Systemic Lupus Erythematosus

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Abstract

Systemic lupus erythematosus is a complex multisystem autoimmune disorder with a heterogeneous presentation and clinical course. The pathogenesis is multifactorial with evidence of genetic susceptibility, environmental triggers, and aberrancy in both the innate and adaptive immune systems. Although significant therapeutic advances have been made in recent decades, there remains a significant increase in mortality, highlighting the need for further understanding of the underlying immune mechanisms.

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune rheumatic disorder with a diverse presentation and clinical course. It is most prevalent in females of childbearing age with a female:male ratio of 9:1 in this population. The prevalence of SLE is also higher in certain ethnicities, reflected in prevalence rates of ~40/100 000 persons in Northern European cohorts in comparison with rates of 200/100 000 persons in studies of patients of African-American descent (Johnson et al., 1995). In addition to the higher disease frequency in this population, patients of Afro-Caribbean and Hispanic origin have also been observed to have an adverse clinical course. Recent studies also support the need for closer monitoring in patients with a juvenile onset of disease and males with SLE, both phenotypic factors that portend the potential for an adverse clinical course (Amaral et al., 2014).

Despite marked improvements in the therapeutics of SLE, there remains a significantly increased mortality in patients diagnosed with SLE. While in the 1970s a standardized mortality rate (SMR, which defines how many persons, per thousand of the population, will die in a given year) of 12.6 was noted in one large study of a cohort with SLE, reassessment of the same population within the last decade reported an SMR of 3.46 (Bernatsky et al., 2006). Although this indicates significant therapeutic advances, it should be highlighted that SLE is a condition that tends to affect a young female population making this statistic all the more clinically relevant. Further understanding of the pathophysiology of the disease with the ultimate goal of identifying unique therapeutic targets is required to further improve the prognosis of individuals with SLE.

Clinical Features

SLE is a condition with a diverse array of clinical features characterized by periods of flare and remission. Its presentation is highly variable and clinical findings are supported by laboratory evidence of autoimmunity. The majority of patients with lupus (>95%) have circulating antinuclear antibodies (ANA) and almost two-thirds also have circulating antidouble-stranded DNA (anti-ds-DNA) antibodies. Other autoantibodies commonly observed in SLE include anti-Ro, anti-La, and anti-Sm antibodies. Other relevant laboratory findings include hypocomplementemia, elevated erythrocyte sedimentation rate with typically normal C-reactive protein levels, and hypergammaglobulinemia. Additional findings may also reflect involvement of particular organ systems (e.g., abnormal renal function in the context of lupus nephritis). The protean clinical manifestations are outlined below:

- Constitutional: fever, lymphadenopathy, fatigue, and weight loss
- Mucocutaneous: photosensitive rash, vasculitis, mucosal ulcers, malar rash, Raynaud's phenomenon, alopecia, and discoid lesions
- CNS: headache, seizures, psychosis, neuropathy, chorea, stroke, migraine, depression, and cognitive impairment
- Renal: hematuria, proteinuria, glomerulonephritis, hypertension, and renal failure
- Musculoskeletal: Arthritis, arthralgia, myalgia, and myositis
- Cardiorespiratory: serositis, myocarditis, interstitial lung disease, alveolar hemorrhage, shrinking lung disease, and premature atherosclerosis
- GI tract: hepatosplenomegaly, pancreatitis, autoimmune hepatitis, serositis, colitis, and esophageal dysmotility
- Hematological: Hemolytic anemia (Coombs positive), thrombocytopenia, and leukopenia (most commonly lymphopenia)
- Ocular: retinal vasculitis, uveitis, episcleritis, and optic neuritis
- Other: secondary Sjogren's syndrome, antiphospholipid antibody syndrome, and hypothyroidism

While individual presentation is highly variable, a recent study from the Euro-lupus project has highlighted a number of interesting clinical aspects of disease presentation. One-third of patients within that cohort presented with a malar rash with ~50% of patients having arthritis at presentation (Cervera et al., 2009). Active lupus nephropathy was found in 28% of patients in this study, a notable finding given the adverse prognosis associated with renal involvement in SLE.

It has been suggested that certain populations may have a propensity to develop particular disease manifestations.

