Published in final edited form as:

Autoimmun Rev. 2010 May ; 9(7): 473–476. doi:10.1016/j.autrev.2010.02.003.

Pathways: Strategies for Susceptibility Genes in SLE

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Abstract

Systemic lupus erythematosus (SLE) is a complex autoimmune disorder marked by an inappropriate immune response to nuclear antigens. Recent whole genome association and more focused studies have revealed numerous genes implicated in this disease process, including ITGAM, Fc gamma receptors, complement components, C-reactive protein, and others. One common feature of these molecules is their involvement in the immune opsonins pathway and phagocytic clearing of nuclear antigens and apoptotic debris which provide excessive exposure of lupus-related antigens to immune cells. Analysis of gene-gene interactions in the opsonin pathway and its relationship to SLE may provide a systems-based approach to identify additional candidate genes associated with disease able to account for a larger part of lupus susceptibility.

Keywords

SLE; opsonin; pathway; genetic association

Systemic lupus erythematosus (SLE) is characterized by autoantibodies to nuclear antigens, immune complex deposition, and subsequent tissue destruction. Both genetic and environmental factors likely contribute to the pathogenesis of SLE. The search for genes and molecular interactions that influence disease has been fruitful although the single gene approach has yet to explain much of the variation. Analyzing molecular pathways represents one means of recognizing candidate genes and proteins involved in multi-factorial pathogenesis. From such a systems-based perspective, investigators have explored the type I interferon (IFN) pathway in SLE etiology [1]. Additional pathways may provide clues for future research and treatment options, similar to those for modifying IFN effects in SLE patients [2].

Recent genome-wide association studies (GWAS) and other more targeted investigations have revealed numerous novel genetic polymorphisms associated with SLE disease susceptibility. A theme shared by many of these SLE-associated polymorphisms is the involvement of the gene product in innate immune system opsonization reactions. Constituents of these opsonin pathways appear a likely focus for additional research, in a systems-based approach, in unraveling the molecular basis of SLE.

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Opsonin Pathways

Opsonization is any process that enhances phagocyte binding and subsequent pathogen clearance during an immune response. It commonly involves coating a target cell with molecules that mask negative membrane potentials that impede direct interaction between the target (e.g. pathogens, apoptotic cells) and phagocyte cell membranes. Examples of these coating molecules, also called opsonins, include immunoglobulins (Ig), complement components, mannose binding lectin (MBL), and C-reactive protein (CRP). Phagocytes express receptors that recognize and interact with opsonins.

Antibodies and Fc Receptors

Antibodies are prototypic opsonins comprising a wide variety of specificities ranging from “natural” antibodies to highly focused products of the adaptive immune system. Since autoantibodies are present in SLE patients [3], investigators have considered the possibility that the genetic code for antibody structure may differ between patients and controls. Indeed, the constant region varies as is observed by Gm and Km allotypes [4], and among Asian and Caucasian SLE patients, the frequencies of Gm haplotypes differ from the frequencies observed in healthy controls [5;6].

When functioning as opsonins, antibodies' constant regions are recognized by Fc Receptors (FcRs) which provide immunoregulatory signals, induction of receptor-initiated cell programs, and enhanced phagocytosis by phagocytes. *FCGR2A* contains a functional single nucleotide polymorphism (SNP) that influences the efficiency of IgG2-mediated binding by altering the antibody binding/recognition site of the receptor [7]. In a meta-analysis of several studies, the “lower efficiency” allele of this polymorphism was associated with a 1.3X greater risk of developing SLE [8]. This SNP was one of the most significant findings in a recent GWAS [9]. Like *FCGR2A*, *FCGR3A* has an allelic variant that alters the affinity of binding of IgG molecules and that is associated with SLE susceptibility [10]. For *FCGR2B*, both a polymorphism that influences the inhibitory potential of B cells [11] and promoter haplotypes associate with an increased risk of SLE. Genetic variation in this family, however, is not limited to SNPs and haplotypes. A copy number variant (CNV) of *FCGR3B* appears to be more common in systemic autoimmunity, including SLE [12;13].

Complement and Cognate Receptors

The complement system contains an array of proteins that opsonize pathogens, irreparably damage membranes of microorganisms, and induce an inflammatory response. Each of the three established complement pathways [classical, mannose binding lectin (MBL), and alternative] results in the generation of C3 convertase. This enzyme cleaves complement component 3 (C3) into C3a, a peptide modulator of inflammation, and C3b, an opsonin. The classical pathway can be initiated by binding of C1q, immunoglobulin or C reactive protein (CRP) to the target. Cleavage of C4 and C2 forms C4b and C2b respectively which combine to form C3 convertase. C4b can also act as an opsonin. MBL function is similar to C1q, likely having developed from gene duplication events with a common ancestor. Once bound to a pathogen, MBL activates mannan-binding lectin associated serine proteases 1 and 2 (MASP1, MASP2), which cleave C4 and C2 producing similar results to the classical pathway. MBL is considered a collectin, which is discussed below. The alternate complement pathway is triggered by spontaneous hydrolysis of C3, influenced by complement regulatory proteins, such as CD46, which, interestingly, is elevated in the serum of SLE patients [14].

