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Systemic Lupus Erythematosus: From Genes to Organ Damage

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Abstract

Systemic lupus erythematosus (SLE) is a disease characterized by inappropriate response to self-antigens. Genetic, environmental and hormonal factors are believed to contribute to the development of the disease. We think of SLE pathogenesis as occurring in three phases of variable duration. A series of regulatory failures during the ontogeny of the immune system lead to the emergence of auto-reactive clones and the production of auto-antibodies (phase I). As the immune response to self-antigens broadens, the auto-antibody repertoire is enriched (phase II) and clinical manifestations eventually ensue (phase III). The final result is tissue damage that if not treated will lead to the functional failure of such important organs as the kidney and brain.

Keywords

Systemic Lupus Erythematosus; Auto-antibodies; Complement; Cell signaling; CD3ζ chain; Fcγ receptor; NFAT; Nephritis

1. Introduction

A prototypic autoimmune disease, systemic lupus erythematosus (SLE) is a syndrome characterized by inappropriate immune response to self-antigens. In SLE, the immune system fails to control auto-reactive T, B, and antigen-presenting cells that produce an array of auto-antibodies and cytokines leading to the cellular infiltration of various organs and the local activation of complement (1). Eventually organ damage occurs that, if left untreated, leads to serious and even fatal complications such as renal failure.

Although the clinical and laboratory findings in SLE are well described, the exact events that lead to the development of the disease are unclear. Schematically, we can hypothesize based on the current evidence that the development of SLE occurs in three phases:

1. The initial break in immunologic tolerance toward certain self-antigens induced by a poorly characterized interplay between environmental, hormonal and genetic factors.
2. The propagation of the abnormal immune response and the appearance of laboratory evidence of immunological dysfunction, such as antinuclear antibodies.
3. The clinical manifestations, with one or more organs such as the joints, skin or kidneys displaying inflammation-induced damage.

In this chapter, we will discuss initially the epidemiology and clinical manifestations of SLE, before addressing the pathogenetic mechanisms that lead to the expression of the disease.

2. Epidemiology: Heredity, Gender and the Environment

SLE is a relatively rare disease affecting approximately 40–50 individuals per 100,000 people in the United States (2), with an incidence of approximately two to three new cases

per year per 100,000 persons (3). Worldwide studies, although showing variable incidence and prevalence among different populations (4–6), agree in that the majority of patients with SLE are women of childbearing age; the female: male ratio is estimated between 6 and 14:1 (7–10). SLE is less common at the extremes of age but can affect both children (11) and elderly individuals (12, 13); interestingly, the difference in incidence between men and women is not as striking in these age groups (13). These observations led to the hypothesis that hormonal factors, either the excess of estrogens or lack of androgens, may be involved in the development of the disease by influencing the development and/or reactivity of the immune system.

In addition to the gender differences in prevalence, SLE prevalence and severity differ among different populations. For example, individuals of African and Asian descent in the United States are more commonly and more severely affected than European-Americans (3, 14, 15). This observation underscores the fact that genetic factors predispose individuals to the development of SLE. Adding further credence to this argument, twin studies have shown a higher concordance rate for SLE among monozygotic versus dizygotic twins (24% vs. 2%) (16).

Nevertheless, genetic factors can not account for all the cases of SLE and therefore both natural factors and infectious agents have been implicated in the development of the disease. One of the first environmental factors that was found to be associated with SLE is sunlight: indeed, a significant proportion of patients display skin sensitivity to light and in particular ultraviolet light (17). No definite association with a particular infectious agent has been made; one exception is the Epstein-Barr virus (EBV), a virus associated with B cell hyperactivity. Patients with SLE are almost universally seropositive for EBV as compared to lower rates in healthy controls. Given this as well as similarity of EBV antigens and auto-antigens targeted by auto-antibodies found in SLE patients' sera, EBV has been suggested as a possible instigator of SLE (18).

The above described epidemiological characteristics of SLE suggest that a host of environmental, infectious and hormonal factors when applied to a genetically predisposed individual may lead to the development of SLE. The exact factors and the processes that trigger the disease are unclear and are the focus of many studies in humans with SLE and animal models of lupus.