Thus, patients of Afro-Caribbean, Hispanic, and Chinese extraction are more likely to develop lupus nephritis, which contributes to the increased severity of disease seen in these groups. Moreover patients with juvenile onset of disease also have an increased frequency of lupus nephritis (Amaral et al., 2014). This group may also have greater rates of hemolytic anemia and a higher mortality rate. The presence of a distinct phenotype in the male lupus patient remains debated. Some reports have suggested an increased rate of lupus nephritis and serositis, but many have found no difference.

Special attention must also be paid to the markedly increased risk of premature atherosclerosis in patients with SLE. This is perhaps most evident from studies of females aged 35–44 where the risk is magnified 50-fold that of an age-matched general population (Manzi et al., 1997). The cause of this is multifactorial but not accounted for solely by traditional risk factors of smoking, hypertension, and hyperlipidemia.

Pregnancy in SLE may be a time of increased disease activity, particularly if some degree of renal involvement is present at conception. Pregnant patients need close monitoring throughout gestation and in the puerperium given the risk of flare. This is minimized by planning conception at a time of low disease activity with appropriate attention to the therapeutic plan at the time (it is safe to continue hydroxychloroquine, low-dose corticosteroids, azathioprine). Women with anti-Ro antibodies also require additional monitoring given the increased (albeit low) risk of congenital heart block (permanent) and facial rash (temporary) in this setting.

There have also been recent advances in the classification criteria for SLE. These were originally formulated in 1982 and updated in 1997, and provided a useful research tool to capture individuals with SLE. Criticism of some aspects of these criteria, such as the lack of a requirement of supportive immunology and the narrow definition of certain aspects of disease (e.g., neuropsychiatric), led to the more recent development of the Systemic Lupus Collaborating Clinic (SLICC) group's criteria which are outlined in **Table 1** (Petri et al., 2012). These criteria are cumulative and should not be relied on for diagnosis, which remains a clinical judgment.

In addition to classification criteria, disease course may be followed using a number of measures of disease activity. While several such indices are available, for example, British Isles Lupus Assessment Group (BILAG); Systemic Lupus Erythematosus Disease Activity Index (SLEDAI); and European Community Disease Activity Measure (ECDAM), the BILAG and SLEDAI are most commonly applied. Damage may be measured and followed using the SLICC damage index.

Pathophysiology

SLE, like many autoimmune conditions, is multifactorial in origin. There have been many efforts to elucidate the pathogenesis of SLE with current recognition of genetic susceptibility, environmental triggers, and disruption in both the innate and adaptive immune systems. This evidence has come from a combination of clinical and preclinical studies, including a number of interesting murine models of disease that are further discussed below.

Table 1 SLICC criteria for classification of SLE

Clinical criteria

1. Acute cutaneous lupus, including lupus malar rash, bullous lupus, toxic epidermal necrolysis variant of systemic lupus erythematosus, photosensitive lupus rash, maculopapular lupus rash, or subacute cutaneous lupus (psoriaform or annular polycyclic lesions or both)
2. Chronic cutaneous lupus, including classic discoid rash (localized/generalized), lupus panniculitis, hypertrophic lupus, mucosal lupus, lupus erythematosus tumidus, chilblains, and discoid lupus/lichen planus overlap
3. Oral or nasal ulcers
4. Nonscarring alopecia
5. Synovitis (two or more joints and at least 30 min of early morning stiffness)
6. Serositis
7. Renal (urine protein–creatinine ratio (or 24 h urine protein)) of 500 mg protein per 24 h or red blood cell casts
8. Neurological: seizures, psychosis, mononeuritis multiplex, myelitis, peripheral and cranial neuropathy, and acute confusional state
9. Hemolytic anemia
10. Leukopenia (<4000 cells per microliter at least once) or lymphopenia (<1000 cells per microliter at least once)
11. Thrombocytopenia (<100 000 cells per microliter) at least once

