Systemic lupus erythematosus and immunodeficiency

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ABSTRACT
Systemic lupus erythematosus (SLE) is a prototypic systemic autoimmune disease that develops in genetically susceptible individuals in response to environmental factors. SLE and primary immunodeficiency disease (PID) share some clinical manifestations in that certain PIDs present with autoimmune phenomena. Patients with SLE become susceptible to infection via three pathways. First, SLE and PID share some genetic factors, such as complement and mannose-binding lectin genes, which predispose patients to infection. Second, patients with SLE have an inherently high risk of infection because of their intrinsic immunological abnormalities induced by SLE. Third, patients with SLE receiving immunosuppressive treatment are at high risk of infection. Further studies delineating the abnormalities related to both autoimmunity and immunodeficiency would be warranted to identify a new potential drug target for SLE.

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1. Introduction

Immunodeficiency results from a defective host defense system involving either innate or acquired immunity, and is characterized by increased susceptibility to infection. It is most common in children and manifests as repeated, severe, opportunistic, or chronic infections involving various types of microorganisms [1]. Immunodeficiency can be classified as primary or secondary. Primary immunodeficiency is caused by an intrinsic or congenital defect of the immune system, which is mediated by genetic mutations that affect the development, differentiation, and function of immune cells. In contrast, secondary immunodeficiency is caused by dysfunction of the immune system as a result of extrinsic factors, such as immunosuppressive drugs, infection (including human immunodeficiency virus), malignancy, aging, malnutrition, and chronic diseases.

Systemic lupus erythematosus (SLE) is a prototypic systemic autoimmune disease that is characterized by loss of immune tolerance to autoantigens, such as nuclear antigens, and production of autoantibodies and immune complexes, leading to tissue inflammation and damage to various organs. SLE is a multifactorial disease caused by the interaction of multiple genetic and environmental factors. Family studies have revealed that the estimated heritability of SLE is 44–66% [2,3]. Association studies based on the candidate gene approach and recent genome-wide association studies (GWAS) have led to the discovery of multiple common susceptibility variants (single nucleotide polymorphisms) contributing to the development of SLE (Table 1) [4–6]. However, Sun et al. demonstrated that the whole set of common genetic variants known at that time accounted for only 24% of SLE heritability [7]. This missing heritability in SLE could be attributed to rare genetic variants, epigenetic effects that regulate gene expression independently of DNA sequence (DNA methylation, histone modifications, and microRNA [miRNA]), and epistasis (gene-gene interactions) for disease susceptibility [8].

Although SLE and immunodeficiency are two distinct disease entities, patients with SLE become susceptible to infection via three pathways (Figure 1). First, some of the pathways that the SLE-susceptible genes are involved in are implicated in the pathogenesis of immunodeficiency, which could predispose patients with SLE to infection. Second, patients with SLE are considered to be inherently susceptible to infection because of immunological abnormalities, such as lymphopenia and low production of interleukin-2 (IL-2). Third, immunosuppression by medication used in the treatment of SLE makes patients with SLE vulnerable to infection. In this review, we discuss the pathophysiology of SLE in light of the genetic backgrounds that are common to primary immunodeficiency.

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2. Infection as a trigger for development of SLE

SLE is a chronic inflammatory disease that develops in genetically susceptible individuals in response to environmental factors. Patients with SLE become susceptible to infection via three pathways. First, some of the genetic factors involved in SLE susceptibility (e.g., mannose-binding lectin deficiency) are related to immunodeficiency and predispose patients to infection. Second, the immunological abnormalities induced by SLE could have direct immunosuppressive effects. Third, patients receiving immunosuppressive drugs as treatment for SLE are at high risk of infection. SLE: systemic lupus erythematosus.

3. Autoimmune manifestations in primary immunodeficiency diseases

Primary immunodeficiency diseases (PIDs) are broadly classified into nine categories: combined immunodeficiency states, combined immunodeficiency states with syndromic features, predominantly antibody deficiencies, diseases of immune dysregulation, defects of phagocyte number or function, defects in intrinsic and innate immunity, autoinflammatory diseases, complement deficiencies, and phenocopies of inborn errors [12].

