venous and arterial thromboses, miscarriage, livedo reticularis, thrombocytopenia and cerebral disease
Complement (C1q)	Rising titres indicative of proliferative glomerular nephritis
Histones	Drug induced lupus (70 per cent of patients)
Red cells and platelets	Haemolytic anaemia and idiopathic thrombocytopenic purpura respectively

pathogenicity remains uncertain. This is due to a number of factors, including the number of autoantibodies and the clinical diversity of SLE. These can be seen in Table 2.

Although other antibodies, including anti-Ro and anti-Clq, have been identified in renal lesions, most attention has focused on dsDNA antibodies as instigators of kidney disease. The pathogenicity of these antibodies is suggested by the correlation of anti-DNA levels and the activity of nephritis: the isolation of anti-DNA from the glomeruli of affected kidneys, the induction of nephritis in normal mice by administration of monoclonal dsDNA,¹³ and similar studies in SCID (severe combined immunodeficient) mice, using human monoclonal anti-dsDNA antibodies. Nephritogenic antibodies are usually of the IgG1 and IgG3 subclasses. The pathogenic potential of renal-localised IgG is largely attributed to effector functions determined by constant-region domains that contain the binding site for Fcγ receptors.¹⁴

Several mechanisms of immune deposition may account for lupus nephritis. Three possible hypotheses have been described for this localisation: circulating immune complex, cross-reactive antibodies and the planted antigen theory.¹⁵⁻¹⁷

Deposition of circulating immune complexes was the first to be described as a likely mechanism, but there has been less enthusiasm over this hypothesis in the last decade. Recent work, however, has shown that some nuclear antigens targeted by lupus antibodies have an intrinsic affinity for particular glomerular basement membrane (GBM) or cell surface constituents and these interactions may mediate renal localisation. Further studies have confirmed that preformed

immune complex containing DNA, DNA-binding proteins and autoantibody, selectively bind to the glomerulus.¹⁴

The premise of the cross-reactive antibody hypothesis is that anti-DNA antibodies are broadly reactive, binding a wide array of molecules such as GBM components. This theory is a variant on the molecular mimicry theme, but it is thought that the polyreactivity of antibodies is less likely to occur than binding to their cognate antigen.

Several observations have led to a general consensus that *in situ* immune complex formation (planted antigen) is likely to be the main mechanism for antibody deposition. Glomerular deposits may form *in situ*, either through direct binding to intrinsic renal antigens or autoantibody reactivity with a planted self antigen.

Another potential mechanism is the alteration of cell function induced by intracellular localisation of autoantibodies. Although once thought to be highly controversial, there are a number of *in vivo* studies suggesting that anti-DNA, anti-U1 RNP and anti-ribosomal P antibodies can penetrate living cells and could produce renal disease by intracellular effects, such as inducing loss of tolerance to self by modification of apoptotic events.¹⁸

Recent *in vitro* work has demonstrated that monoclonal anti-dsDNA antibodies from a particular strain of mice penetrate live renal tubular cells. Site-directed mutants showed that some residues of the variable region of an antibody are necessary for DNA binding, suggesting that antibody penetration depends on a membrane determinant resembling DNA.¹⁹

Murine monoclonal antibodies can penetrate cells and cause pathological abnormalities.²⁰

The mechanisms by which the antibodies produce renal injury are through recruitment of inflammatory mediators with activation of the cytokines and complement cascade which leads to dysregulation of cell function.

CELLULAR ABNORMALITIES

In SLE, several functional defects have been recognised among the cells of the immune system, including T and B lymphocytes, natural killer (NK) cells and accessory cells (known as antigen presenting cells or APCs). The consequence of this is the breakdown of immunological tolerance through the reversal of clonal energy, activation of self-reactive autoaggressive T cells and defective T cell suppression.

The numbers of circulating lymphocytes, from both T and B cell populations, are extremely variable and relate to disease activity and duration.^{5,21}

The most marked defect in SLE is the increase in numbers of activated B lymphocytes which contributes to the hypergammaglobulinaemia associated with reactivity to self antigens. There is also an increase in interleukin-2 (IL-2) receptor levels on circulating B cells, while expression of CR1 receptor is decreased.