Immunological criteria

1. Antinuclear antibody (concentration greater than laboratory reference range)
2. Antidouble-stranded DNA antibody concentration greater than laboratory reference range or twofold above the reference range when measured by ELISA
3. Anti-Sm: presence of antibody to Sm nuclear antigen
4. Antiphospholipid antibody positivity as determined by any of the following: positive test results for lupus anticoagulant, false-positive test result for rapid plasma reagin, medium titer or high-titer anti-cardiolipin antibody concentration (IgA, IgG, or IgM) or positive test result for anti-beta 2 glycoprotein 1 (IgA, IgG, or IgM)
5. Low complement C3, low C4, low CH50
6. Direct Coombs tests in the absence of hemolytic anemia

Genetic Susceptibility

The evidence implicating genetic susceptibility in SLE is supported by the concordance rate of 25% reported in monozygotic twins in comparison to that of 2% in dizygotic twins (Sullivan, 2000). Family studies have also been informative in identifying particular susceptibility loci outlined in **Table 2** (Rahman and Isenberg, 2008). These include genes that encode components of the complement cascade, which are important molecules in the removal of potentially pathogenic anti-DNA-nucleosome complexes. While deficiency in C1q, C2, or C4 are well-described predisposing factors in SLE development, it is noteworthy that, while rare, complete C4 deficiency results in a significant 75% incidence of a lupus-like disease with a particular phenotype (prominent cutaneous and articular involvement with less-frequent nephropathy and immunological findings) (Yang et al., 2007).

With the aid of comparatively recent genome-wide association studies, a number of additional disease-associated candidate genes have been described (outlined in **Table 3**; Rahman and Isenberg, 2008). The strongest of these include ITGAM, FcγR, PRDM1-ATG5, and TNFAIP3. To date, the exact mechanisms by which these genetic loci contribute to

Table 2 Genetic associations of SLE identified from family studies

Cytogenetic location	*Candidate genes with the loci*	*Immune response*
1q23	CRP	Innate
	FCGR2A	Innate
	FCGR2B	Adaptive
	FCGR3A	Adaptive
	FCGR3B	Adaptive
1q25-31		
1q41-42	PRP	Adaptive
	TLR5	Innate
2q35-37	PDCD1	Adaptive
4p16-15.2		
6p11-21	MHC class II: DRB1	Adaptive
	MHC class III: TNF	Adaptive
	C2, C4	Innate
12q24		
16q12-13	OAZ	Adaptive

Table 3 Genetic associations of SLE identified by genome-wide association studies (GWAS)

Main known function of gene	*Genes associated with SLE*
Dendritic cell function and IFN signaling	IRF5, STAT4, SPP1, IRAK1, TREX1, TNFAIP3, TNIP1, PRDM1, PHRF1, TYK2, SLC15A4, TLR8
T cell function and signaling	PTPN22, TNFSF4, PDCD1, IL10 BCL6, IL16, TYK2, PRL, STAT4, RASGRP3
B cell function and BCR signaling	BANK1, BLK, LYN, BCL6, RASGRP3
Immune-complex processing and innate immunity	ITGAM, C1QA, C2, C4A, C4B, FCGR2A, FCGR3B, KLK173, KLRG1, KIR2DS4
Cell cycle, apoptosis, and cellular metabolism	CASP10, NMNAT2, PTTG1, MSH5, PTPRT, UBE2L3, ATG5, RASGRP3
Transcriptional regulation	JAZF1, UHRF1BP1, BCL6, MECP2, ETS1, IKZF1
Other genes	PXK, ICA1, XKR6, SCUBE1

evolution of disease is unclear. Interestingly a number of the genes identified through this process have been implicated in interferon α signaling, a cytokine which has previously been associated pathogenically with SLE. Others suggest a chromosomal hypothesis for SLE. This theory is supported by a dramatic 10-fold increase in the incidence of SLE in males with Kleinefelter's syndrome who possess an XXY genotype (Stern et al., 1977). Furthermore women with Turners syndrome (XO) are comparatively protected from disease; this theory is complicated by both lyonization and skewed X inactivation, which requires further study (Chabchoub et al., 2009).

Environmental Factors

Sun protection is one of the cornerstone principles in the treatment of SLE, as ultraviolet light is an important environmental disease trigger. Additional environmental triggers include medication (most commonly procainamide, quinidine, hydralazine (Rubin, 2002)). Within this group, the TNF inhibitors merit particular attention given their increasing use in the treatment of a number of conditions, notably rheumatoid arthritis. While immunological dyscrasia (e.g., ANA positivity) is quite prevalent in those receiving this class of drugs, true clinical SLE is very rare (Mohan et al., 2002).

