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Understanding the role of environmental factors in the development of systemic lupus erythematosus

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A B S T R A C T

Systemic lupus erythematosus (SLE) is a multisystem disease with a complex etiology. Its risk is higher among women, racial and ethnic minorities, and individuals with a family history of SLE or related autoimmune diseases. It is believed that genetic factors interact with environmental exposures throughout the lifespan to influence susceptibility to developing SLE. The strongest epidemiologic evidence exists for increased risk of SLE associated with exposure to crystalline silica, current cigarette smoking, use of oral contraceptives, and postmenopausal hormone replacement therapy, while there is an inverse association with alcohol use. Emerging research results suggest possible associations of SLE risk with exposure to solvents, residential and agricultural pesticides, heavy metals, and air pollution. Ultraviolet light, certain infections, and vaccinations have also been hypothesized to be related to SLE risk. Mechanisms linking environmental exposures and SLE include epigenetic modifications resulting from exposures, increased oxidative stress, systemic inflammation and inflammatory cytokine upregulation, and hormonal effects. Research needs to include new studies of

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environmental risk factors for SLE in general, with a focus on lifetime exposure assessment. In addition, studies in susceptible subgroups, such as family members, studies based on genetic risk profiles, and studies in individuals with evidence of pre-clinical autoimmunity based on the detection of specific auto-antibodies are also required. Understanding the role of environmental exposures in the development of SLE may help identify modifiable risk factors and potential etiological mechanisms.

Introduction

Systemic lupus erythematosus (SLE) is a complex multisystem autoimmune disease with an incidence of approximately 5–20 per 100,000 in the U.S. population [1,2]. Female predominance of SLE (9:1 female to male), and higher SLE incidence in African Americans and native Americans in particular, indicate an important role of both intrinsic and extrinsic non-genetic factors [3,4]. Genome-wide association studies are identifying increasing number of genes contributing to SLE pathogenesis and clinical manifestations [5,6]. Having a family history of SLE or related autoimmune diseases dramatically increases the risk of SLE [7], but the low to modest penetrance of genetic risk factors and concordance in twins highlight the importance of environmental factors [8].

There is strong epidemiologic evidence concerning the association of SLE with several environmental factors, including crystalline silica exposure [9,10], alcohol consumption (decreased risk) [11], current cigarette smoking [12], and exogenous estrogens (oral contraceptives and postmenopausal hormones) [13,14]. Evidence also indicates potential associations between other exogenous factors, as reviewed below (e.g., UV radiation, solvents, pesticides; Fig. 1). Associations of SLE with intrinsic factors, including birthweight, reproductive history (e.g., parity, age at menarche and menopause), endometriosis, and latent infections such as Epstein-Barr virus (EBV) may reflect an indirect role of environmental exposures [15–17]. Considerable knowledge gaps remain regarding potential mechanisms by which these environmental factors may be involved in the pathogenesis of SLE. Epigenetic regulation, whereby environmental stimuli lead to biochemical epigenetic modifications, may be a potential link [18]. Differential DNA methylation patterns have been reported in twins discordant for SLE [19]. Metabolic mechanisms that modify gene expression and precipitate SLE have also been proposed [20]. Oxidative stress has been shown to inhibit ERK pathway signaling in T cells, leading to DNA demethylation, upregulation of immune genes, and auto-reactivity, and could contribute to SLE onset among genetically predisposed individuals [21,22].

In this review, we summarize current knowledge about environmental factors associated with SLE risk on the basis of epidemiologic research, with a focus on modifiable extrinsic exposures. Potential biologic mechanisms have been recently reviewed in other contexts [23], and therefore, we highlight specific instances when evidence is particularly strong or novel. To provide a critical perspective on the literature, we start with a framework for understanding the current state of knowledge and end with needs for new epidemiological and translational research studies of the role of the environment in SLE.

Considering the role of environmental factors in SLE pathogenesis

There is no doubt that experimental and mechanistic studies in SLE animal models and clinical studies help elucidate potential causal exposures and etiological pathways. Observational research also has been critical for identifying and confirming the role of environmental exposures in the development of SLE. Potential associations are often first revealed in descriptive observational studies and confirmed across multiple populations (e.g., research on crystalline silica described below) before being substantiated in experimental studies. Understanding the strength and limitations of

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