3. Clinical Manifestations: Evaluating and Treating Systemic Inflammation

The initial clinical presentation, course and outcome of SLE are highly variable. The diagnosis is based on the presence of certain clinical and laboratory findings that are listed in Table 1 (19). Typically the disease course in most patients is characterized by periods of high activity (flare) and remission. The duration and frequency of these flares, their severity and precise clinical picture differ significantly among patients. This makes SLE a challenging disease to diagnose and treat.

The symptoms and signs of SLE can be broadly categorized as constitutional (a result of systemic inflammation), and organ-specific (20–23). Constitutional symptoms that patients with SLE may experience include high fevers, fatigue, and weight loss. More importantly the overwhelming majority of patients with SLE will present with specific organ involvement. Approximately 60–90% of the patients will develop some form of inflammatory skin rash which is oftentimes caused or exacerbated by sunlight (ultraviolet radiation) (17). The joints are affected in a significant percentage of patients in the form of inflammatory arthritis with pain and swelling. Inflammation involving the serous membranes (pleuritis, pericarditis) manifesting as chest or abdominal pain, is also common (10–30% of the patients) (20, 21). SLE affects the hematologic system with a decrease in the

levels of white cells, platelets, and red cells; life threatening thrombocytopenia and severe anemia although uncommon can be seen in patients with SLE. In the most severe forms of SLE, the kidney and the central nervous systems are affected (23). The patients with renal lupus will present with abnormalities in the urine (blood and/or protein in the urine) and oftentimes edema. If left untreated, renal lupus may lead to severe complications including renal failure and vascular disease. Patients with central nervous involvement present with neurological complications (e.g., strokes, pain due to nerve damage) and/or psychiatric manifestations (mania, depression). SLE may also affect other organs such as the muscles (myositis), the lung (pneumonitis), and the heart (myocarditis). Overall, SLE symptoms and signs are caused by local inflammation in various organs that if left untreated may result in permanent organ damage.

The treatments to date are based on immunosuppressive regimens that nonspecifically inhibit the immune system. When intervening early on, before permanent damage occurs, these medications can be effective albeit with significant side effects. For skin and joint manifestations, the antimalarial hydroxychloroquine, nonsteroidal anti-inflammatory medications, and low to moderate doses of corticosteroids are often times sufficient. For moderately severe disease such as persistent skin rashes, pleuritis, severe arthritis, higher doses of corticosteroids are used with or without the introduction of an immunosuppressive medication such as methotrexate or azathioprine (24, 25). For the most severe life or organ-threatening manifestations (kidney, nervous system lupus), cytotoxic medications (cyclophosphamide) are used (22, 23). Clinical trials are ongoing for the use of less toxic medications such as mycophenolate mofetil in renal lupus (26, 27).

4. Clinical Laboratory Findings: A Window in the Pathogenesis of SLE

Studies of patients with SLE have shown that the above described clinical manifestations are caused by an exuberant immunological activation in the absence of a readily recognizable infectious agent. Both the humoral and cellular components of the immune system are activated. The serum of patients with SLE contains an array of antibodies that recognize self antigens and in particular nuclear antigens (reviewed in (28)). Some of these antibodies have been associated with specific manifestations of the disease; for example anti-dsDNA and anti-Sm antibodies are associated with nephritis (29), while anti-Ro antibody is associated with dry mouth (sicca) and neonatal lupus (20, 28). Some, but not all of these autoantibodies have been shown to cause damage. Examples include the antiplatelet antibodies that can reduce the number of platelets leading to bleeding (immune thrombocytopenia); the antiphospholipid antibodies directed against the components of the cell membrane that can mitigate platelet aggregation and thrombosis. It has to be noted that auto-antibodies can be found in the sera of patients with SLE long before the clinical manifestations of the disease, as shown in a study evaluating sera of military recruits who developed SLE (30). In this landmark study it was shown that auto-antibodies can be found in the serum of SLE patients long before the diagnosis is made. Importantly, there was a temporal progression of the autoantibody repertoire whereas antinuclear (ANA) antibodies appeared first, followed by anti-dsDNA and antiribonucleoprotein antibodies.