Hormonal

There is strong interest in the role of hormones in SLE. Both the striking predilection for lupus to affect females of childbearing potential and the well-described flares of disease at times of rapid hormonal change (pregnancy, puerperium, potentially with exogenous estrogen) lend support to this theory. At a molecular level, endogenous sex hormones can modulate both the innate and adaptive immune systems (Zen et al., 2010; Cohen-Solal et al., 2006; Grimaldi et al., 2002; Siracusa et al., 2008). Estrogen supports Th2 polarization which is characteristic of SLE, through stimulation of production of particular cytokines (IFN-γ, IL-4, IL-10, TNF, IL-1, and IL-5). Both estrogen and prolactin can also stimulate autoreactive B cells, thus promoting failure of self-tolerance (Cohen-Solal et al., 2006; Grimaldi et al., 2002). Despite the plethora of studies implicating hormonal pathways in SLE pathogenesis, there have been disappointing results noted in clinical trials of hormonal therapy in SLE.

Apoptotic Clearance

Defects in complement-mediated clearance of cellular debris have been described in SLE and have been implicated in its pathogenesis. While the initiating events may vary, the resultant excessive apoptotic debris is likely to play an important pathogenic role. In the early apoptotic phase, cells attract phagocytes and express cell surface molecules which initiate phagocyte-mediated engulfment. If this process is inefficient, nuclear fragments can be presented by antigen-presenting cells and, via consequent interactions with T and B cells, lead to the formation of ANA, typical of SLE.

Cytokines

Much interest has been expressed in the role of cytokines in the pathogenesis of SLE. While the earliest studies focused on the type 1 interferon family, more latterly many other cytokines have been implicated in the causality of SLE and many have been proposed as potential therapeutic targets.

Serum levels of type 1 interferons are increased in patients with SLE and have been found to correlate with disease activity (Bengtsson et al., 2000). Moreover, PBMCs in SLE express IFN-inducible genes that correlate with disease activity (Baechler et al., 2003). It is proposed that interferon secretion from dendritic cells can increase the antigen-presenting capability of dendritic cells that have been activated by immune complexes (Lovgren et al., 2004). Additionally, type 1 interferon can promote dendritic cell maturation, upregulation of MHC class I and II, and modulate B cell function (Baccala et al., 2007).

Other cytokines implicated in the development of SLE include interleukin (IL)-6, IL-10, IL-17, BLys (BAFF), and

TNF. Many of these molecules are found at increased levels in serum from patients with SLE and, like Type 1 interferon, correlate with disease activity. Preclinical studies targeting IL-6 in the NZB/NZW mouse model reported a reduction in the degree of proteinuria, reduced anti-DNA antibodies, and improved survival (Mihara et al., 1998). From a therapeutic aspect, Blys, has recently received increased attention given the approval of belimumab, a monoclonal antibody targeting this cytokine, for the treatment of SLE (Navarra et al., 2011). BLys binds three surface receptors (BCMA, TACI, and BAFF-R); and is a powerful stimulator of B cell proliferation, immunoglobulin class switching; and can upregulate the production of a number of cytokines. The role of TNF blockade in SLE is more contentious. Murine models of disease such as the NZB/NZW model suggest that TNF may be protective (Gordon et al., 1989). In contrast, inhibition of TNF therapeutically can lead to the induction of ANA and less often, clinical features suggestive of lupus. However, in small studies, infliximab administered to patients with SLE suggests a potential benefit in the treatment of lupus arthritis and nephritis (Aringer et al., 2004). Later studies were less compelling, thus, the precise role that TNF plays in SLE remains unclear at present.

Adaptive Immunity

T Cells

SLE is classically described as a Th2-mediated disease. We now know that additional T helper subsets also contribute to disease, with particular evidence of implication of the Th17 and regulatory T cell subsets. Raised amounts of IL-17 and a high proportion of IL-17-producing T cells have been found in lupus patients and correlate with disease activity (Apostolidis et al., 2011). They can also produce cytokines that stimulate B cell division and Ig class switching, which are of clear importance in the pathogenesis of SLE.