Depending on the genetic defects responsible for immunodeficiency, certain PIDs are associated with a unique set of autoimmune manifestations. For example, common variable immune deficiency (CVID) is a heterogenous primary immunodeficiency syndrome characterized by failure to produce immunoglobulin, which leads to hypogammaglobulinemia and chronic bacterial infections mainly affecting the respiratory tract and gastrointestinal tract [13,14]. About 20–30% of patients with CVID develop autoimmune manifestations, particularly autoimmune thrombocytopenia and hemolytic anemia, followed in descending order by autoimmune thyroid disease, vitiligo, pernicious anemia, psoriasis, rheumatoid arthritis, and SLE [14–17]. Although the etiology of autoimmunity in CVID is unknown, disturbance of T-cells, including diminished numbers of regulatory T-cells [18,19], B-cells [20], and cytokines [21], has been reported in patients with CVID [22].

With regard to the mechanisms responsible for the autoimmune manifestations observed in PID, it has been demonstrated that in certain PIDs the mutation responsible for PID affects the checkpoints that govern T-cell tolerance [23]. For example, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, also known as autoimmune polyglandular syndrome type 1, is an autosomal recessive disorder with a mutation of the autoimmune regulator (AIRE) gene that causes antigen-specific T-cells for the endocrine glands to escape central tolerance in the thymus [24]. Another example is the syndrome of immune dysregulation, polyendocrinopathy, enteropathy, and X-linked inheritance, that is, X-linked IPEX, which is caused by genetic mutations in the FoxP3 transcription factor that is essential for development of CD25+ regulatory T-cells [25].

In contrast, Arkwright et al. proposed that in certain types of PID, such as virus-associated hemophagocytic lymphohistiocytosis in Chediak–Higashi syndrome and Griscelli syndrome, the autoimmunity associated with PIDs is not a breakdown of self-tolerance but rather the inability of an inherently defective immune system to eradicate persistent microbial immunogens, leading to bystander tissue damage as the host attempts to remove these immunogens [26].

4. SLE and immunodeficiency

SLE and PID presenting with the SLE phenotype are two distinct disease entities. However, there is overlap between the genes that confer susceptibility to SLE and those responsible for PIDs. With regard to the common genetic susceptibility to SLE (Table 1), deficiency of the TYK2, TNFAIP3, TERT, RNASEH2C, RASGRF1, MBL, LYST, IRF7, IRF8, IRAK1, IL10, IL12B, IKZF1, and BACH2 genes are also listed as being responsible for PIDs [12]. The consequences of all the identified genetic variants on function or expression levels have not been fully elucidated experimentally. Nonetheless, for IRF7, the major SLE-susceptible variant confers elevated activation...
of IRF-7, which presumably leads to activation of the IFN pathway downstream [27]. Therefore, it is suggested that the genetic variant does not appear to be involved in immunosuppression in patients with SLE. On the other hand, for TNFAIP3, the SLE risk alleles in the TNFAIP3 locus harbored an enhancer element resulting in a defect in expression of TNFAIP3 [28]. TNFAIP3 plays an important role in nuclear factor (NF)-κB pathways and its deficiency results in immunodeficiency. Thus, an SLE-susceptible genetic variant could possibly yield multiple deleterious effects in the immune response due to decreased level of TNFAIP3 [29]. Another possibility is that the immunosuppressive effect mediated by the genetic variants is not complete, so it may not necessarily be associated with immunodeficiency. It would be necessary to annotate the function of SLE risk genes in the post-GWAS era, and further studies investigating the immunocompromised status of patients with SLE burdened with multiple genetic variants presumed to be involved in immunodeficiency would be warranted to delineate the relationship between SLE diathesis and vulnerability to infection.

### 4.1 Complement deficiency

The rare genetic variants responsible for the mono- genic forms of SLE that occur in patients with a single gene defect also contain those shared by PIDs (Table 2) [30,31]. For example, deficiency of the three-prime exonuclease 1, identified in familial chil- blain lupus and Aicardi–Goutieres syndrome, results in the accumulation of nucleic acid fragments during the DNA damage sensing response, which stimulates production of type I interferon. Defects in other components of the DNA damage sensing and repair pathways that result in the upregulation of type I interferon and a lupus-like phenotype include RNASEH2A/B/C, SAMHD1, ADAR, and IFIH1 [32].