Another characteristic of the serum of patients with SLE is the low level of complement proteins C3 and C4; this is thought to be due to complement activation by immune complexes in the tissues and circulation. Importantly, in a significant number of patients (especially patients with nephritis), falling C3 and rising anti-dsDNA levels may predate clinical deterioration (31). These findings in the peripheral blood of patients with SLE show that there is a hyperactive B cell compartment of the immune system that produces autoantibodies against cellular components.

Several studies have addressed the nature of organ and tissue damage in SLE. Biopsies of the skin and the kidneys, two organs that are affected in a significant proportion of patients with SLE, have clearly shown that the components of the immune system, both cellular and humoral, are found in these target-organs. Skin biopsies in cutaneous lupus show a lymphocytic infiltration of the dermis and deposition of immunoglobulin and complement along the dermal–epidermal junction (32). Depending on the level of inflammation and the location of the infiltrating cells, various clinical manifestations ensue: acute superficial rashes, chronic discoid lesions, bullae formation or deep layer inflammation (panniculitis); oftentimes ulcers and scars form. Similarly, kidney studies have shown that lymphocytes infiltrate the interstitium while immunoglobulin (IgG, IgM, and IgA) and complement deposit in the glomeruli. The result of this inflammatory process is scarring of the glomerular tuft and tubular damage. Clinically these processes are manifested by leakage of protein and cells in the urine, and in the extreme cases by uremia (22, 23).

5. Etio-Pathogenesis: Integrating Genes, Environment and the Immune System

The epidemiological features, clinical manifestations and clinical laboratory findings have been invaluable in creating a model for the development of SLE and the propagation of the autoimmune response. The immunological abnormalities that lead to SLE seem to start long before the clinical manifestations become apparent; genes, infections and environmental factors as well as hormones influence the development of the immune system in the early years of life, facilitating the emergence and activation of autoimmune lymphocytic clones.

Given the difficulties studying the preclinical phases of SLE at least in humans, most research efforts to understand the etio-pathogenesis of SLE have focused on two fronts:

- a. The characterization of the immune deregulation in SLE and the identification of the key pathways involved in it.
- b. The unraveling of the genetic background of patients with SLE and the potential role of these genes to disease pathology.

In the next sections, we will try to provide the links between SLE risk conferring genes and the immunological abnormalities found in patients with active disease. In addressing this issue, both intra- and intercellular signaling aberrations as well as changes in soluble mediators will be examined. It has to be noted that no single abnormality has been recognized to date as dominant in SLE but rather an array of signaling aberrations lead to the expression of the syndrome.

6. Cell Signaling: Auto-Reactivity, Deficient Regulation, and Inappropriate Activation

One of the first and the most significant susceptibility locus that has been found to be associated with SLE resides within the highly polymorphic major histo-compatibility complex (MHC) class II locus. In particular, Caucasians that have the DR2 (*HLA-DRB1*1501*) or DR3 (*HLA-DRB1*0301*) alleles have a two- to threefold increase in their relative risk to develop SLE; the risk conferred by these alleles though, is not as prominent in the other populations (33, 34). The MHC class II locus encodes proteins that are involved in antigen presentation to CD4+ T cells. Beyond being simply associated with SLE risk, certain *MHC class II* genes have been found to be associated with the production of specific autoantibodies. For example, MHC class II allele *HLA-DRB1*03* was associated with the expression of anti-Ro and anti-La antibodies in patients with SLE (35). Similarly modest associations were found between *HLA-DQA1*0601*, and *DQB*0201* with anti-Ro and *HLA-*

*DQA1*0501*, and *DQB*0201* with anti-La antibodies. Although certain clinical manifestations tend to be more prevalent in patients with these alleles, the associations between clinical picture and genotype are modest at best. Given these findings, it has been hypothesized that certain MHC class II molecules expressed on antigen-presenting cells (APC) of SLE patients may preferentially or aberrantly present certain (auto)-antigens to helper CD4+ T cells leading to abnormal T cell responses to antigenic stimuli that should have been ignored under normal conditions.

Indeed, multiple studies have shown that T cells that recognize and react against auto-antigens are present in the peripheral blood of patients with SLE. Among the self-antigens, the T cells from SLE patients have been shown to recognize histones, native DNA, and small nuclear ribonucleoproteins. These T cells are able to provide cognate help to B cells and lead to the production of potentially pathogenic anti-dsDNA auto-antibodies (36, 37).

