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Environmental Influences on Systemic Lupus Erythematosus Expression

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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 prior to the onset of clinically symptomatic autoimmune disease.^{5,6} Although first degree relatives 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 be devoted to studies of the “exposome” to complement the advances that have been made in “genome” research.¹¹ Ultimately, methods

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need to be developed for measuring an individual's environmental exposures with the same precision that we measure an individual's genome. 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 of SLE etiology.

What is understood with regard to the epidemiology of the relationship between environmental exposures and SLE, as well as emerging areas of study, will be reviewed herein.

Interplay between environmental factors, genetics and epigenetics (Figure 1)

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 for SLE. Each susceptibility gene present in an individual's genome contributes to that individual's relative risk of developing SLE and can influence age of disease onset and clinical manifestations.¹² Although over 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

Non-encoded gene expression regulation 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 can result from both inherited DNA sequences and environmental exposures. Even monozygotic twins, epigenetically nearly indistinguishable at birth, later develop important differences in their epigenomic landscape.¹⁴ Reduced DNA methylation, histone hypoacetylation and hyperacetylation and the overexpression of certain miRNAs, resulting in altered immune responses, have been associated with the onset and progression of SLE.^{15,16} Along these lines, it is interesting to note that procainamide and hydralazine can cause drug-induced lupus through epigenetic mechanisms by inhibiting DNA methylation in T cells.¹⁷

Dietary influences on SLE

Although alterations in diet can reduce the risk of associated conditions such as atherosclerosis and metabolic syndrome,¹⁸ definitive evidence is lacking that dietary factors influence human SLE disease development or disease activity. Conflicting results have been found with certain dietary factors, some of which may have had supporting evidence from animal models or case reports. For example, an association between alfalfa sprout consumption and development of SLE was seen in the Baltimore Lupus Environmental Study,¹⁹ however a Swedish case-control study found no association between alfalfa sprouts and SLE risk.²⁰

Epigenetic changes in response to diet and other environmental exposures have important implications for the development of SLE, including potential targets for prevention. Studies by Strickland *et al* have shown in a mouse model of SLE that manipulation of DNA

methylation via changes in dietary methyl donor content can significantly influence disease susceptibility and severity.²¹ Little is known about the influence of diet on DNA methylation in human disease pathogenesis.

Although case-control studies have shown associations between vitamin D levels and SLE, no association was found between dietary intake of vitamin D and future risk of developing SLE among women in the Nurses' Health Study cohorts.^{22,23} There are limitations with relying on self-reported vitamin D intake to represent vitamin D status, since dietary sources account for a small proportion of circulating vitamin D which is better reflected by measurement of serum 25-hydroxyvitamin D (25(OH)D) levels. Studies which have examined associations between 25(OH) D levels and SLE are discussed below.

The Nurses' Health Study cohorts were also utilized to examine whether antioxidants from foods and supplements influenced the future development of SLE. Total antioxidant intake, including vitamins A, C, and E, α -carotene, β -carotene, β -cryptoxanthin, lycopene, lutein, and zeaxanthin, was not associated with the risk of developing SLE.²⁴ Inability to generalize results outside of Caucasian females is a limitation of the vitamin D and antioxidant intake studies due to the demographics of those enrolled in the Nurses' Health Study.

There has not been an adequate extent of investigation into whether other foods, chemicals in foods, or dietary supplements are associated with the risk or course of SLE.

Established environmental risk factors for SLE

The triggers, mechanisms and timing of disease development in SLE remain largely unknown despite many lines of experimental and epidemiologic investigation. Many potential environmental triggers of SLE have been investigated, often as part of large-scale epidemiologic studies, but compelling evidence of a causative role has thus far only been reported with silica dust and to a lesser extent smoking and Epstein Barr virus (EBV) exposure.²⁵

A National Institute of Environmental Health Sciences (NIEHS) Expert Panel was convened in 2010 to evaluate levels of confidence about existing research on environmental influences in the development of autoimmune diseases and to identify promising areas for further investigation.²⁵ Using established guidelines to assess causality, associations between each exposure and autoimmune disease were classified as "confident," "likely," or "unlikely" based on published evidence. Many associations were considered to have "insufficient" data to support classification and therefore not included in the published report.