Other examples include deficiency of the complement system including the mannose-binding lectin (MBL) pathways. The complement system is involved in the innate immune response, consists of more than 30 plasma and cell-membrane proteins, and is divided into three pathways: classical, alter- native, and lectin. Activation of the complement

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**Table 1.** Systemic lupus erythematosus-susceptible genes identified by candidate gene and genome-wide association studies as common genetic variants.

| Chromosome | Gene |
|------------|------|
| 1          | PTPN22, FCGR2A, 3A, 3B, FCGR2B, TNFSF4 (OX40L), NCF2-SMGG, PTPRC (CD45), IKBKE, IL10, LYST, LBH, SPRED2, IFIH1 (MDA5), STAAT4, IKZF2, RASGRF3, ABHD6, CD80, PXK, IL12A, LPP. |
| 2          | BACH2, PRDM1, TNFAIP3. |
| 3          | HHB, CD40, CD80, PXK, IL12A, LPP. |
| 4          | BANK1, DGKQ, TCF7, TNIP1, MIR146A, IL12B, TERT. |
| 5          | ATG5, ATXN1, MHC region. |
| 6          | DEF6, UHRF1BP1, BACH2, PRDM1, TNFAIP3, LRRC16A (CARMIL1), SLC17A4. |
| 7          | JAZF1, IKZF1, GTF2IRD1-GTF2I-NCF1, IFI5, NCF1. |
| 8          | BLK, FAM68B3P, PLAT. |
| 9          | JAK2, WDFY4, ARID5B, MBL2. |
| 10         | CXCR5, IRF7, CD44, RNASEH2C, DDX6. |
| 11         | DMC1, NADSYN1, ETS1, PCNW3, SH2B1, SLC15A4. |
| 12         | TNFSF13B (BAFF), RAD51B, CSK, RASGRF1. |
| 13         | CIITA, SOCS1, CLEC16A, ITGAM, ZFP90 (FIR), IRF8. |
| 14         | PRRNK8, PRRNK8, PRRNK8, PRRNK8. |
| 15         | PRRNK8, PRRNK8, PRRNK8, PRRNK8. |
| 16         | PRRNK8, PRRNK8, PRRNK8, PRRNK8. |
| 17         | PRRNK8, PRRNK8, PRRNK8, PRRNK8. |
| 18         | PRRNK8, PRRNK8, PRRNK8, PRRNK8. |
| 19         | PRRNK8, PRRNK8, PRRNK8, PRRNK8. |

**Table 1. Continued.**

| Chromosome | Gene |
|------------|------|
| 22         | SIgLEC6, UBE2L3, SYNGR1. |
| X          | TLR7, TLR8, CXC16A, ITGAM, ZFP90 (FIR), IRF8. |

*aAdapted from [5,6,46].*
cascade leads to provocation of inflammation, strengthening of phagocytic activity, and lysis of invading bacteria. In terms of the relationship between the complement gene and development of SLE, the variations in the copy number of C4 and a deficiency in the C4A gene have been confirmed to play an important role in the risk and manifestations of SLE [33].

The complement system has two roles in the pathogenesis of SLE. Therefore, the activation of the classic complement cascade by immune complexes leads to tissue damage, such as lupus nephritis, suggesting that the complement system has an exacerbating role in SLE. In contrast, it is known that patients deficient in the early components of the classical complement pathway (complement C1q, C1r, C1s, C4, C2, and C3) frequently present with SLE-like clinical manifestations in the addition to susceptibility to infection, suggesting the development of the immunosuppressive effects of SLE. The approximate frequency of SLE as a complication is more than 90% in patients with C1q deficiency, 70% in those with C4 deficiency, 60% in those with C1r or C1s deficiency, and 30% in those with C2 deficiency [34,35]; the development of SLE in these patients is considered to be mediated by defective uptake and processing of immune complexes in the spleen [36], decreased clearance of apoptotic cells [37], decreased ability of autoantigen presentation to B-cells [38], and increased production of IFN-alpha [39].