The relationship between complement and SLE pathogenesis has long been noticed since levels of complement are lower in SLE patients and since those individuals with renal manifestations have antibody complexes and complement components found in glomerular biopsies [15;16].

Since complement assists with clearing, via opsonization, apoptotic debris and cellular fragments that may release nuclear antigens, it is understandable that low complement levels predispose individuals to SLE. One of the strongest (and earliest reported) genetic associations with SLE susceptibility is the deficiency of early classical complement components such as the C1 complex subunits (C1q, C1r, C1s), C2, and C4 [16], which shows the potential for CNVs to influence disease risk. This has been verified more recently in additional studies where a low copy number of *C4* increases susceptibility for SLE [17]. In addition to CNVs, a SNP that is linked to lowered C1q production has been associated with cutaneous lupus erythematosus [18] and with SLE in varied racial groups [19]. An allele of a *C3* SNP, which has been shown to result in lowered C3 expression levels, is also associated with risk of developing SLE [20]. Complement component C5 may also be contributory since the TRAF1-C5 locus on Chromosome 9 has been associated with multiple autoimmune conditions including SLE [21], although this finding is not consistent in all populations [22;23].

During opsonization, complement components such as C3b engage phagocytes through complement receptors. Complement receptor 1 (CR1, CD35) is expressed on macrophages and neutrophils with transcription levels affecting disease severity in SLE [24]. CR1 recognizes C3b on a pathogen surface and induces a phagocytic response when the cell is co-stimulated by C5a binding to the C5a receptor. In contrast, CR2 (CD21) and CR3 [also known as macrophage receptor 1 (MAC1)] engagement with C3b can directly lead to phagocytosis without a co-stimulant. CR2, which functions on antigen-presenting B cells in binding C3b and presenting the bound immune complexes, has several SLE-associated polymorphisms that influence alternative splicing [25] and SLE-associated haplotypes [26]. CR3 is composed of integrin subunits encoded by *ITGAM* and *ITGB2*. CR4 is also composed of the integrin subunit *ITGB2*; however, it is differentiated from CR3 in the inclusion of *ITGAX* in place of *ITGAM*. The locus that encodes *ITGAX-ITGAM* on Chromosome 16 provided a strong association with SLE susceptibility in separate recent GWAS [9;27] and replication studies involving multiple populations [28]. Taken together, these data provide clear evidence of the involvement of complement receptor in SLE pathogenesis.

Other Opsonins – Pentraxins, Collectins, and Ficolins

Collectins are a family of well-conserved C-type lectins that contain a collagen-like domain and a carbohydrate recognition domain. Collectins interact with complement proteins to effect opsonization of pathogens. They are traditionally classified into three groups – mannose binding lectin (MBL), surfactant protein A (SFTPA), and surfactant protein D (SFTPD).

MBL is the prototypic C-type lectin opsonin and functions by interacting with complement components during the innate immune response. It assists in clearing apoptotic debris that could trigger an anti-nuclear autoimmune response. Genetic variants of MBL, including a promoter SNP and a SNP in exon 1, are associated with SLE risk [29], as are variants of *MBL2*, a molecule that modifies MBL expression level. Both low MBL levels [30] and presence of anti-MBL antibodies [31] are correlated with SLE providing additional evidence for the involvement of MBL in disease.

SFTPA, encoded by a cluster of genes on Chromosome 10q22, targets pathogens and apoptotic debris for phagocytosis by alveolar macrophages. SFTPD, which has a collagen domain structurally homologous with C1q, can enhance phagocytosis by alveolar macrophages via FcR and complement receptor engagement. The roles of surfactants as candidate genes for SLE, including pulmonary manifestations [32], is unexplored.

COLEC11 (CL-K1), another collectin family member, recognizes sugars on bacterial surfaces, while COLEC12 (CL-P1) functions as a scavenger receptor that binds microorganisms and oxygen radical damaged phospholipids to speed recognition by phagocytes. Not all collectins

function directly in opsonization though since some, such as COLEC10, are only found in the cytoplasm.

