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Review

The genetics and molecular pathogenesis of systemic lupus erythematosus (SLE) in populations of different ancestry

George N. Goulielmos[a,*,1], Maria I. Zervou[a,1], Vassilis M. Vazgiourakis[a], Yogita Ghodke-Puranik[b], Alexandros Garyfallos[c], Timothy B. Niewold[b]

[a] Section of Molecular Pathology and Human Genetics, Department of Internal Medicine, School of Medicine, University of Crete, Heraklion, Greece
[b] Colton Center for Autoimmunity, Departments of Medicine and Pathology, New York University School of Medicine, New York, NY, USA
[c] 4th Department of Internal Medicine, Hippocratio Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece

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ABSTRACT

Systemic lupus erythematosus (SLE; OMIM 152700) is a highly heterogeneous disorder, characterized by differences in autoantibody profile, serum cytokines, and a multi-system involvement commonly affecting the skin, renal, musculoskeletal, and hematopoetic systems clinical manifestations involving. Disease features range from mild manifestations, such as rash or arthritis, to life-threatening end-organ manifestations, such as glomerulonephritis or thrombosis, and it is difficult to predict which manifestations will affect a given patient. SLE is caused by interactions between susceptibility genes and environmental factors resulting in an irreversible loss of immunologic self-tolerance. Incidence is highest in women during the reproductive years; however, people of all ages, genders, and ancestral backgrounds are susceptible. A striking 9:1 female to male differential appears in incidence, which remains largely unexplained. However, people of both sexes and all ages and ethnic backgrounds are susceptible. Distinct differences regarding the pathogenesis of SLE between patients of different ancestral backgrounds have been observed so far, including differences in specific clinical manifestations, disease-susceptibility genetic variants and IFN levels. Genome-wide association studies (GWAS) have attempted to elucidate partially the complex genetic architecture of SLE and to point out the existing differences in risk variants across different continental populations, considering that some alleles have not been found in all ancestral backgrounds. Levels of circulating IFN-α is a heritable risk factor in SLE with causal role in pathogenesis, they differ between SLE patients from different ancestral backgrounds and this information could be important as therapeutics is developed to target this pathway. This review highlights some recent findings referred to the multilevel differences appearing in SLE patients from different ancestral backgrounds and further understanding of this knowledge may permit the development of personalized treatments based on patients' ancestry.

1. Introduction

Systemic lupus erythematosus (SLE, OMIM 152700) is an autoimmune disease characterized by production of large quantities of antibodies directed against ubiquitous self-antigens, particularly double-stranded DNA (dsDNA) and small nuclear RNA-binding proteins such as Ro, La, Sm, and nRNP. SLE is characterized by multisystem involvement commonly affecting the skin, renal, musculoskeletal, and hematopoietic systems. SLE is caused by interactions between susceptibility genes and environmental factors, which can include ultraviolet light, infections, and viruses, resulting in an irreversible loss of immunologic self-tolerance (Harley et al., 2006). The incidence of the disease is highest in women of childbearing age (Lopez et al., 2003).

SLE-associated autoantibodies and high serum interferon alpha (IFN-α) are two important heritable phenotypes in SLE which are thought to play a role in disease pathogenesis (Ramos et al., 2006; Niewold et al., 2007). Women of childbearing age are preferentially affected at a rate nine times that of men, and those of African American and Asian ancestries are affected more frequently and manifest more severe disease than those of European ancestry (Petri, 2002).

Abbreviations: SLE, systemic lupus erythematosus; GWAS, genome wide association study; SNP, single nucleotide polymorphism; dsDNA, double-stranded DNA; IFN-α, interferon α; HA, Hispanic-American; AA, African-American; EA, European-American

* Corresponding author at: Section of Molecular Pathology and Human Genetics, Department of Internal Medicine, School of Medicine, University of Crete, Voutes, Heraklion 71003, Greece.
E-mail address: goulielmos@med.uoc.gr (G.N. Goulielmos).
[1] Contributed equally.