The increase in B cells is accompanied by T lymphocytopenia, especially of cells bearing the CD4⁺/CD45R⁺ phenotype. This population of cells "helps" to induce suppression by providing a signal to the CD8⁺ (suppressor) cells and the reduction in this subset may contribute to the failure of the T cells to suppress the hyperactive B cells. Anti-lymphocytic antibodies may play a role in the depletion of this cellular subset. The titre of anti-T cell antibodies correlates with both disease activity and the level of T cell killing, with flares in disease being associated with increased CD4/CD8 killing, while remission is associated with a decrease.²² CD8⁺ cells and NK cells may behave aberrantly by providing help, rather than suppression, to B cells and hence stimulating production of autoantibodies.

It may be that patients with lupus have a primary T cell signalling disorder and that T cell dysfunction is a by-product of abnormal biochemical pathways, resulting in altered regulation of effector function.^{21,23}

CYTOKINES

Cytokines (soluble substances secreted by cells which have a variety of effects on other cells) have been implicated in regulating disease activity and the involvement of different organs in SLE. Rather than determine disease susceptibility, the cytokine profile changes with the different disease phenotypes and severity of the disease.

T helper (Th) cells can be divided into different subsets depending on their

Table 3: Role of cytokines in SLE

Cytokine	Clinical and experimental observations
IL-10	Increased in sera of patients with SLE. Suppresses Th1 cells and impairs cell-mediated immunity Increased production by macrophages and B cells, leading to defective B7-1 expression, leading to a reduction in APC function Increased B cell function and increased production of pathogenic autoantibodies, by autocrine pathway Anti IL-10 blocks anti-DNA antibody production by peripheral blood mononuclear cells (PBMCs) from lupus patients in SCID mice (Anti IL-10 delayed disease onset and increased TNF α production in the New Zealand black and white mice murine model) Disease severity correlates with increased ratio of IL-10: IFN γ secretion in lupus PBMCs
IL-4	Increased secretion by antigen-primed cells
IFN γ	Decreased production in patients with lupus, leading to impaired macrophage and NK cell-mediated cytotoxicity Recombinant IFN γ therapy side effect: autoantigen expression and anti-ssDNA and anti-dsDNA production
TNF α	Protective role in lupus. Produced by Th1 cells, B cells, NK cells and mononuclear phagocytes MHC linked production: Increased TNF α seen in haplotypes DR3 and DR4 associated with a low incidence of lupus nephritis Decreased TNF α seen in haplotypes DR2 and DqW1 associated with lupus nephritis
IL-1	Decreased production in patients with lupus. T cells unresponsive, possibly due to defective IL-1 receptor
IL-6	Increased levels in sera and cerebral spinal fluid of patients with lupus. Localised in nephritic kidneys Increased mRNA in PBMCs from patients. B cells have increased IL-6R and spontaneously produce IL-6 (autocrine) and increased antibody production
IL-2	Decreased <i>in vitro</i> CD4 and CD8 proliferative response to mitogens/foreign antigens Decreased T cell maturation and decreased CD8 suppressor function. CD4 cells have low affinity IL-2 receptors

cytokine profile. Th1 cells increase macrophage activation and produce IL-2, interferon gamma (IFN γ) and TNF α . Th2 cells stimulate antibody production and upregulate immune humoral and allergic responses. They produce IL-4, IL-5, IL-6, IL-10 (in mice) and IL-13. Th3 cells are regulatory cells that can act to induce immune tolerance and characteristically produce transforming growth factor beta (TGF β), IL-4 and IL-10. Th0 cells can produce cytokines of all three types.²⁴ The pattern of cytokine production in different disease states may be described as a Th1, Th2 or Th3 response, based on the cytokines produced. Recent experimental observations suggest a key role for IL-10 in the pathogenesis of SLE²⁵ as it has a particular ability to encourage B cells to make antibodies.

A synopsis of the function of cytokines in SLE is summarised in Table 3.

