Editorial

Unraveling the Etiology of Systemic Autoimmune Diseases: Peering into the Preclinical Phase of Disease

Systemic lupus erythematosus (SLE), along with systemic sclerosis and Sjögren's disease, is marked by a striking female predominance, with women representing at least 90% of patients[1]. Incidence rates for SLE among African-American women peak in the reproductive years (i.e., ages 20–40)[2,3], but in other populations, the highest age-specific incidence rates occur after age 40 years[4-6]. What accounts for this female predominance in these specific diseases? Scientific focus on X- or Y- chromosome genes and on the role of estrogen and testosterone in immune response in animals[7] has evolved and expanded during the past 20 years to include DNA methylation and epigenetic alteration of gene expression[8]. One potential sex-mediated mechanism involves CD40L overexpression, which can occur only in women since CD40L is encoded on the X chromosome[9]. This type of genetic and molecular research offers promising avenues for understanding the etiology of systemic autoimmune diseases and the development of new therapies. Additional insights into disease risk and pathogenesis can also be gained from an epidemiologic perspective, focusing on the experiences of individuals and populations.

In this issue, Ulff-Møller, et al examine the influence of pregnancy and pregnancy outcomes on the risk of SLE[10]. This cohort study encompasses the entire population of Denmark (about 4.4 million), with a 30-year followup period (1974–2004). The classification of SLE for the purpose of this study was based on a national database of hospitalization records, with the first record of SLE in the database taken as the age at SLE diagnosis. Reproductive history, defined as a pregnancy resulting in a live birth, was obtained from the national hospital registry. Other types of birth outcomes were also obtained from the hospitalization and other national databases.

Among women, Ulff-Møller, et al found that risk of SLE decreased with increasing number of live births, and that an increased risk of SLE was associated with idiopathic pregnancy losses (spontaneous abortion, missed abortion, and stillbirth)[10]. Similar patterns with respect to parity have been reported in a study of scleroderma, based on hospitalization registry data in Sweden[11]. These associations could arise from shared etiologic pathways or risk factors, or from immunological changes in a preclinical disease phase that affects fecundability and ability to carry a pregnancy to term.

There are several aspects of the design that should be noted as one considers how to interpret the results, and how one would build upon this study in designing additional studies. Ulff-Møller, et al suggest that the observed associations could "reflect the impact of subclinical immunological processes in women destined to develop SLE"[10]. Fundamental to this interpretation of the data is the premise that the reproductive history represents the experience of patients before disease onset, rather than a reflection of reproductive complications or impairment that arise as the result of SLE. The authors took steps to address the potential error that would arise due to reliance on hospitalization data rather than more detailed medical record and patient interview data to pinpoint age at onset, for example, by excluding pregnancy losses that occurred in the 5 years before the first SLE-related hospitalization. In addition, in the analysis of the time since most recent pregnancy loss, the 5 years before SLE hospitalization is divided into relatively narrow strata (< 1 year, 1–2 years, 3–4 yrs), revealing little variation in the observed association across these time periods.

Is a 5-year period long enough to account for the difference between age at diagnosis and age at first hospitalization? In the absence of data derived specifically from SLE patients in Denmark, it seems like a reasonable choice. Chakravary et al's medical claims data analysis from California and Pennsylvania in 2000 indicated that about 25% of SLE patients are hospitalized each year[12], and in unpublished data from the Carolina Lupus Study cohort, 68% of patients had been hospitalized at or since their diag-

See Reproductive factors and risk of SLE, *page 1903*

nosis, after a followup of 2–6 years (median 4 yrs). But even assuming no delay between the initial symptoms and diagnosis, age at diagnosis does not necessarily represent the onset of disease. Disease-specific autoantibodies can predate the diagnosis of SLE[13] and rheumatoid arthritis[14] by several years. Focusing on this preclinical phase offers many opportunities, and many challenges: opportunities and challenges that an epidemiologic approach is well suited to meet.

Focusing on the period before someone presents to a physician with frank expression of SLE would provide the means to address important clinical and etiological questions. "What proportion of people who develop (a specific type or level of autoantibody) go on to develop (a specific autoimmune disease)?" Does this vary depending on the presence of a family history of (a specific autoimmune disease, or autoimmune diseases in general)? What characteristics of the individual influence the development of autoantibodies in response to specific environmental exposures? What influences the ability to clear these autoantibodies versus developing a sustained, progressively detrimental immunologic response? These are the questions that can be examined in prospective epidemiological studies, combining focused immunological and genetic markers at a molecular level with a fuller ascertainment of the experiences and exposures that may affect the loss of self tolerance.

Studies of a preclinical disease phase (defined, for example, as the development of persistent autoantibodies of a particular type) may also be more efficient than studies of clinical disease. The time between exposure and the outcome may be shorter and there is potential for higher statistical power due to increased sample size achieved by focusing on intermediate biomarkers of effect. The feasibility and efficiency of large, prospective studies can be enhanced by focusing on high risk populations, such as specific geographic areas or ethnic groups, or first degree relatives of patients with a disease[15]. These approaches have been used in studies of type 1 diabetes[16,17]. Combining these approaches, focusing on first degree relatives in areas or groups with relatively high incidence rates may be optimal for diseases that are less common. The increasing evidence of shared genetic[18] and environmental[19] factors and co-occurrence of a number of autoimmune diseases within individuals and within families[20] provide additional support for a design that includes a spectrum of conditions (e.g., SLE, rheumatoid arthritis, and other systemic autoimmune diseases) in a study of the progression from autoimmune response to autoimmune disease.

If it is possible to characterize a subclinical or preclinical immunological disease state, it may also ultimately be possible to interfere with what Ulff-Møller, et al[10] describe as a "destiny to develop SLE." Focusing on this phase of autoimmune diseases may allow us to prevent the occurrence of symptoms and irreversible disease damage; however, early

intervention is only beneficial if it can be targeted appropriately so that people do not receive unnecessary medical care, including unnecessary use of powerful immunosuppressant drugs that carry their own risks of complications. The multi-disciplinary and multisite collaboration needed for a prospective epidemiological study of preclinical disease in chronic diseases with long latency periods (such as breast cancer[15]) is feasible. The opportunities presented by application of this model to systemic autoimmune diseases would be highly valuable, from the perspective of mechanistic research and clinical relevance.

GLINDA S. COOPER, PhD,
Senior Epidemiologist,
US Environmental Protection Agency,
and Department of Environmental and Occupational Health,
George Washington University School of
    Public Health and Health Services,
1200 Pennsylvania Ave NW, 8601-P
Washington, DC 20460 USA.

Address correspondence to G.S. Cooper; E-mail: cooper.glinda@epa.gov
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Protection Agency.

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