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Candidate-gene studies and genome-wide association (GWA) scans have been successful in identifying new loci that contribute to disease susceptibility. Collectively, these studies have identified and confirmed ~90 loci that contribute to the pathogenesis of SLE. These data highlight the importance of several pathways, including those involving lymphocyte activation and function, immune-complex clearance, innate immune response, and adaptive immune responses (Moser et al., 2009). However, much of the heritable risk has yet to be identified. In these studies, subjects from different ethnicities and races have been analyzed so far, including European Americans, Europeans, African Americans, Asians, Hispanics as well as populations of Gullah and Amerindian ancestry. The histocompatibility leukocyte antigen (HLA) region has been known to contribute to the risk of SLE and other related autoimmune diseases since the 1970s (Nies et al., 1974; Reinertsen et al., 1978). In the early 2000s, gene expression studies determined that, compared to healthy controls, individuals with SLE overexpress genes in the interferon pathway (Bennett et al., 2003; Kirou et al., 2004). Many recent studies have highlighted the role of the type I interferon (IFN) pathway in SLE pathogenesis and susceptibility (Crow, 2007; Niewold, 2008). Indeed, serum IFN-alpha (IFN-α) activity was shown to be a heritable risk factor for SLE (Niewold et al., 2007) and many genetic variants associated with SLE susceptibility are associated with increased serum IFN-α activity in lupus patients (Kariuki et al., 2008; Niewold et al., 2008b; Kariuki et al., 2009b; Salloum et al., 2010). Additionally, age-related patterns of serum IFN-α activity are present in both lupus patients and their healthy family members which mirror peak SLE incidence rates, with an earlier age of peak serum IFN-α in female patients as compared to male patients (Niewold et al., 2008a). Current models of human SLE pathogenesis place plasmacytoid dendritic cells in a central role, promoting type I IFN production, which leads to the eventual loss of self-tolerance (Kyogoku and Tsuchiya, 2007). Increased production of type I IFN in SLE skin lesions has been observed, and plasmacytoid dendritic cells accumulate in cutaneous lupus lesions (Farkas et al., 2001).

Seven recent genome-wide association studies (GWAS) of SLE performed in European and Asian populations have uncovered > 35 common SLE risk loci that achieve genome-wide significance ($p < 5 \times 10^{-8}$) (Graham et al., 2008; Harley et al., 2008; Hom et al., 2008; Kozyrev et al., 2008; Gateva et al., 2009; Han et al., 2009a; Yang et al., 2010). Given the design of these studies and stringent statistical criteria used in GWAS, it is likely that many susceptibility genes remain hidden within the statistical "noise" inherent to GWAS (Pearson et al., 2007).

2. SLE clinical manifestations differ between world populations

SLE is a sexually dimorphic autoimmune disease which occurs more than nine times more frequently in women than in men (Whitacre, 2001). While it is more prevalent in women, men who develop SLE often experience a more severe disease (Blum et al., 1991). The sex chromosome complement and hormonal differences might play a role in the female sex bias of SLE. However, the degree to which sex-specific genetic differences contribute to SLE susceptibility has not been fully studied. A significant sex–gene interaction was seen primarily in the human leucocyte antigen (HLA) region but also in IRF5, whereby men with SLE possess a significantly higher frequency of risk alleles than women. Surprisingly, the genetic effect observed in *KIAA1542* is specific to women with SLE and does not seem to have a role in men (Hughes et al., 2012).