— APOPTOSIS

The dysregulation of programmed cell death (apoptosis) has been shown to be part of numerous human diseases, particularly the autoimmune disorders.²⁶

As a consequence of apoptosis, nuclear structures are brought to the surface of the dying cells within "blebs" and become exposed to the immune system. Because apoptosis is thus the source of nucleosome production it has been suggested that programmed cell death could be increased in SLE, leading to an increase in nucleosome release. Indeed, lymphocytes of both SLE patients²⁷ and lupus mice have been shown to undergo an increased rate of apoptosis.²⁸

Apoptotic defects involving at least two genes, Bcl-2 and Fas, have been extensively investigated in the pathogenesis of SLE. Bcl-2 is a proto-oncogene located on the inner

mitochondrial membrane. Bcl-2 is unique among oncogenes in that it promotes lymphoid cell survival by interfering with apoptosis rather than by inducing cell proliferation. The Bcl-2 gene product exerts a regulatory function on adult tissues by preventing apoptosis of specific cell types. It is involved in T cell development and thymic selection, and is also found in long lived B cells within the follicular mantle zone. There is now considerable evidence that Bcl-2 expression is enhanced in a proportion of peripheral T cells, but not in B cells, of SLE patients, and that Bcl-2 levels correlate with overall disease activity.²⁹ Transgenic mice with B cells expressing Bcl-2 show prolonged B cell survival, production of autoantibodies and prolonged B cell memory. In addition, clonal deletion of self-reactive B cells is inhibited. These mice, on an appropriate genetic background, can develop anti-DNA, anti-Sm antibodies and glomerulonephritis.³⁰

Fas (Apo-1/CD95) is the surface cell protein responsible for induction of apoptosis in lymphocytes through induction of several signalling pathways. The Fas receptor (FasR) is found at very low levels on normal resting peripheral T and B cells, but is upregulated on activated cells, which undergo apoptosis if they are not re-stimulated by antigen. Three independent mutations of the FasR or its ligand (FasL) have arisen in three different mouse strains. Mutations in either the Fas gene (1pr) or the gene for FasL (C3H gld) result in FasL expressing cytotoxic T cells, which fail to remove autoreactive B cells, resulting in overproduction of antibodies.³¹ Elevated levels of a soluble form of Fas (sFas) have been described in the plasma of 30 per cent of patients and related with a specific HLA profile.³² Unlike the murine models, a quantitative abnormality of the Fas

molecule has only sporadically been found in SLE patients: 1 in 75 patients had a defect in the FasL molecule.³³ However, in 143 patients screened, no mutations or polymorphisms of the FasL gene were found, suggesting that a FasL defect is not a major contributor to the pathogenesis of SLE in humans.³⁴ It is now evident that patients with SLE lack major abnormalities in Bcl-2 and Fas expression. Furthermore, it has been suggested that the problem in lupus patients is not apoptosis itself, but rather the inefficient removal of apoptotic material.³⁵ Thus, the potentially immunogenic nucleosome material (perhaps altered in some way) is exposed to the immune system for much longer than normal.

— CELL ADHESION MOLECULES

Leucocyte adhesion is regulated by changes in the expression and avidity of adhesion molecules (selectin, integrin and immunoglobulin supergene family groups). These molecules mediate the interactions between lymphocytes and vascular endothelial cells during the inflammatory and autoimmune response. They also play an important role in the interaction between APCs and T cells, ensuring effective T cell help or cytotoxic function.

In SLE, E-selectin, leucocyte function associated molecule-1 (LFA-1)/intercellular adhesion molecule-1 (ICAM-1) and very late antigen-4 (VLA-4)/vascular cell adhesion molecule-1 (VCAM-1) appear to provide the predominant adhesive interactions at inflammatory sites.^{36,37}

Ng *et al*³⁸ described an intracellular signalling defect associated with a β 1 integrin and autoantibody production in 20 per cent of SLE patients studied. Skin biopsies from lupus patients show upregulation of surface

expression of E-selectin, VCAM-1 and ICAM-1 on dermal vessel endothelial cells. Levels of adhesion molecules directly correlated with disease activity and in several cases decreased with clinical improvement. These adhesion molecules are also found to be elevated in skeletal muscle with perivascular infiltrates compared with controls. E-selectin is increased even in the absence of perivascular infiltration. Increased glomerular expression of ICAM-1, and also VLA-3, has been found in patients with SLE who had rapidly progressive glomerulo-nephritis. These patients also express elevated levels of E-selectin on glomerular and tubular epithelium, and VCAM-1 is upregulated on the endothelium of interstitial vessels. A summary of the distribution, function and ligands of adhesion molecules is found in Table 4.