Silica exposure and SLE

In regard to SLE, the NIEHS Panel determined that occupational exposure to silica was the only exposure classified as "confident" in its contribution to the development of disease.²⁵ This was based on positive associations between occupational exposure to silica and development of SLE in 3 population-based case-control studies^{26–28} and 3 cohort studies^{29–31} (659 cases total) from Europe and North America. The case-control studies used structured interviews and detailed occupational histories to ascertain exposure status,

whereas the cohort studies followed highly exposed populations. An additional case-control study comparing 51 lupus nephritis patients to age- race- and sex-matched patients with other renal diseases did not find an association with silica exposure ascertained by a self-administered questionnaire.³²

Exposure to particulate silica (crystalline silica or quartz) most commonly comes from mining and “dusty trades” such as sandblasting, granite cutting, construction work, cement work, brick and tile laying. Exposure can also result from proximity to agricultural work in areas with high soil silica content. The studies of silica exposure and SLE provide evidence to support a dose-response with higher risk in those with higher exposure. Overall the estimated risk ratios for SLE ranged from 1.6 (any silica exposure) to 4.9 (high silica exposure) within the general population and the risk ratio was > 10 among highly exposed populations (i.e., people with silicosis).²⁵

Cigarette smoking and SLE

Current cigarette smoking was considered by the NIEHS Panel to “likely” contribute to the development of SLE based on multiple studies with variable results. A meta-analysis of smoking and SLE risk studies by Costenbader *et al* found a modestly increased risk of SLE with current smoking compared to never smoking (OR 1.50, 95% CI of 1.09 – 2.08).³³ Based on the 7 case-control and 2 cohort studies available for the meta-analysis, the risk with past smoking compared to never smoking was not elevated (OR 0.98, 95% CI of 0.75 – 1.27).³³ In contrast, a more recent case-control study not included in the meta-analysis, with 223 SLE patients and 1,538 controls from Finland, found a higher risk for SLE with past smoking compared to never smoking (OR 1.80, 95% CI 1.15 – 2.83).³⁴

Smoking also appears to influence the course of disease among patients with SLE, particularly skin manifestations with current smoking associated with active SLE rashes and having ever smoked associated with discoid rash and photosensitivity.³⁵ Although cigarette smoke contains hundreds of potentially toxic components, is unclear whether its influence on SLE is attributable to an individual component or if the culprit is a mixture of tars, nicotine, carbon monoxide, polycyclic aromatic hydrocarbons, and/or others.

Smoking and the role of gene – environment interactions

There is a growing awareness of gene-environment interactions relevant to diseases such as SLE which help explain why individuals respond differently to the same environmental exposure; why some may develop disease while others do not. As genetic risk variants are further defined for SLE, genetic pathway analyses can help determine potential interactions with certain environmental exposures and potential differences between demographic groups.

For example, several case-control studies have found a small increased risk of developing SLE among those who smoke cigarettes, but the risk is higher among those with certain polymorphisms in genes for metabolic enzymes involved in reactive oxygen species production. A Japanese case-control study of SLE found that the combination of smoking

and two candidate gene polymorphisms in CYP1A1 and GSTM1 was associated with SLE susceptibility.³⁶

EBV exposure and SLE

Many infectious agents, including viruses, bacteria, and parasites, have been proposed as triggers of autoimmune diseases, including SLE.³⁷ The infectious agent with the most compelling evidence to date for contributing to the pathogenesis of SLE has been Epstein Barr virus (EBV). Epidemiologic data supports a connection between EBV infection and SLE.^{38,39} Infectious mononucleosis shares clinical features with active SLE and results in antinuclear antibody (ANA) positivity and production of SLE-related autoantibodies such as anti-Sm. One of the initial epitopes for autoantibody generation in SLE is thought to be 60 kDa antigen Ro which is cross-reactive with EBV-nuclear antigen1 (EBNA1).⁶ The appearance of autoantibodies which cross-react with EBV proteins sometimes several years prior to the onset of clinical symptoms is hypothesized to be due to molecular mimicry of SLE-associated autoantigens (specifically anti-Sm and anti-Ro).