The Th17 subset is expanded in the peripheral blood of patients with SLE. Serum levels of IL-17, a cytokine specific to the Th17 subset are also increased in patients with SLE, correlating with levels of disease activity (Apostolidis et al., 2011). Supporting evidence implicating the Th17 subset also comes from genetic studies that identified loci within genes encoding for transcription factors for cytokines involved in the generation of Th17 cells (International Consortium for Systemic Lupus Erythematosus Genetics (SLEGEN) et al., 2008). Finally T regulatory (Treg) cells have been found to be dysfunctional in SLE where Treg cells isolated from patients with this condition display less suppression of T cell proliferation and IFN-γ production than those of controls (Sakaguchi et al., 2008).

B Cells

B cells undergo intense polyclonal activation in SLE with a population shift toward an immature B cell phenotype, independent of disease activity (Dorner et al., 2011). Moreover, abnormalities in memory B cells and B regulatory cells have recently been recognized. SLE is associated with an increase in $CD27^{+}/IgD^{-}$ postswitched memory B cells, a cell type that is less susceptible to immunosuppression (Nimmerjahn and Ravetch, 2007). $CD27^{-}/IgD^{-}$ memory B cells are also increased and correlated with disease activity and lupus nephritis. Finally, a population of dysfunctional regulatory B cells ($CD19^{+}/CD24^{high}/CD38^{high}$) that secrete IL-10 have been reported in SLE (Blair et al., 2010). From a clinical perspective, the success in clinical trials of belimumab (which blocks B cell–activating factor known as BLyS or BAFF) and in clinical series of rituximab (which binds $CD20^{+}$ B cells), agents that target B cell–survival factors and B cells directly, respectively, supports a strong role for B cells in SLE pathogenesis.

Autoantibodies

Greater than 95% of patients with SLE have detectable serum ANA. Anti-ds-DNA antibodies are highly specific for SLE, present in 65–70% of patients with SLE (versus 0.5% of the healthy population) (Isenberg et al., 1985). Following the titer of these antibodies may be of utility by reflecting disease activity, notably in those with renal and pulmonary disease. In addition, a rapid increase in DNA antibody binding in SLE patients in remission, especially if accompanied by a fall in the C3 level, may herald a flare. Anti-ds-DNA antibodies, anti-Ro, anti-La, anti-C1q, and anti-Sm antibodies have been demonstrated histologically in renal biopsy specimens (Mannik et al., 2003). The pathological consequence of these antibodies, however, remains largely unclear. A number of particular antibodies have been associated with particular disease manifestations. To this end, anti-ds-DNA is strongly linked to renal disease. Anti-Ro and antinucleosome antibodies have been most strongly associated with cutaneous lupus (Sontheimer et al., 1982). In CNS lupus, the administration of serum from individuals with CNS lupus who have anti-ds-DNA and anti-NMDA antibodies leads to hippocampal damage and cognitive impairment in mice (Kowal et al., 2006). More directly, hemolytic anemia and thrombocytopenia are mediated by antibodies targeting red cells and platelets, respectively (Quisimoro, 2007; Pujol et al., 1995).

From a mechanistic perspective, it may be that circulating antibodies cross-react directly with local proteins with a resultant direct inflammatory response. Alternatively, they may form complexes with, for example, nucleosomes in the context of anti-ds-DNA antibodies, prior to local deposition, complement fixation, and ensuing inflammation (Berden et al., 1999).

Animal Models

Animal models of SLE have been used extensively to help explore the pathogenetic mechanisms which underlie the human condition and as a testing ground for new therapies. The enormous heterogeneity among human patients with lupus means that no single animal model will capture all of the possible clinical presentations. Thus while lupus is characterized by a variety of clinical features, notably skin, joint, lung, and renal involvement and an array of autoantibodies against nuclear and other cell-based antigens, most animal models display a restricted set of clinical features and serological abnormalities. The topic of lupus animal models is enormous and has been reviewed in depth elsewhere (Hahn and Kons, 2013).

