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Systemic Lupus Erythematosus

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Abstract

The actual pathogenesis of systemic lupus erythematosus (SLE) remains unknown. There is likely to be a complex and multifaceted interplay between multiple hereditary and environmental factors. Multiple genes influence illness susceptibility. The interaction of sex, hormonal milieu, and hypothalamo-pituitary-adrenal axis influences susceptibility and clinical manifestation of the disease. Defective immune regulatory systems, such as apoptotic cell and immune complex clearance, play an essential role in the development of SLE. immunological tolerance loss, increased antigenic load, excess T cell assistance, faulty B cell suppression, and a change from Th1 to Th2 immunological responses all contribute to B cell hyperactivity and the creation of pathogenic autoantibodies. Finally, certain environmental elements are likely required to cause the condition.

Keywords: Aetiology, Pathogenesis, Genetic, Interaction, Autoimmune.

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1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease affecting different organs and system. Despite the etiology of the disease is not fully clarified, a multifactorial pathogenesis is largely accepted with genetic, environmental and hormonal factors contributing to its development. The SLE course is variable, mainly characterized by remission and relapse periods. Patients could experience a wide heterogeneity in terms of clinical manifestations leading to different degrees of severity and requiring personalized management and treatments [1].

1.1. Epidemiology of SLE

SLE is a disease distributed worldwide that occurs in both genders and across racial/ethnic and age groups; however, higher rates are observed in adults, women, and non-Caucasians. Genetic, environmental, sociodemographic, and methodological issues are responsible for these differences and for the variable course and outcome of the disease [2]. SLE is a rare disease with an incidence of approximately 1.5–11 per 100,000 person-years and a prevalence of 7.7–13.5 per 100,000 person-years [3].

1.2. Descriptive epidemiology

1.2.1. Sex

SLE is predominantly a disease of women, although the excess female preponderance varies with age. Before puberty, SLE is approximately twice as common in girls. During the childbearing years, the female-to-male ratio climbs and reaches a peak ratio of approximately 12: 1. After menopause, the disproportionate incidence rates in women decline to approximately twice those in men. Several studies have reported that lupus in men, though rarer, is more severe than that in women [3].

1.2.2. Age

SLE may develop at any age, although its peak incidence occurs during the childbearing years (15 to 45) in women. In comparisons with adult SLE cohorts, the small populations of children and adolescents appear to have more active SLE, especially lupus nephritis, both at initial evaluation and over time [4].

2. Ethnicity and geography

SLE occurs worldwide. SLE is more frequent and more severe in Asian (especially Chinese), African, and Hispanic populations [5].

2.1. Etiology and pathogenesis

The precise etiology of SLE is unknown. It is hypothesized that, like most systemic autoimmune conditions, SLE is triggered by one or a series of external stimuli in a genetically susceptible individual.

The exact etiology and pathogenesis of SLE remain unknown but has been shown to result from complex multifactorial interactions between genetic, hormonal and environmental factors that eventually result in the loss of self-tolerance [6].

2.2. 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, 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 [7]. In the last decade, with the development of genome-wide association study technology, more than 80 genetic loci with common variants have been shown to have a confirmed association with SLE (Figure 2). 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 [8]. 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) [9].

2.3. Hormonal/reproductive factors

Given the otherwise unexplained female excess, hormonal factors have long been of great interest in studies on the pathogenesis of SLE. Significantly lower androgen (testosterone and dehydroepiandrosterone sulfate) and higher estradiol and prolactin levels were found in women with SLE than in controls in a meta-analysis of clinical studies [10]. Doctors think the hormone estrogen might play a part in lupus because females show a much higher incidence of disease than men. Estrogen makes women's immune systems stronger than men's, So, women with lupus get symptom flare-ups around their period or during pregnancy when estrogen levels are higher [11]. In addition, estrogens and prolactin promote autoimmunity, increase the B-cell activation factor production, and modulate lymphocyte and plasmacytoid dendritic cells (pDC) activation. The use of estrogen-containing contraceptives and postmenopausal hormone replacement therapy can cause flares in patients with SLE and have been associated with a higher incidence of SLE [12].

2.3.1. Infections

It has been reported that aberrations of the physiological and protective processes of the immune system may occur during viral, bacterial, parasitic, or fungal infections in genetically prone subjects [13]. Different etiopathogenetic mechanisms have been associated with the activation of autoreactive T and B cells, and it has been hypothesized that these mechanisms are mediated by diverse infectious agents. For example, molecular mimicry is one of these, and it is based on the activation of autoimmune responses by microbial peptides that possess a structure similar to human self-antigens [14]. The viruses that have been suggested to be linked to the pathogenesis of SLE include: Epstein-Barr virus (EBV), cytomegalovirus (CMV), parvovirus B19, and human herpes virus (HHV)-6, -7, and -8 [15]. In systemic lupus erythematosus, many genetic-susceptibility factors, environmental triggers, antigen-antibody responses, B-cell and T-cell interactions, and immune clearance processes interact to generate and perpetuate autoimmunity [13]. Other immunologic mechanisms may also be important, including defects in macrophage phagocytic activity or handling of immune complexes. In addition, deficiencies of complement components, including C4, C2, and C1q, have been associated with lupus, likely due to defective clearance of immune complexes [15] (Figure 3).

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