Although EBV exposure is highly prevalent in the adult population, patients with both pediatric and adult-onset SLE are more likely to have molecular and antibody markers of EBV.^{40,41} A meta-analysis of 25 case-control studies by Hanlon *et al* evaluated the prevalence of serum anti-EBV antibodies between patients with SLE and matched controls.⁴² Although publication bias could not be excluded, a significantly higher prevalence of anti-viral capsid antigen (VCA) IgG positivity (OR 2.08; 95% CI 1.15–3.76) but not anti-EBNA1 (OR 1.45; 95% CI 0.7–2.98) was found in SLE cases compared to controls. Anti-early antigen (EA)/D IgG and anti-VCA IgA were also significantly higher among patients compared to controls (OR 4.5; 95% CI 3.00–11.06 and OR 5.05 (95% CI 1.95–13.13) respectively).⁴²

Differences in immunologic responses to EBV exposure being dependent on the genetic background of the exposed individual serve as another example of gene-environment interaction. Several SLE susceptibility genes play a role in EBV replication and immune evasion,⁴³ with an individual's immune response to EBV infection being a significant role in the development of early autoantibodies.

Influence of vitamin D status on SLE

Vitamin D, an essential steroid hormone with well-established effects on mineral metabolism and skeletal health, also has important effects on the immune system.⁴⁴ A high prevalence of vitamin D insufficiency has been found in SLE patient populations around the world, particularly among those with darker skin pigment, and observational studies suggest that insufficiency contributes to multiple comorbid conditions and potential complications of SLE. It is notable that the same ethnic disparities seen in the prevalence of vitamin D deficiency are seen in the prevalence of SLE, with African Americans and Hispanics having a disproportionately high risk for developing SLE and having severe disease manifestations.

Cohort studies have examined potential links between vitamin D status and SLE disease activity and disease features with the largest studies to date showing a significant correlation

between higher disease activity and lower 25(OH)D.^{45–49} Case-control studies comparing levels of 25(OH)D are confounded by SLE patients avoiding sun exposure due to photosensitivity, even when using an inception cohort of patients.⁵⁰

To address the question of whether vitamin D status influences development of SLE, it is important to assess reliable pre-clinical markers of disease. Ritterhouse et al demonstrated among healthy controls that vitamin D deficiency was associated with autoimmunity (ANA positivity)⁴⁸ and with altered T and B cell responses,⁵¹ consistent with low levels of 25(OH)D being a potential risk factor in the pathogenesis of SLE. Although causality remains to be determined, studies to date suggest a possible role for vitamin D in the pathogenesis of SLE.

Less established environmental risk factors

Metals and SLE

Although experimental studies in rodent models suggest that metals may play a causative role in SLE, the epidemiologic data is currently lacking. Metals such as mercury have been associated with antinuclear antibody and inflammatory cytokine production in some exposed individuals.⁵² The one published study to date of occupational and avocational metal exposures in SLE cases compared to controls found that exposure to mercury in the occupational setting at least once per week was associated with a modestly (but not significantly) higher risk of SLE (OR 3.1; 95% CI 0.8 – 12.7).²⁸ Exposure to five or more days of stained or leaded glass as a hobby was also more common among SLE cases than controls, but the rarity of these exposures led to an imprecise effect estimate (OR 3.0; 95% CI 0.8 – 11.6).²⁸ More studies are needed to determine if, and in whom, exposure to certain metals influences the risk and/or course of SLE.

Pesticides, persistent organic pollutants and SLE

Exposure to pesticides has been a suspected risk factor for SLE based on a higher risk of disease reported among farmers and accelerated disease in pesticide-treated lupus-prone mice.^{53,54} However, there is insufficient evidence based on current published data that exposure to pesticides play a causative role in the development or progression of human SLE.