Although on rare occasions, for example, in dogs, a lupus-like disease has been described in animal species, the majority of animal models that are widely used for research are the result

Table 4 Main mouse models of SLE

Strain	*Lupus feature – clinical*	*Serological changes*	*Other comments*
NZB	Hemolytic anemia, nephritis (mild)	ANA, ds-DNA	Peptic ulcer (common)
NZB/NZW, F1	Nephritis (proliferative) Coombs positive anemia	ANA, anti-ds-DNA	Choroiditis, oophoritis – both common, lymphoid neoplasia
NZB/SWR, F1 (SNF1)	Nephritis (proliferative)	ANA, anti-ds-DNA	
MRL/Mp-lpr/lpr	Nephritis (proliferative), arthritis, skin disease, massive lymphoproliferation	ANA, anti-ds-DNA	Sialadenitis, conjunctivitis, choroiditis, oophoritis – all common
MRL/Mp-++	Nephritis (proliferative, but mild), arthritis, mild-skin disease	ANA, anti-ds-DNA	Sialadenitis, conjunctivitis, choroiditis, oophoritis – common
BXSB[a]	Nephritis (proliferative)	ANA, anti-ds-DNA, antierythrocyte	
NZW/BXSB, (WBFI)	Atherosclerosis	↑ Antiphospholipid antibodies	

[a]The only model common in males.
In addition to the 'classic models' shown above a large array of more recent mouse models based upon gene targeting experiments deregulated B cell and T cell proliferation and point mutations many using knockout mice have also been described. For details see Hahn and Kons (2013).

of major genetic manipulation. Table 4 highlights some of the more commonly used models indicating the major clinical and serological features.

Individual Models

The New Zealand black (NZB) mouse is perhaps the best-known 'classical' model of human lupus. It was developed by Dr Marianne Bielschowsky and her colleagues at the University of Dunedin in New Zealand, and the animals were selected for inbreeding on the basis of a solid black color coat. In the main, this model is primarily used to study autoimmune hemolytic anemia. Disease in this animal model is, interestingly, not sex-linked and there is 50% survival at approximately 18 months. The anemia begins around the age of 9 months and is found in virtually all of the animals by 12 months with splenomegaly often found. The model is characterized serologically by the presence of antierythrocyte antibodies and antibodies to both single and ds-DNA and other nuclear components. The pale swollen kidneys that invariably develop indicate kidney disease. The histology is that of the membranous form of glomerulonephritis with principal deposition of IgG. Lymphoid neoplasia is present in 10–20% of these animals.

The NZB/W mouse is the result of a cross between the NZB and New Zealand white (NZW) mouse. Interestingly the latter does not develop frank autoimmunity but the hybrid has been widely used for over 30 years as a reasonably good model for human lupus. It develops principally in the female with clinical symptoms becoming apparent from 6 months and most animals dying from nephritis by 9 months. The renal disease is accompanied by the presence of a strongly positive antinuclear antibody and anti-ds-DNA antibodies. Immunoglobulin and complement are found in the mesangium and capillary basement membrane. These deposits increase with age – the basement membrane becoming more fibrous and necrotic with time.

As the mice age, a marked reticulocytosis and positive Coombs' test can be found together with lymphocytic infiltration of both the lacrimal and parotid glands. This combination of features resembles those seen in Sjogren's syndrome. These animals may also develop antibodies to RNA, synthetic polynucleotides, and heat shock protein 90.

The susceptibility genes that contribute to lupus development in the NZB/W mouse have long been sought. In NZB mice susceptibility loci on chromosomes 1, 4, 7, 13 seem to be major contributors to the development of nephritis but it seems likely that the non-MHC genes from the NZW mouse also make a contribution. In the NZB/NZW-related NZM 2140 lupus-prone mouse strain, three recessive loci Sle1, Sle2, and Sle3 on chromosomes 1, 4, and 7, respectively, have been shown to trigger the development of overt lupus nephritis on a C57BL/6 nonautoimmune background.

The MRL/lpr/lpr mouse was derived almost 40 years ago by Murphy and Roths. These mice have extremely aggressive glomerulonephritis – the disease being evident at 3 months of age, causing death by 6 months in most cases. These animals develop a profound degree of lymphoproliferation affecting the peripheral lymph nodes and spleen. Intriguingly some of these animals develop joint lesions resembling those seen in rheumatoid arthritis. The animals may also develop vasculitic skin lesions, hair loss, and necrotizing arteritis.