In addition to auto-reactivity, T cells in SLE show a variety of signaling defects and abnormalities. Once the T cell receptor (TCR) is engaged, SLE T cells show a very robust and early influx of calcium and phosphorylation of Tyrosine residues on early signaling molecules (38). Two main reasons have been recognized as underlying the abnormal early signaling events of SLE T cells: Preaggregated lipid rafts (39) and the substitution of the CD3 ζ chain by the Fc ϵ RI γ chain (40). The lipid rafts are platforms on the membrane of lymphocytes that help bring together all the important molecules that participate in the activation of the cells once their receptor has been engaged by its cognate ligand. In SLE T cells, as opposed to control T cells from healthy individuals and patients with other autoimmune diseases, the lipid rafts are already aggregated thus facilitating the early signaling events that lead to the influx of calcium and activation of kinases and phosphatases. In addition to the ready-made signaling platform, SLE T cells employ a different (rewired) (41) TCR/CD3 molecular complex that is more efficient in transducing the activating signal than the TCR/CD3 complex found in control nonactivated cells. Under normal conditions the main signaling molecule responsible for the transduction of the signal is the CD3 ζ chain. SLE T cells have decreased CD3 ζ chain levels and instead express in its place the Fc ϵ RI γ (40), a molecule initially recognized to be associated with the Fc ϵ receptor on mast cells. This change results in the recruitment of Syk kinase instead of the Zap70 to the CD3 complex and leads to a more robust downstream signaling (41, 42). The expression of CD3 ζ and Fc ϵ RI γ are at least in part dictated by the activity of their respective genes, both of which are controlled by the transcriptional factor Elf-1: Elf-1 binding to its *cis* element on the *CD3 ζ* promoter leads to gene transcription while it acts as a transcription repressor on the *Fc ϵ RI γ* gene. Elf-1 production is defective (43) in SLE T cells thus tilting the balance toward the production of Fc ϵ RI γ . Other mechanisms such as alternative splicing of the *CD3 ζ* gene also contribute to the decreased CD3 ζ chain levels in SLE T cells (44, 45).

In many respects, SLE T cells appear to be hyperactive, but nevertheless their ability to produce interleukin-2 (IL-2) upon activation is limited (46). IL-2 is a cytokine that is important for T cell activation, activation-induced cell death (AICD) and the survival of T regulatory cells (Treg). Its deficient production may therefore be linked to the prolonged survival of T cells (including auto-reactive cells) and insufficient inhibition of autoreactive processes by Treg (47, 48). Multiple transcription factors have to cooperate in order for the *IL-2* gene to be transcribed. In SLE T cells the transcription activators NF- κ B (49), AP-1 (a c-fos/c-jun dimer) (50) and p-CREB (51) are deficient while the transcription repressor CREM (52, 53) binds strongly to the promoter of *IL-2*. This combination of increased repressors and deficient activators is responsible for the inappropriately low production of IL-2 by activated SLE T cells.

The robust calcium flux once the T cell receptor is engaged does translate though into high NFAT (a calcium dependent transcription activator) translocation into the nucleus of T cells (54). NFAT because of deficiency of AP-1 does not stimulate the production of IL-2 but is able to bind to the promoter and stimulate the production of CD154 (also called CD40 ligand). CD154 is a costimulatory molecule that helps the T cells provide help to B cells therefore leading to the production of pathogenic auto-antibodies (55). In addition SLE T cells evade activation induced death (AICD) by yet another mechanism. These cells over-express cyclo-oxygenase 2 (Cox-2) (56), a molecule that facilitates their survival after activation.

Recently, it has been identified that SLE T cells upregulate CD44, a molecule that facilitates their migration in tissues such as the kidneys (57). There they produce proinflammatory cytokines such as IL-17 (58) that enables the recruitment of other immune cells and the propagation of the inflammatory process resulting in tissue damage.