Although the etiology of SLE is largely unknown, its pathogenesis most likely involves a complex interplay between environmental (e.g., UV light, Epstein-Barr virus infection, etc.) and genetic (e.g., *MHC, IRF5* [MIM 607218], etc.) components (Moser et al., 2009). A sibling risk ratio of approximately 30 in SLE illustrates a strong genetic (Alarcon-Segovia et al., 2005), and the fact that observational studies have identified many families with multiple cases of SLE and other autoimmune conditions suggests the potential for shared genetic predisposition (Sestak et al., 1999; Arora-Singh et al., 2010). SLE is frequently characterized by inappropriate type I IFN responses driven by small nuclear self-antigens (Pascual et al., 2006). Humoral autoimmunity is a hallmark of disease, and the formation of immune complexes containing self-antigens leads to local and systemic inflammation and subsequent clinical symptoms. The pathogenesis of SLE likely involves both environmental and genetic triggers; the latter highlighted by the observation that siblings of affected individuals have a 20- to 30-fold increased risk of developing SLE (Tsao et al., 2002). Candidate gene studies and, more recently, genome-wide association studies (GWAS), have begun to elucidate the complex genetic architecture of SLE with identification of > 90 risk loci (Moser et al., 2009). These studies have collectively established the importance of several pathways in SLE, including innate immune responses, activation of lymphocytes, and immune complex clearing (Moser et al., 2009). However, apart from the high number new loci that have been identified as contributing to the pathogenesis of SLE, they collectively do not explain all the risk contributed by heritable factors. Symptoms of SLE are varied and range from mild arthritis to renal failure. The disease affects at least 5 million people worldwide. Despite substantial effort over many years, conclusive answers regarding the etiology, pathogenesis, and treatment of lupus have remained elusive. However, recent research, including genome-wide genetic and transcriptional analysis has revealed potential roles for many different factors. This understanding of the disease is beginning to bear fruit with the development of therapeutics for lupus. Cytokine dysregulation is likely to play a role in the loss of immune tolerance that leads to lupus and in the damage resulting from the disease. Excess interferon alpha and interferon alpha responsive gene expression have been identified as hallmarks of many cases of lupus. IL-10 and IL-21 are cytokines that show increased expression in lupus, and which regulate lymphocyte development and tolerance. Another cytokine, IL-17, is dysregulated in lupus enhancing the pathogenesis of the disease. These and other proinflammatory cytokines are likely to not only contributed to loss of tolerance and the symptoms associate with lupus, but they likely accelerate atherosclerosis in lupus patients. Other cytokines, such as IL-2, are under expressed in lupus, with detrimental effects on immune tolerance and T-regulatory cell development.

It is well known that differences in autoimmune disease risk variants exist across different continental populations. SLE prevalence varies substantially by ethnic ancestry. African-Americans (AA) have a 3 to 5 fold increased risk of SLE compared to individuals with European ancestry (Petri et al., 1991; Reveille et al., 1998; Fernandez et al., 2007). Furthermore, SLE is more prevalent in African-American (AA), Asian (AS) and Hispanic (HI) populations compared to Europeans (Serdula and Rhoads, 1979; Hart et al., 1983; Bae et al., 1998). Hispanic and African-American populations have genomes which reflect recent admixture on ancient substructures (Bryc et al., 2010). Hispanic cohorts have rich diversity of source ancestry with Southern European, Amerindian and West African contribution to the inherited genome and the forced diaspora of Africans to the Americans also resulted in gene flow and two-way admixture between previously reproductively isolated West African and European ancestral populations (Winkler et al., 2010). Hispanic and African-American populations have been observed to be disproportionately affected by SLE (Molina et al., 1997) and health disparities in these groups show onset at a younger age (Fernandez et al., 2007).

Lupus nephritis (LN) is one of the most severe complications, drastically increasing the morbidity and mortality of SLE patients, with up to 60% of adult and 80% of pediatric SLE cases developing renal abnormalities during the course of the disease (Cameron, 1999). The incidence of LN is higher in AA, HI and AS compared to populations of European ancestry: one study showed that incidences of renal disease for African Americans and Hispanics (HI) are 68.9% and 60.6% respectively compared to Europeans (EA) (29.1%) after 5.5 years of