A history of mixing pesticides for agricultural work was associated with development of SLE (although only 8% of SLE cases and 1% of controls reported the exposure), but pesticide application was not associated with SLE in the same study.⁵⁵ In an analysis of the Women's Health Initiative cohort, 50- to 79-year-old women who reported personally mixing/applying insecticides (mostly in a residential setting) had higher risks of developing SLE during the study follow-up, with trends of increasing risk by frequency and duration of use.⁵⁶ A history of living on a farm was also associated with higher risk of developing SLE.⁵⁶

Persistent organic pollutants (POPs) are halogenated organic compounds that are resistant to environmental degradation through chemical, biological, or photolytic processes. POPs include broad classes of compounds, such as organochlorine pesticides (and pesticide

metabolites), polychlorinated biphenyls (PCBs), dioxins, and furans. Many are considered contaminants of emerging concern as these chemicals with potential adverse health effects are becoming more common in the environment with increasing levels in humans.⁵⁷

There have been few epidemiologic studies of POPs in relation to SLE. One study of U.S. electrical workers (typically exposed to PCBs) reported 30% significantly more mortality from musculoskeletal system diseases (ICD-9 codes 710–739) and 40% more mortality from ICD-9 codes 710–725, classifications that include the ICD-9 code for SLE.⁵⁸ One cohort study with 24 years of follow-up in a Taiwanese population that was accidentally exposed to high levels of PCBs and furans through consumption of contaminated rice found higher mortality from SLE, with PCB-related deaths starting 10 years after the exposure.⁵⁹ An ongoing study of environmental triggers of SLE among Gullah African Americans found ANA positive controls (48% at baseline) had higher mean levels compared to ANA negative controls for PFOS (75.1 vs 48.2 ng/ml, $p=0.06$), PFOA (7.0 vs 5.8, $p=NS$) and PFNA (3.2 vs 2.1, $p=0.04$).⁶⁰ Serum PFOS and PFNA ($p=0.02$ and 0.03) directly correlated with annual servings of seafood and 40% consumed local species known to contain high levels of POPs. Although it is possible that POPs increase the risk of SLE, more studies investigating the association are needed.

Other environmental agents and SLE

Other exposures worth investigating but with currently little data on SLE associations include asbestos, industrial chemicals and solvents, personal care products (e.g., cosmetics), UV radiation, and air pollution. For example, case-control studies performed in Boston,²⁷ Canada,²⁸ and the Carolinas⁵⁵ included questions about past exposure to solvents but found mixed results and overall a low prevalence of exposure to many of the specific solvents examined. A meta-analysis, which included those same 3 studies of SLE, found a significant association between organic solvent exposure and development of disease when multiple autoimmune diseases were combined as the outcome (OR 1.54, 95% CI 1.25 – 1.92).⁶¹ There is also a paucity of research on immune health risks associated with relatively widespread synthetic chemical exposures, such as plasticizers (e.g., phthalates and bisphenol A), which can act as endocrine or immune disruptors. More research is needed on these and other industrial chemicals in consumer products to determine whether they may play a role in the development of SLE.

The only exposure deemed by the NIEHS Panel to be “unlikely” to contribute to autoimmune disease was the use of hair dyes and development of SLE, of which multiple case-control studies have not found an association.²⁵

This lack of confident associations in either direction calls attention to the difficulties inherent in investigating environmental risk factors. Progress is limited by multiple barriers including but not limited to: difficulty obtaining high-quality exposure data and timing of exposure, lack of consistent and validated assessment tools, difficulty defining which of multiple simultaneous exposures contributes to disease, and inadequate interdisciplinary training and collaboration between clinicians, epidemiologists, and environmental scientists. Additionally, we lack clear definitions of susceptibility windows related to age,

developmental state, and hormonal changes, which would help inform the timing of exposures and latencies of their effects.

