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Juvenile-onset systemic lupus erythematosus (jSLE) – Pathophysiological concepts and treatment options

Christian M. Hedrich [a, b, *], Eve M.D. Smith [a, b], Michael W. Beresford [a, b]

[a] Department of Women's & Children's Health, Institute of Translational Medicine, University of Liverpool, Liverpool, UK
[b] Department of Paediatric Rheumatology, Alder Hey Children's NHS Foundation Trust Hospital, Liverpool, UK

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A B S T R A C T

The systemic autoimmune/inflammatory condition systemic lupus erythematosus (SLE) manifests before the age of 16 years in 10–20% of all cases. Clinical courses are more severe, and organ complications are more common in patients with juvenile SLE. Varying gender distribution in different age groups and increasing severity with younger age and the presence of monogenic disease in early childhood indicate distinct differences in the pathophysiology of juvenile versus adult-onset SLE. Regardless of these differences, classification criteria and treatment options are identical. In this article, we discuss age-specific pathomechanisms of juvenile-onset SLE, which are currently available and as future treatment options, and propose reclassification of different forms of SLE along the inflammatory spectrum from autoinflammation to autoimmunity.

* Corresponding author. Department of Women's & Children's Health, Institute of Translational Medicine, University of Liverpool, Institute in the Park at Alder Hey Children's NHS Foundation Trust Hospital, East Prescott Road, Liverpool, L14 5AB, UK.
E-mail address: christian.hedrich@liverpool.ac.uk (C.M. Hedrich).

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Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune/inflammatory disorder that can affect any organ system. The disease presentation, clinical course and outcome vary significantly between individuals, ethnicities and age groups. Variable presentations are reflected by the 11 American College of Rheumatology (ACR) classification criteria for SLE, four of which need to be fulfilled for a patient to be classified as having SLE [1,2].

The pathophysiology of SLE is not fully understood. Familial clusters, the relatively high prevalence of disease concordant monozygotic twins and poor prognosis of individuals of African or Asian descent independent of their current location indicate a key contribution of heritable genetic predisposition to disease expression [2–6]. The observation that gender distribution varies between age groups with almost equal risk for boys and girls under 5 years of age, a 4- to 5-fold higher prevalence in girls under the age of 16 years and a female-to-male ratio of 10:1 in the adult age group are a strong demographic indicator that hormonal factors are a central contributor to disease expression in SLE [2,7]. Finally, environmental factors including infections, medication and UV irradiation play a role in the pathophysiology of SLE in genetically predisposed individuals, where they appear to contribute to the breach of self-tolerance, enhancement of pre-existing but sub-clinical inflammation and the development of tissue damage [2,3] (Fig. 1).

An estimated 10–20% of all patients with SLE develop clinical disease before the age of 16 years and are therefore classified as childhood-onset or juvenile-onset SLE (jSLE) [7,8]. Peak disease onset in the jSLE cohort is between 12 and 14 years. Patients with disease onset before 5 years of age are very uncommon and may be referred to as early-onset SLE (eoSLE) [9,10]. Of note, jSLE, particularly eoSLE cases, is characterised by more severe clinical phenotypes, a high prevalence of pre-existing organ damage at diagnoses, more complications and less favourable outcomes compared to adult-onset SLE

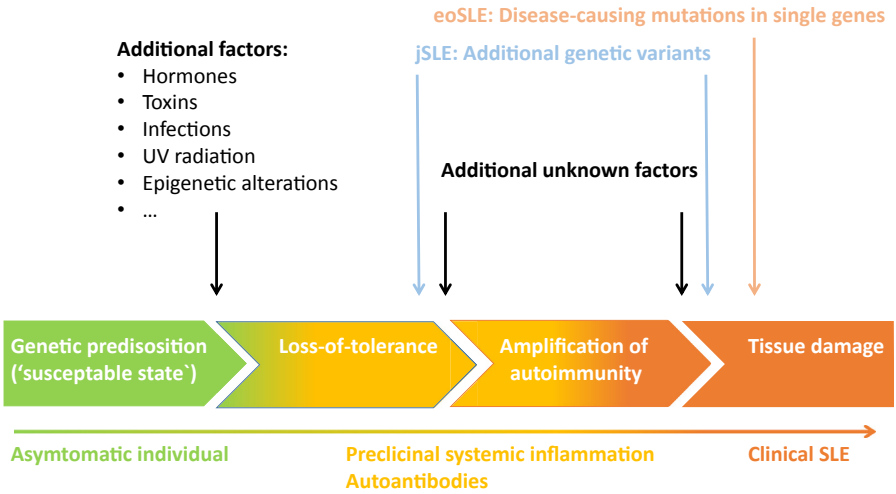

Fig. 1. Model of SLE pathogenesis and disease progression. The clinical picture of SLE is the net result of diverse, inter-individually variable molecular mechanisms. Genetic predisposition is a key factor in SLE pathology. However, in most individuals, individual genetic factors are not strong enough to confer disease. An exception to this may be eoSLE. Most likely, the majority of patients with eoSLE carry disease-causing mutations in single genes that mediate early-onset tissue damage and disease expression. Patients with juvenile-onset SLE carry an increased number of risk alleles compared to those with aSLE. This increased genetic risk may centrally contribute to disease onset in childhood or adolescence. Most patients with SLE (>80%) develop disease in adulthood. In most of these patients with 'classical' aSLE, genetic predisposition results in a 'susceptible' state and additional factors trigger loss of tolerance, chronic immune activation, and initially 'subclinical' systemic inflammation. For this, environmental (e.g. toxins, UV light, etc.) and additional endogenous (e.g. hormones) factors may need to accumulate to trigger loss of self-tolerance. Furthermore, additional currently unknown factors may be necessary to amplify inflammation and autoimmune processes that finally result in tissue damage and in the diagnosis of SLE.

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