Environmental Influences on Systemic Lupus Erythematosus Expression

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KEYWORDS

• Systemic lupus erythematosus • Etiology • Vitamin D • Environment • Risk factors

KEY POINTS

- The etiology of systemic lupus erythematosus (SLE) is unknown, but multiple genetic, epigenetic, and environmental risk factors have been implicated.
- The inheritance of genes alone is not sufficient for developing SLE, suggesting the influence of environmental triggers on disease expression.
- Despite the tremendous amount of progress in elucidating potential environmental risk factors of SLE, much more needs to be done.
- An interdisciplinary approach to studies of the causes and, ultimately, the prevention of SLE is needed.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic and potentially severe systemic autoimmune disease that disproportionately affects young women, African Americans, and Hispanics.[1–4] The etiology of SLE is unknown, but multiple genetic, epigenetic, and environmental risk factors have been implicated. The inheritance of genes alone is not sufficient for developing SLE, suggesting the influence of environmental triggers on disease expression.

It is known that SLE develops through multiple steps, with the loss of self-tolerance and development of autoantibodies occurring sometimes several years before the onset of clinically symptomatic autoimmune disease.[5,6] Although first-degree relatives

Disclosure Statement: The author declares that she has no conflicts of interest or financial disclosures.
Dr D.L. Kamen's work was supported by funding from the National Institutes of Health (NIH): R21 ES017934 from National Institute of Environmental Health Sciences and P60 AR062755 from National Institute of Arthritis and Musculoskeletal and Skin Diseases.
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Rheum Dis Clin N Am 40 (2014) 401–412
http://dx.doi.org/10.1016/j.rdc.2014.05.003 **rheumatic.theclinics.com**
0889-857X/14/$ – see front matter

of patients with SLE overall have a higher prevalence of autoantibodies and a higher risk of SLE and other autoimmune diseases,[7,8] some develop SLE-specific autoantibodies but never develop clinical disease,[9] implying that there are protective factors as well. The multifactorial nature of the genetic risk of SLE and the low disease penetrance emphasize the potential influence and complexity of environmental factors and gene-environment interactions on the etiology of SLE.[10]

Despite the significant role of the environment in modulating autoimmunity pathogenesis, the specific mechanisms by which it acts remain poorly understood. In 2005, Christopher Paul Wild called for increased resources to be devoted to studies of the "exposome" to complement the advances that have been made in genome research.[11] Ultimately, methods need to be developed for the measurement of an individual's environmental exposures with the same precision that an individual's genome is measured. This call has been answered in a small part by "omics" technologies of transcriptomics, proteomics, and metabolomics, but these investigations are in their infancy when answering questions regarding SLE etiology.

This article reviews what is understood with regard to the epidemiology of the relationship between environmental exposures and SLE, in addition to emerging areas of study.

INTERPLAY BETWEEN ENVIRONMENTAL FACTORS, GENETICS, AND EPIGENETICS

Knowledge of the genetic contributions to SLE risk has grown exponentially over the past decade, and has contributed to recent improvement in understanding the role of genetic risk factors in SLE (**Fig. 1**). Each susceptibility gene present in an individual's genome contributes to that individual's relative risk of developing SLE, and can influence the age of disease onset and clinical manifestations.[12] Although more than 50 susceptibility loci for SLE have been discovered to date, these risk loci collectively explain only a minority of the genetic risk. Utilization of next-generation sequencing techniques and exploration of gene-gene and genetic-epigenetic interactions are expected to account for much of the "missing heritability" in SLE.[13]

Nonencoded regulation of gene expression provided by epigenetic mechanisms (DNA methylation, modifications of histone tails, and noncoding RNAs) plays a role in SLE susceptibility that is still being deciphered. These epigenetic modifications

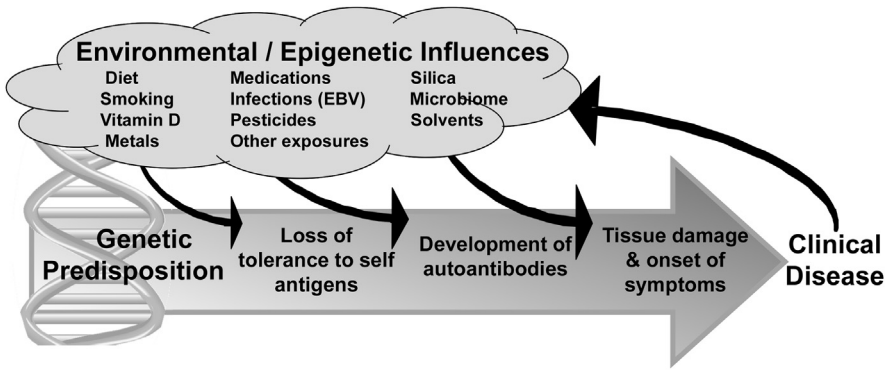

Fig. 1. Interplay between environmental factors, genetics, and epigenetics. Systemic lupus erythematosus develops through multiple steps, with the loss of self-tolerance and development of autoantibodies occurring sometimes several years before the onset of clinically symptomatic autoimmune disease. EBV, Epstein-Barr virus.