Ficolins, another family of molecules with opsonic properties, include a collagen-like domain that provides them with homology to collectins. Ficolin 2 can bind DNA leading to increased attachment and engulfment of necrotic cells by macrophages. Ficolin 3 has been observed at increased levels in the serum of SLE patients [33], which is consistent with a function in reducing auto-inflammation by clearing apoptotic debris.

Pentraxins are innate immune molecules that recognize microbial, nuclear, and apoptotic antigens, initiate complement activation, and bind directly to phagocyte FcRs. One pentraxin family member, C-reactive protein (CRP), is an acute phase molecule known to mediate phagocytic responses by binding microorganisms and nuclear materials such as histones and chromatin. Impairment of nuclear antigen clearance by CRP may be one way it influences the pathogenesis of SLE since lowered serum levels of CRP have been related to disease presence and clinical activity [34]. Genetic variation linked to reduced CRP expression has associated with SLE in a British study [35], and a promoter SNP, rs3093061, is associated in African-Americans and Caucasians [36]. *CRP* variants can also influence clinical manifestations in SLE such as development of nephritis and vascular disease.

Amyloid P component of serum (APCS) [also called serum amyloid P], also functions as an opsonin for microorganisms. Its gene is located near *CRP* on Chromosome 1 within a lupus susceptibility region [35]. Like CRP, APCS binds chromatin and signals through FcRs, thereby, potentially playing a role in a nuclear-based autoimmune condition such as SLE. While elevated levels of APCS have not been reported in SLE patients, there is an inverse relationship between the presence of anti-dsDNA antibodies, a common serological marker for SLE, and APCS DNA complexes. This is consistent with the decreased amount of APCS DNA complexes measured in SLE patients [37]. Serum levels of anti-APCS antibodies are, however, raised in SLE patients and relate to disease activity, further suggesting a pathogenic role for this opsonin [38].

Pentraxin 3 (PTX3) binds to apoptotic cells to influence phagocytosis; it sequesters pathogenic debris from antigen-presenting cells to limit autoimmune reactions in inflamed tissues. However, unlike CRP, a correlation between levels of PTX3 SLE risk has not yet been observed [39].

Opsonins, Gene-Gene Interactions, and SLE Susceptibility

Functioning as part of the innate immune system, opsonins (Ig's, C1q, CRP, MBL) target apoptotic cells and nuclear debris for more efficient disposal. Creating immune complexes with Ig's, CRP or collectins and engaging complement components as amplifiers of the opsonic process, both Fc receptors and complement receptors serve both activation by and uptake of debris (Figure 1). Remarkably, evidence for genetic variants of opsonins, amplifiers and cognate receptors contributing to lupus susceptibility is available through candidate gene studies. It is surprising, therefore, that currently reported genome-wide association studies have not identified more than the Fc receptors and CR3 as susceptibility genes.

Incomplete genomic coverage can limit the discovery of contributing genes, and studies with more advanced platforms and much greater marker density are being developed. However, single-locus analysis strategies are also limiting in that they do not accommodate interactions between genes and function in biological pathways. When a genetic factor functions as part of a complex mechanism, the effect can be missed in single-locus analyses.

The opsonin pathway for the clearance of apoptotic cells and nuclear debris is such a complex mechanism. When the pathway does not function properly, it appears that immune mediated disease may ensue. Thus, additional investigation into dysfunction or deficiency of opsonization may provide insight into mechanisms of SLE pathogenesis. Genetic findings of a single polymorphism produce small odds ratios and only then with a large sample size. Analyzing pathways or epistatic interactions may allow detection of novel causal variants or uncover new associations. Identifying combination of molecules with a common link may ease the translation from an understanding of the genetic etiology to functional research.

As a pathway, opsonins provide interesting implications for understanding disease since it is actually a subset of a more generalized idea of target recognition systems – a concept which has been gaining attention in recent years. However, what separates opsonization as unique from other recognition systems is the variety of recognition strategies employed. There are pattern specific innate-immune recognition systems such as CRP and MBL; there are antigen-specific adaptive-immune recognition systems such as antibodies; and there are recognition amplifiers such as complement that both interact directly by recognizing antigens and increase the efficiency of other opsonins by catalyzing phagocytosis. Examining a role for recognition systems in general, particularly mechanisms known to recognize and clear nuclear antigens, may identify additional candidates for involvement in SLE pathogenesis.

Take Home Points

- Recent genome wide association studies have implicated molecules involved in the opsonization pathway as influencing SLE susceptibility.
- Pathway analyses focused on the opsonin pathway may reveal new insights into SLE pathogenesis.

Acknowledgments

The authors received salary support from NIH R01-AR33062, R01-AR42476, P01- AR49084, and T32 AR07450 (NIAMS).

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Figure 1.
The Opsonization Pathway.