SEX HORMONES

SLE is predominantly a disease of females, particularly during their reproductive years. The female to male ratio is 9:1 in adult years. Prior to puberty, the ratio of females to males is lower (approximately 3:1) and after menopause the ratio also falls. Androgens are known to be immunosuppressive and oestrogens are immunoenhancing. Abnormal oestrogen metabolism has been described in women with SLE. This results in an excess of 16 α -hydroxyestrone and estrone metabolites, with chronic hyperestrogenism. Sex hormones might stimulate the central nervous system

to release immunoregulatory peptides, affect monocyte/macrophage systems and thus their cytokines, or cause release of other immunomodulatory hormones. The anterior pituitary hormone prolactin has been found to be immunostimulatory in SLE and has been reported to be elevated in several studies of both male and female patients.³⁹ Oestrogens have also been shown to increase the spontaneous production of antibodies in mice, while testosterone treatment reduces lupus symptoms. When a pregnancy occurs during active SLE, rising oestrogen levels may possibly cause exacerbation of the clinical disease, although the data are conflicting. Oestrogen has been shown to decrease *in vitro* apoptosis of peripheral blood mononuclear cells (PBMC) from women with SLE and this may be a mechanism allowing increased cell survival in patients. Levels of TNF α were also decreased in oestrogen treated cultures.⁴⁰ A recent study revealed that 17 β -estradiol increases the total IgG production, in PBMC, in normal donors but does not induce dsDNA production. In PBMC of SLE patients an increase in dsDNA production was found, but patients with less active disease showed a less pronounced increase.⁴¹ An interdependence of the neuroendocrine and immune systems, involving many different hormones, has been observed in recent years.³⁹

INFECTIOUS AGENTS

A common but still unproven hypothesis is that SLE, and other autoimmune dis-

eases, are triggered by infectious agents including viruses.⁴²

Co-immunisation with virus-self complexes has been shown to be a possible mechanism capable of breaking tolerance and generating autoimmunity.⁴³ Healthy mice were immunised with complexes of murine intracellular protein, p53, and simian virus large T antigen (SVT); anti-p53 autoantibodies were generated which could subsequently be elicited using p53 alone. This is consistent with the idea that once tolerance is broken, self antigen can perpetuate the autoimmune response. It is hypothesised that cryptic epitopes of self antigen, against which the host is not tolerised, are exposed due to altered processing of the p53 due to its association with SVT or anti-p53 antibody.

Using the technique of epitope mapping, antigenic epitopes of Sm and native RNP (nRNP) autoantigens have been identified. Researchers have found a striking similarity between these regions and antigenic peptides derived from Epstein-Barr virus nuclear antigen (EBNA-1), suggesting a possible role for these agents in the aetiology of lupus.⁴⁴

Anti-dsDNA antibodies have been shown to be inducible by polyoma virus BK in lupus-prone mice. The trigger of SLE by immunisation has also been reported in humans, with different types of vaccines being implicated.⁴⁵

Recently, James *et al*⁴⁶ have shown a highly significant increased prevalence of Epstein-Barr virus infection in young patients with lupus compared with controls. This may thus prove to be an important trigger.

THE ENVIRONMENT

UV radiation has been shown to trigger and exacerbate the photosensitive lupus rash, but there is also evidence that UV light may actually be capable of altering the structure of DNA, leading to the genesis of autoantibodies.

