Advances in systemic lupus erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a heterogeneous course and systemic involvement. It is the result of a complex pathogenic pathway that culminates in autoantibody formation. The interaction between environmental triggers and genetic susceptibility is key in this process. Genome-wide association study technology has allowed the recognition of >80 loci associated with SLE that lead to the formation of key proteins, each contributing a small increase to the risk. Advances in the management of the disease include new validated standardized tools to capture disease activity, damage and quality of life, for clinical and research purposes. The prognosis of SLE has much improved in the last 50 years because of better general management and specific treatment, including better use of immunosuppressive agents and development of a new group of drugs – biological therapies.

Keywords Disease activity index; management; MRCP; pathogenesis; systemic lupus erythematosus; treatment

Key points

- Systemic lupus erythematosus (SLE) is a complex disease with multisystemic involvement
- It is more common in female patients
- There is a higher prevalence of SLE in patients with African heritage, with more severe disease and poorer clinical outcomes
- Classification criteria and tools to measure disease activity should be used in clinical practice
- The Systemic Lupus International Collaborating Clinics classification criteria (2012) are more sensitive than the revised American College of Rheumatology criteria, requiring at least one clinical and one immunological feature to be present
- Biological agents are effective for treating different features of SLE and have an important corticosteroid-sparing effect

Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystemic autoimmune disease with a highly heterogeneous pattern of clinical and serological manifestations. Its course differs in different individuals and is unpredictable within the same patient over time, which makes it interesting and challenging to manage. The pathogenesis of SLE is the result of interactions between genes, hormones and the environment, but its precise aetiology is mostly unknown. Recently, >80 risk genes for the disease have been described. Certain genetic features are also associated with increased disease activity.

In the last 30 years, major efforts have been made to define some key aspects of the condition, notably disease activity and damage, using standardized indices. These tools are essential for comparing different cohorts, assessing disease progression and prognosis, and measuring response to treatment. This approach is particularly important now that new biological drugs are beginning to show encouraging signs of efficacy in lupus. This review focuses mostly on the recent advances in understanding and managing SLE.

Understanding

Epidemiology

SLE is a rare disease. Its incidence is estimated to be 1–10 per 100,000 person–years, and its prevalence 20–200 per 100,000.[1,2] The incidence may be increasing, probably because of greater awareness of the disease. The prevalence has also been thought to be increasing, which may reflect an improvement in survival rates as well as chronicity.

SLE is more frequent and more severe in African, Hispanic, Chinese and Asian descendants. These patients have more haematological, serosal, neurological and renal manifestations in general, although clinical profiles vary in specific populations. Study of the LUMINA (Lupus in Minorities: Nature vs Nurture) cohort concluded that, especially in African-American and Hispanic populations (from Texas), there is an association with high disease activity and damage. Besides ethnicity, other predictors of damage are age, disease duration, disease activity and corticosteroid use.[3]

Socioeconomic status is also associated with a worse prognosis, particularly with respect to the later manifestations of the disease. Poor social support is more commonly found among ethnic minorities, which makes it difficult to distinguish if this is an independent contributor to disease severity.[1]

SLE is more frequent among women of childbearing age, in a ratio that varies between populations but is on average 10:1. Although the age of diagnosis also depends on ethnicity, it is most commonly described as the third and fourth decades of life.

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Males and female patients show little difference in their disease manifestations or severity, although presentation at the extremes of life is associated with increased severity.

Pathogenesis

There is a complex interaction between gene susceptibility, hormonal influences and environmental triggers with a breakdown of immune tolerance, resulting in autoantibody production and consequent dysregulation of the inflammatory response, leading to induction and maintenance of the disease.

Genetic factors

A genetic component in SLE pathogenesis was first suggested by evident concordance between monozygotic twins in 24–69% of cases, compared with 1–5% in dizygotic twins,[1,2] and also by the different prevalence in various ethnic groups. An 8–20-fold increased risk of developing SLE has been reported in siblings of SLE patients.[2]

In the last decade, with the development of genome-wide association study technology, >80 loci with common variants have been shown to have a confirmed association with SLE. These genes lead to the formation of key proteins involved in innate and adaptive immunity. Each appears to make a small contribution to the complex pathogenesis of lupus, suggesting that they work cumulatively.