The NZB/SWR F_1 mouse model is also a hybrid between an autoimmune strain (NZB) and a nonautoimmune strain (SWR). This too has an accelerated development of nephritis with virtually all females being dead within a year. These mice have a classic IgG2b anti-ds-DNA antibody profile that deposits along the glomerular basement membrane. It appears that autoimmune disease seen in these mice arises from the expression of 'forbidden' T cell receptors by double-negative T-helper cells and this suggests an abnormality in thymic selection or deletion.

The BXSB mouse strain was also developed by Murphy and Roths. It is a recombinant inbred strain that results in high frequencies of homozygosity at many loci. The initial pairing was between a C57BL/6 female and a satin beige (SB/Le) male, and the model develops acute severe glomerulonephritis, marked lymphoproliferation, high immunoglobulin levels, and high levels of ANA and anti-ds-DNA antibodies. Intriguingly the unique feature of this model is the fact that it is predominantly found in the male, which seems to be due to a major disease accelerating locus *Yaa* on the Y chromosome (Y-linked accelerated autoimmunity and lymphoproliferation

transposition). This mouse also makes antibodies to C1q (which in human lupus are linked to nephritis) and to a variety of brain cells and occasionally to erythrocytes. The affected mice are usually dead by 5 months of age and invariably due to the glomerulonephritis.

Over 20 years ago, claims were made that it was possible to induce lupus in healthy mice by using very small intradermal injections of a human monoclonal anti-DNA antibody. This model was rather controversial and hard to reproduce. Few, if any, laboratories still attempt to use it.

Many of the traditional models are of a spontaneous multigenic character. Attempts to induce lupus by immunization of various cells and products have tended to be less successful.

Therapeutics

General Measures

All patients with SLE should be advised to use high factor sun screen (minimum SPF 30) and close attention should be paid to bone health. In particular, vitamin D levels should be assessed and replaced when deficient, given the need for regular sun protection, and the suggestion that vitamin D deficiency may have an adverse effect on disease (Kamen and Aranow, 2008).

Immunosuppressive Approaches

The improved mortality in SLE outlined previously clearly indicates that significant therapeutic advances have been made in recent times. It is noteworthy that, despite this, only one new drug, the BLyS (BAFF)-targeting belimumab, has been approved by the FDA for the treatment of SLE since the 1950s. At that time, the recognition of the potent anti-inflammatory and immunosuppressant properties of corticosteroids led to a vast symptomatic improvement in a significant proportion of patients with SLE. We now recognize that long-term high-dose corticosteroid therapy is associated with unacceptable side effects and, more worryingly, are significant contributors to both damage accrual and mortality in patients with SLE (Gladman et al., 2003). Hydroxycholoroquine, however, also approved for SLE treatment in the 1950s, remains a cornerstone of treatment in lupus. It acts as an immunomodulatory agent via alteration of lysosomal pH and altered activation of Toll-like receptors 7 and 9. It is most useful in the treatment of the articular, cutaneous, and constitutional symptoms of SLE. Additional benefits are supported by a recent systematic review indicating that hydroxychloroquine also improves global disease activity, reduces mortality, damage accrual and has potential benefits on thrombotic risk, lipid profile, renal involvement, and cardiovascular disease (Ruiz-Irastorza et al., 2010).

Many other immunosuppressant medications have been used for the treatment of SLE. The common nonbiological immunosuppressants commonly used in SLE are summarized along with their mechanism of action and typical dosages in Table 5. For organ- or life-threatening presentations, high-dose corticosteroids are typically combined with either intravenous cyclophosphamide (now commonly administered using the 'Euro-lupus protocol,' see Table 5), mycophenolate, or more recently rituximab. In relation to the latter, the disappointing results of two randomized placebo-controlled clinical trials, EXPLORER and LUNAR, designed to explore the utility of