Methodologic limitations in studies of environmental influences

Although increasingly sensitive and specific biomarkers of exposure and disease continue to be discovered and utilized, the majority of environmental risk studies to date rely on questionnaires to ascertain exposure and/or outcomes of interest. Cohort studies which are utilized to make determinations about environmental risk factors often include questionnaires and other assessments which were not built to formally assess SLE or other autoimmune diseases. If SLE is not one of the primary conditions under study, there is a greater chance of misclassification of disease outcome. The current methods of capturing environmental exposure are also limited by an excessively long lag-time between time of exposure of interest and time of assessment, particularly problematic in light of SLE having a long pre-clinical phase and in today's rapidly changing environment.

Defining the SLE “exposome”

The concept of the “exposome” encompasses the complex interplay between an individual's exposures and their genome and epigenome, which result in an impact on that individual's health.¹¹ Study of the exposome, or exposomics, relies on the measurement of both internal and external exposures. Measurement of internal exposures (e.g., hormones, inflammation, oxidative stress, gut microbiota) involves the use of biomarkers of endogenous processes. Measurement of external exposures (e.g., chemicals, infectious agents, UV radiation, diet, tobacco, medications) involves the use of direct measurements and survey instruments to capture environmental and lifestyle factors.

The question arises as to how to find the environmental risk factors for the large proportion of SLE that remains unexplained by currently known genetic and environmental influences. Determining the risk (and protective) factors for SLE will continue to be highly challenging using traditional epidemiological approaches in which exposures are gleaned from self-reported questionnaires. To help overcome these limitations, a hypothesis-free “exposomic” approach is needed. This approach focuses on the ‘internal chemical environment’ arising from exposures and includes internally generated biomarkers of exposure to assist in defining exposure-response relationships.⁶² Progress is being made identifying and validating new exposure biomarkers that can be used in population-based studies of diseases such as SLE, many of which are supported as part of the Genes, Environment and Health Initiative (GEI) and the Gene Environment Association Studies (GENEVA) consortium.⁶³

FUTURE CONSIDERATIONS/SUMMARY

There has been a tremendous amount of progress in elucidating potential environmental risk factors of SLE yet so much more needs to be done. An interdisciplinary approach to studies of the causes, and ultimately the prevention, of SLE is needed. Increasing dialog and collaboration between epidemiologists, biostatisticians, bioinformatics experts, laboratory and environmental scientists, and lupus clinical researchers (lupologists) will advance our collective contributions to an understanding of the causes of SLE. Ultimately these

collaborations will improve environmental exposure assessment, enable us to examine risk within biomarker-defined subgroups (e.g., genetic polymorphisms or autoantibody status), and aid the discovery of diagnostic and prognostic biomarkers.

Understanding of the environmental risk factors for SLE will allow us to design preventive measures based on well-informed predictive risk models. Ultimately, our goal is to improve the quality of multidisciplinary research on the human health effects of environmental exposures and develop effective strategies for exposure reduction and autoimmune disease prevention.

Important discoveries are being made regarding the pathways that allow environmental stresses to influence an individual's expression of autoimmunity and autoimmune disease. For example, there is now ample evidence that the epigenome is dynamic and changes in response to environmental exposures, including diet. This has important implications for prevention as our understanding grows of how epigenetic regulation of DNA is influenced by modifiable environmental and dietary exposures, and how these variations play a role in SLE disease development.

There is urgency in undertaking this quest for understanding SLE etiology, due in part to the rising incidence of SLE with more than 16,000 new cases diagnosed annually in the United States alone. Also important is the potential for what we learn about SLE etiology to benefit other autoimmune diseases and the likelihood that many other health conditions result from similar exposures.

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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.
- There has been a tremendous amount of progress in elucidating potential environmental risk factors of SLE yet so much more needs to be done.
- An interdisciplinary approach to studies of the causes, and ultimately the prevention, of SLE is needed.

Figure 1.

Interplay between environmental factors, genetics and epigenetics. SLE develops through multiple steps with the loss of self-tolerance and development of autoantibodies occurring sometimes several years prior to the onset of clinically symptomatic autoimmune disease.