One of the chromosomal regions having the strongest association with SLE is the human leucocyte antigen (HLA) locus, especially the class II region containing HLA-DRB1, -DQA1 and -DQB1. There are also associations of some of these loci with specific clinical features (e.g. DRB1 and renal disease) and serological features (e.g. DR2 and anti-Sm antibodies, and DR3 and anti-Ro antibodies).[2]

Although hormonal influences have a greater importance in determining the higher prevalence of SLE in women, some X-chromosome-linked genes have been described that might contribute to this (e.g. *IRAK1*, its neighbour gene *MECP2* and presence of CD40L).[2]

In the last decade, the importance of the interferon (IFN) signature in the pathogenesis of SLE has been recognized. IFNα is a key mediator in activation of the innate response and also in the adaptive immune system (normally in response to a viral infection). It enhances natural killer cell activity, stimulates maturation of antigen-presenting cells, prevents apoptosis of T cells, suppresses regulatory T cells and promotes B cell differentiation and antibody production. In patients with SLE, IFNα expression is increased in the absence of appropriate stimuli, because of overexpression of the regulating genes, and IFNα concentration is associated with disease activity.[2]

It is also now realized that post-translational modifications are likely to be contributors to the complex inheritance and incomplete concordance between homozygotic twins. In SLE, epigenetic modifications such as abnormalities in DNA methylation and histones have been reported.[2] For example, an elevated interleukin (IL)-6 concentration may contribute to the proliferation of B cells via DNA methylation.

Environmental influences and triggers

The importance of the environment has been suggested by epidemiological studies. The 'prevalence gradient hypothesis' describes a higher prevalence of SLE in the Afro-Caribbean population living in Europe and North America, whereas the prevalence in Western Africa is very low.[1] However, this observation may result from an environmental influence on the manifestations of SLE or from inadequate health systems in Africa that fail to recognize the condition.

Infections can modulate the immune system protecting against autoimmunity, but can also trigger the disease. An association between SLE and Epstein–Barr virus (EBV) infection has been described in children; this virus can trigger a flare because of antigenic mimicking (EBV protein EBNA-1 can cross-react with the self-antigen Ro).[3] An association between cytomegalovirus and SLE has also been suggested.

Oestrogens increase the risk of the disease and are a recognized trigger for flares, which probably contributes to the higher prevalence of SLE in women. Women treated with hormonal replacement therapy (but less so with oral contraceptives) have a higher risk of developing SLE[3] and also a higher risk of mild to moderate flare; in addition, associations between SLE and early menarche, menstrual irregularities and early or surgical menopause have been described.

Other environmental triggers reported include ultraviolet light, cigarette smoking and silica. Drugs implicated in drug-induced lupus include hydralazine, D-penicillamine, minocycline, lithium and more recently tumour necrosis factor (TNF)-α blocking agents.[3]

Pathological mechanisms

The complex pathogenesis of SLE seems to involve almost every component of the immune system that culminates in antibody formation. The principal mechanisms are listed here.[2]

B and T cell signalling abnormalities include an abnormal T cell receptor complex, alterations on proteins that influence the T cell response to inflammation in various ways (such as mitogen-activated protein kinase), decreased concentrations of blunting molecules such as Lyn (LCK/Yes-related novel tyrosine kinase), impaired signalling via the B cell inhibitory receptor FcgRIIB, and a faster response to a B cell proliferation stimulus such as a proliferation-inducing ligand (APRIL) or B lymphocyte stimulator (BLyS).

Autoantigen-specific T cells have been described. T cells stimulate B cell proliferation and are necessary for the secretion of high-affinity class-switched immunoglobulin (Ig) G antibodies, in a process called T lymphocyte help. These antibodies are strongly associated with tissue damage in SLE. T regulatory cells, which suppress T helper cells and B cells, are impaired in SLE.

Dysregulated apoptosis and defective clearance of cellular debris increases autoantigen exposure and tolerance breakdown. In SLE, apoptosis (particularly of T lymphocytes) is dysregulated in a Fas/Fas ligand-dependent pathway that is hyperexpressed and correlates with SLE activity and autoantibody concentrations. Abnormalities in the innate immune system, including that of phagocytes and complement, are also linked to impaired recognition and clearance of apoptotic bodies. Subsequently, abnormal prolonged exposure of nuclear antigens that undergo multiple alterations creates neoepitopes or uncovers hidden

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