Table 5 Nonbiological drugs used for treatment of SLE

Drug	*Mechanism of action*	
Corticosteroids	Potent immunosuppressive drugs. Induce anti-inflammatory cytokines (interleukin-10, interleukin-1Ra, and annexin 1), decreased production of adhesion molecules, and inflammatory cytokines(IL-2, IL-6, TNF), inhibits processing of antigens by monocytes for presentation to lymphocytes	Useful for all features of systemic disease. Dose dependent on severity of involvement
Hydroxychloroquine	Immunomodulative. Increases lysosomal pH and interferes with antigen processing, modulates activation of TLR 7 and 9	Useful for arthritis, cutaneous features, and fatigue. Commonly prescribed at doses of 200–400 mg day^{-1}
Cyclophosphamide	Forms active alkylating metabolites. Prevents division of cells by cross-linking DNA and suppressing DNA synthesis	Euro-lupus protocol recommends 6 pulses of intravenous cyclophosphamide at a dose of 500 mg every 2 weeks, replacing monthly NIH protocol, used for severe systemic disease, e.g., lupus nephritis
Azathioprine	Purine analog; suppresses DNA synthesis by inhibiting synthesis of xanthylic and adenylic acids	Useful for systemic features and maintenance therapy of lupus nephritis. Option for induction of lupus nephritis in very select patients. Typical dose 1–2.5 mg kg^{-1}
Methotrexate	Folate antimetabolite, inhibits DNA synthesis. Binds dihydrofolate reductase reducing purine synthesis	Used for nonorgan-threatening disease (articular/cutaneous disease)
Ciclosporin	Forms complex with cyclophilin, disrupts activation of calcineurin. Inhibits production of IL-2 and arrests T cell cycle between G0 and G1	Moderate-severe systemic lupus; steroid sparer
Mycophenolate mofetil	Inhibits monophosphate dehydrogenase; blocks synthesis of guanosine nucleotides, and proliferation of T and B cells	Induction and maintenance therapy of lupus nephritis and moderate–severe SLE. Doses 1–3 g day^{-1}
Tacrolimus	Calcineurin inhibitor	Lupus nephritis (especially grade V) and cutaneous SLE
Intravenous immunoglobulin	Natural polyclonal antibodies, mainly IgG fraction	Option in patients with active disease

rituximab in SLE, have been highly criticized (Merrill et al., 2010; Rovin et al., 2012). Not only were the endpoints deemed too stringent, but also the high doses of concomitant immunosuppression may have masked a potential benefit derived from rituximab coadministration. There have been numerous case reports, case series, and a recent systematic review outlining positive clinical experience with rituximab, including many cases of lupus nephritis (Duxbury et al., 2013). With particular reference to lupus nephritis, rituximab may offer the potential benefit of eliminating the need for prolonged high-dose steroids (Condon et al., 2013).

Belimumab is the first biological medication approved for the treatment of SLE and is indicated in the treatment of non-renal/non-CNS lupus based on the results of two clinical trials, BLISS 52 and BLISS 76 (Navarra et al., 2011; Furie et al., 2011). Both of these trials met their primary endpoint using a dose of 10 mg kg^{-1} and encourage investigation into the role and therapeutic potential of other agents targeting B cells and their differentiation and survival.

While there are a number of other studies completed or ongoing in relation to specific biological targets in SLE such as anti-CD22 (epratuzumab), TACI-Ig (atacicept), and anti-CTLA-4 (abatacept), these agents are not currently approved or in widespread use for the treatment of SLE though the early trials with the first two of these were very encouraging, and further trials are awaited to support their utility.

Conclusion

SLE is a challenging multisystem disorder for both clinician and scientist. Its complexity is underlined by the multitude of abnormalities identified in both the innate and adaptive immune systems. It is encouraging that our increased understanding of aspects of the associated aberrant immune response has led to the identification of a number of novel therapeutic targets. From a clinical perspective, SLE should remain within the differential diagnosis of patients who present, not only with typical manifestations of SLE, but also in individuals with unexplained systemic symptoms.

See also: **Autoimmunity:** Animal Models of Autoimmunity; Autoimmune Diseases Arising out of Single Gene Defects; Complex Genetic Control of Autoimmune Disease; Rheumatoid Arthritis. **Cytokines and Their Receptors:** Roles of TNF and Other Members of the TNF Family in the Regulation of Innate Immunity. **Molecular Aspects of Innate Immunity:** Classical Complement Pathway. **T Cell Activation:** Th17 and Th22 Cells.

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