Genetic studies have tried to shed light into the underlying causes for the aberrant function of SLE T cells. Of particular interest has been the observed association of SLE with genes encoding molecules that prevent or dampen T cell activation. One such molecule is the cytotoxic T cell antigen-4 (CTLA-4). CTLA-4 is similar in structure to CD28, which by binding to the CD80/86 molecules on APC augments T cell activation. CTLA-4 blocks the CD28:CD80/86 interaction by potently binding to the CD80/86 and at the same time delivers an inhibitory signal into the cell (59). Therefore CTLA-4 brings T cell activation to an end and induces a state of anergy. This function is an important check-point that prevents over-activation of the immune system and is thought to prevent autoimmune diseases by promoting long-lived anergy (60). Preliminary studies looking at several polymorphisms of the *CTLA-4* gene showed that a T/C substitution at the -1,722 site is associated with SLE (61). Of note though, soluble CTLA-4 was shown to be increased in SLE patients, especially ones with active disease (62). More studies are therefore needed to address the potential role of CTLA-4 in SLE.

Another gene that encodes a negative regulator of T cell activation and has been associated with SLE is *PTPN22*. This gene encodes the lymphoid tyrosine phosphatase (LYP) that prevents T cell activation (63, 64). A missense polymorphism (R620W) (65) in the *PTPN22* gene may impair the negative signaling transduced by LYP thus lowering the threshold for T cell activation.

The serum of patients with SLE contains various auto-antibodies, some of which have clear pathogenic capacity. These are produced by activated auto-reactive B cells, which are clearly abnormal. Although auto-reactive B cells are part of the immunological repertoire of normal individuals, SLE B cells show clear evidence of aberrant function possibly resulting during their maturation process. It has been shown that the peripheral B cell population in patients with active SLE has an increased number of CD127 high plasma cells and decreased number of naïve B cells (66). Looking even further at the naïve B cell population, a study of a limited number of young patients with SLE showed that a large proportion of B cells from these patients (up to 50%) are auto-reactive even before their first encounter with antigens (67). These studies suggest failure of important checkpoints in the maturation of B cells with the resulting survival of a higher number of auto-reactive B cells that may produce auto-antibodies as well as secrete cytokines and act as (auto)antigen-presenting cells. Given these findings, a recent report identifying the *BLK/C8orf13* as a risk conferring area for SLE (68) is very interesting. *BLK* encodes for a src family tyrosine kinase that signals downstream to the B cell receptor. A polymorphism upstream of the *BLK* gene that in B cell lines led to the decreased production of BLK mRNA was associated with SLE. BLK is mainly found in immature B cells and therefore its decreased expression may affect B cell

ontogeny (69). Under normal conditions, immature B cells that encounter and react to auto-antigens during their maturation process will undergo receptor editing or apoptosis (negative selection); these mechanisms prevent the emergence of auto-reactive B cells in the periphery. Immature B cells that recognize self-antigens but due to impaired signaling (as in the case of decreased BLK activity) do not undergo negative selection, will escape to the periphery.

Abnormal maturation and increased help from T cells cause multiple signaling aberrancies of SLE B cells. On the one hand, similar to T cells, SLE B cells upon the engagement of their receptor have increased tyrosine phosphorylation and intracellular calcium flux (70). On the other hand, inhibitory signaling such as via the Fc receptor FcγRIIb (a negative regulator of B cell receptor (BCR) signaling) are depressed (71). In addition, memory SLE B cells do not upregulate FcγRIIb as readily as controls (72). Genetic studies have shown an association of a polymorphism (FcγRIIb-232 I/T substitution) with SLE (33). The final result of this imbalance between inhibitory and activation signals in SLE B cells is augmented antibody production.

SLE B cells can also influence the function of T cells as they have been shown to produce antibodies that react with the CD3 molecule on T cells and activate the calcium and calmodulin dependent kinase IV (CaMKIV) (73) in these cells. In turn, CaMKIV causes binding of the repressor c-AMP response element modulator (CREM) to the *IL-2* promoter, blocking the transcription of the gene.

In summary, the hyperresponsive SLE B and T cells (see Fig. 1) contribute to the production of autoantibodies, cytokine imbalance and cell tissue infiltration that lead to the clinical manifestations of SLE.