UV light has also been shown to induce apoptosis in human keratinocytes, resulting in blebs of nuclear and cytoplasmic autoantigens on the cell surface. This provides a mechanism whereby nuclear antigens, which are frequent autoantibody targets, can reach the cell surface. Antihypertensive drugs, among others, have been shown to give rise to drug-induced lupus. However, this disease is associated with antibodies to ssDNA and histones rather than dsDNA. Although skin and joint disease are common, renal or CNS pathology is virtually unknown and the disease is reversed on curtailment of the drug involved.⁵

Table 4: Adhesion molecules

Family	Member	Cell	Ligand	Function
Selectins	ELAM-1	Endothelial	Leucocyte surface carbohydrate	Inflammation, leucocyte extravasation
	CD62	Platelets	?	T-cell recruitment to inflammatory sites
	LECAM-1	T and B cells	?	Polymorphonuclear cells, lymphocytes and monocytes binding to endothelium
Integrins	LFA-1	Lymphocytes, polymorphonuclear cells, monocytes, macrophages	ICAM-1,2,3	T-cytotoxic cells or target cells, antigen-specific T-cell proliferation, leucocyte adhesion to endothelium
Immunoglobulins supergene	ICAM-1	Monocytes, endothelial cells, CD43	LFA-1, MAC-1	T-T, T-B, T-APC interactions. Induced by IFN, IL-1, TNF
	VCAM-1	Endothelial cells, tissue M	VLA-4	Leucocyte recruitment

Key: ELAM = endothelial leucocyte adhesion molecule, CD = cluster differentiation, LECAM = leucocyte adhesion molecule. LFA = leucocyte function associated molecule, ICAM = intercellular adhesion molecule, MLR = mixed lymphocyte reaction, VCAM = vascular cell adhesion molecule, VLA-4 = very late antigen-4

Table 5: Clinical features of SLE

Feature	ACP (percentage)*	Feature	ACP (percentage)*	Feature	ACP (percentage)*
Musculoskeletal:		Gastrointestinal continued:		Cerebral continued:	
Arthralgia/arthritis	90	Ascites	< 10	Meningitis	1
Tenosynovitis	20	Abdominal pain	30	Migraine	40
Myalgia	50	Hepatomegaly	25	Haematological:	
Myositis	5	Splenomegaly	10	Anaemia (iron deficiency)	30
Cardiopulmonary:		Renal:		Anaemia (of chronic disease)	75
Shortness of breath	40	Haematuria	10	Autoimmune haemolytic anaemia	15
Pleurisy	35	Proteinuria	60	Leucopenia	60
Pleural effusion	25	Casts	30	Lymphopenia	60
Lupus pneumonitis	5	Serum albumin < 35g/L	30	Thrombocytopenia	25
Interstitial fibrosis	5	Serum creatinine > 125 µmol/L	30	Circulating anticoagulants	15
Pulmonary function abnormalities	85	Reduced 24-hour creatinine clearance	35	Dermatological:	
Cardiomegaly	20	Cerebral:		Butterfly rash	40
Pericarditis	15	Depression	15	Erythematous maculopapular eruption	35
Cardiomyopathy	10	Psychosis	15	Discoid lupus	20
Myocardial infarction	5	Seizures	20	Relapsing nodular non-suppurative panniculitis	< 5
Gastrointestinal:		Hemiplegia	10	Vasculitic skin lesions	40
Anorexia	40	Cranial nervous lesions	10	Livedo reticularis	20
Nausea	15	Cerebellar signs	5	Purpuric lesions	40
Vomiting	< 10			Alopecia	70
Diarrhoea	< 10				

* ACP: the approximate cumulative prevalence as a percentage

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CLINICAL FEATURES

Probably the most common symptom in SLE is undue fatigue. This can often be marked, without evidence of involvement of any particular organ. Unstable SLE may also be characterised by unexplained weight change.⁴⁷

Table 3 shows the clinical features of SLE and their approximate cumulative prevalence (ACP).

SUMMARY

SLE is a complex autoimmune rheumatic disease whose aetiology is multifactorial, involving hormonal, genetic and environmental factors. In order to improve the treatment currently available for SLE, there is a continuing need to improve our understanding of its cause. In particular, much greater understanding of the precise antigenic targets and knowledge of the long term drive to produce antibodies are needed. Although lupus no longer carries the same "death threat" as it did 50 years ago, it continues to cause considerable morbidity for many patients.

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