7. Humoral Factors: Apoptosis, the Complement System and Cytokines

Two of the most important findings in the serum of patients with SLE are the presence of various auto-antibodies and the decrease in the concentration of complement. Under normal conditions, natural auto-antibodies and complement are important as they play a major role in the clearance of auto-antigens contained in apoptotic material (74). It has been hypothesized that the appearance of auto-antibodies and the activation of complement seen in patients with SLE are a result of inappropriate cellular debris (waste) disposal (75). According to this theory, debris from cells that have undergone cellular death (by apoptosis or necrosis) is not handled correctly by the body with a resultant stimulation of autoantibody production, creation and tissue deposition of immune complexes, and complement activation leading to tissue damage.

This theory has been further strengthened by the fact that several complement components encoding genes have been associated with susceptibility to SLE. Individuals with deficiency in C1q, C2 or C4 have a much higher risk to develop SLE than control individuals. In the case of C1q deficiency, a very rare genetic trait, the rate of development of SLE is very high, approximately 90%. Similarly, 10% of patients who have a genetic deficiency in C2 develop SLE as well as up to 75% of patients with a complete lack of C4 (75–77). These observations point to the fact that complement is essential not only as a first line of defense against pathogens, but also is instrumental in averting the emergence of autoimmunity. Complement coats (opsonizes) auto-antigen:antibody complexes facilitating their removal from the circulation. This prevents the inappropriate presentation of auto-antigens to immune cells and emergence of autoimmunity (74) as is probably the case in SLE patients with complement deficiency.

Besides complement components of the classical pathway, SLE has also been associated with components of the lectin pathway of complement activation. More precisely a proportion of SLE patients have been shown to have deficiency of the mannose binding lectin (MBL) (78), a molecule that is similar to C1q in structure and function. Another study has associated polymorphisms in the promoter or coding region of *MBL* gene with SLE (79). The MBL pathway is crucial for the opsonization of bacteria and its deficiency in SLE may be important for both decreased antimicrobial vigilance (80) and the poor handling of auto-antigens.

Complement fragments C3b and C4b coating apoptotic material bind through the complement receptor 1 (CR1) (CD35) onto erythrocytes. An association between a structural variant of CR1 (CR1 S) and SLE in Caucasians has been suggested in a meta-analysis (75) of genetic studies in SLE; this observation suggests that even in patients with normal complement activity in the serum, slow removal of the immune complexes from the circulation may result in further immune activation of cells by the auto-antigens as well as the increased deposition of immune complexes in the tissues.

Cellular waste is also cleared by the cells of the reticulo-endothelial system (RES) mainly via the interaction of IgG with its receptor. IgG-coated auto-antigens (debris) bind to one or more of the various Fc γ receptors (Fc γ R) on the surface of the cells of the RES. The affinity of the Fc γ R for the different IgG subclasses can be influenced by the substitution of a single aminoacid in their extracellular domain. It is therefore not surprising that variants of the *FCGR* gene that result in changes of the aminoacid sequence of these chains are associated with altered binding to IgG. These subtle changes can in turn influence such important immune functions as phagocytosis, antibody-dependent cell cytotoxicity (ADCC), and the clearance of immune complexes. Several studies have recognized the 1q23 region that contains the genes *FCGR2A*, *FCGR3A*, *FCGR3B* and *FCGR2B* which encode for low affinity IgG receptors as a susceptibility locus (33) for SLE.

FCGR2A has two codominant alleles that encode the different forms of Fc γ RIIa (CD32), a receptor found primarily on polymorphonuclear cells, mononuclear phagocytes and platelets. Fc γ RIIa binds IgG2 and C-reactive protein (CRP) (81). The two forms of Fc γ RIIa differ from each other by one single aminoacid at position 131. IgG2 binds stronger to the Fc γ RIIa that bears histidine at position 131 (H131) than to the molecule that has arginine at the same position (R131) (82). IgG2 is a poor activator of classical complement pathway and therefore its binding to the Fc γ RIIa is important for the clearance of immune complexes that contain IgG2. Multiple studies in different populations concluded that patients with the Fc γ RIIa-R131 polymorphism are at higher risk for SLE (33) but not nephritis (83, 84).

Altered CRP expression may independently or in conjunction with altered expression of Fc γ RIIa contribute to the development of SLE. Under normal conditions CRP is important for the disposal of cellular debris. In SLE, the defective expression of CRP may lead to deficient disposal of products of apoptosis making them available for presentation to T cells. SLE has been associated with a single nucleotide polymorphism (CRP-4) in the 3' region of the *CRP* gene (85).

Similar to *FCGR2A*, *FCGR3A* has two codominant alleles that encode for two different forms of Fc γ RIIIa (CD16), a receptor expressed on natural killer (NK) and mononuclear cells. Fc γ RIIIa binds IgG1 and IgG3. The two forms of Fc γ RIIIa differ at position 176 with the one form having valine (V176) and the other phenylalanine (F176). The Fc γ RIIIa from individuals that are homozygous for the V176 form bind IgG1 and IgG3 more efficiently than Fc γ RIIIa from individuals homozygous for the F176 (82). A meta-analysis of data

derived from 11 independent studies of the weaker FcγRIIIa-F176 form found a modest association with SLE (84).

Along the same lines SLE patients lacking the enzyme DNase I were reported (86). DNase I deficiency may lead to a decreased breakdown of DNA-protein complexes, eventually giving rise to immunological targeting of native DNA and its associated proteins.

These data suggest that proper waste handling fails at multiple levels in SLE with defective coating of the auto-antigens by complement and CRP and decreased binding to the Fc receptors.

Besides auto-antibodies and complement, the immune function in SLE is influenced by an array of cytokines that are aberrantly produced or missing (87). Genes encoding cytokines such as tumor necrosis factor (TNFα) (88) and interleukin-10 (IL-10) (89) as well as the TNF receptor (90) have been associated with SLE. It has been shown that both IL-10 and TNF are aberrantly produced in SLE. More importantly though it has been found that peripheral blood mononuclear cells (PBMC) taken from SLE patients, especially ones with active disease, bear an interferon signature (91); in essence this means that genes that depend on type I interferons are activated in SLE patients. Genetic studies have shown that genetic polymorphisms of two genes that encode transcription factors related to interferon, *STAT4* (T allele; rs7574865) (92) and *IRF5* (T allele; rs2004640) (93) are associated with higher risk for development of SLE. Multiple inflammatory cytokines such as tumor necrosis factor and interleukin-6 are upregulated by these transcription factors (94). It is therefore plausible that the cells of SLE patients over-interpret interferon-mediated signals, such as those elicited by viral responses leading to the inappropriate activation of the immune system.

8. Conclusion

Genetic and functional studies have shown that SLE pathogenesis is complex. On the one hand, the failure of toleragenic mechanisms results in the generation of autoreactive immune cell clones. On the other hand, the deficient removal of apoptotic debris due to complement and/or Fc receptor abnormalities leads to the increased total burden of self-antigens. With these mechanisms in place, external stimuli are over- or mis-interpreted by the immune system, and result in aberrant antigen presentation, lymphocyte activation, and the production of an array of inflammatory cytokines. These in turn lead to tissue deposition of immune complexes, complement activation, and target-organ cell infiltration. Current and future trials aim at understanding the complex mechanisms in every step of SLE pathogenesis so that we may design more effective and less toxic therapeutic interventions.

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Fig. 1.

Aberrant T:B cell cooperation in SLE. SLE T cells display an aberrant phenotype upon activation. They express persistently CD154 (CD40 ligand) that provides help to B cells and do not undergo readily activation-induced cell death due to the upregulation of cyclo-oxygenase 2 and deficient production of interleukin-2. At the same time, IL-17+ T cells infiltrate tissues and contribute to local inflammation. Impaired toleragenic mechanisms lead to the escape to the periphery of auto-reactive B cells, which are prone to produce autoantibodies with help by T cells. Apoptosis of cells (such as keratinocytes after UV exposure) leads to ample auto-antigen availability that is not handled appropriately by the reticulo-endothelial system. In turn, immune complexes containing autoantigens and autoantibodies deposit in tissues causing complement-mediated injury.

Table 1

Criteria for the diagnosis of systemic lupus erythematosus

1.	Malar rash
2.	Discoid rash
3.	Photosensitivity
4.	Oral ulcers
5.	Arthritis
6.	Serositis
7.	Renal disorder
8.	Neurologic disorder
9.	Hematologic disorder
10.	Immunologic disorder
11.	Antinuclear antibody (ANA)