### 4.2 MBL deficiency

MBL is a serum protein of the collectin family that contains a C-type lectin (carbohydrate-recognition) domain attached to a collagen-like structure and binds to a variety of sugar chains, including mannos [40]. MBL is involved in innate immunity as a trigger for the lectin pathway of the complement system. Thus, binding of MBL to the sugar chains on the surface of a pathogen activates MBL-associated serine proteases, which further activate C4 and C2.

As with the components of the complement system, several studies have suggested an association between MBL deficiency and increased susceptibility to infection and development of SLE. The most frequent cause of MBL deficiency is a genetic mutation that causes substitution of an amino acid at position 54 in Asians and Caucasians and at position 57 in Africans, leading to alteration in the structure of the protein in a way that induces instability and subsequently enhances degradation of MBL in homozygous individuals (approximately 5–10% in all races). MBL deficiency has not been shown to be associated with susceptibility to infection in healthy individuals but was shown to be a significant risk factor for severe bacterial infection in immunocompromised hosts, such as children, patients with human immunodeficiency virus infection, and patients undergoing hematopoietic stem cell transplantation [40].

A number of studies, including meta-analyses, have demonstrated an association of MBL gene polymorphisms causing MBL deficiency with development of SLE [41–47], although there have also been several studies that did not find supportive evidence [48,49]. The association of genetic MBL variation with SLE is presumably explained by the defective handling of apoptotic cells because of MBL deficiency, which leads to accumulation of autoantigens. Therefore, MBL binds to apoptotic cells and cellular material (e.g., DNA) in the disease process, leading to phagocytosis and exclusion of these autoantigens by phagocytic cells with MBL receptors. Alternatively, it is possible that the increased risk of infection caused by MBL deficiency could trigger development of SLE as an environmental factor in genetically susceptible individuals.

### 4.3 IgM deficiency and SLE

With regard to SLE and immunodeficiency, there are several case reports and case series describing an association of SLE with immunodeficiency syndrome presenting with hypogammaglobulinemia, including CVID and selective immunoglobulin deficiency. In a cross-sectional study by Perazzio et al., over a quarter of 300 consecutive patients with SLE were identified as having humoral immunodeficiency with predominantly low IgG subclass and

### Table 2. Systemic lupus erythematosus (SLE)-susceptible genes identified as rare genetic variants.

| Chromosome | Gene          |
|------------|---------------|
| 1          | C1Q, ADAR, FASLG, IFIH1, TREX1, DNASEI, PRKCD, TMEM173, C2, C4, NCF1, FAS, SHOC2, RAG1/2, C1R, C1S, KRAS, PTPN11, DNASE1, RNASE2A, C3, PEPD, ACP5, SAMHD1, CYBB |
| 2          |               |
| 3          |               |
| 4          |               |
| 5          |               |
| 6          |               |
| 7          |               |
| 8          |               |
| 9          |               |
| 10         |               |
| 11         |               |
| 12         |               |
| 13         |               |
| 14         |               |
| 15         |               |
| 16         |               |
| 17         |               |
| 18         |               |
| 19         |               |
| 20         |               |
| X          |               |

*Adapted from [5,6].*
IgM serum levels [50]. Of interest, when Saiki et al. investigated serum IgG, IgA, and IgM levels in 54 patients with SLE, they found that the serum levels of IgM were low and inversely associated with disease duration, and selective IgM deficiency (47 mg/dL) was observed in 12 patients, including 1 with an undetectable level of serum IgM [51].

5. Infection as a cause of mortality in SLE

The prognosis and life expectancy of patients with SLE have improved greatly as a result of corticosteroid therapy [52] and intravenous administration of methylprednisolone [53,54], as well as advances in immunosuppressive therapy such as use of cyclophosphamide and supportive treatment such as hemodialysis. However, the burden of infection is high in patients with SLE receiving immunosuppressive therapies; the leading cause of morbidity and mortality in patients with SLE is infections, including those that are opportunistic.

To determine the magnitude of risk from all-cause and cause-specific mortality in patients with SLE, Yurkovich et al. performed a meta-analysis involving 12 studies that included 27,123 patients with SLE (4993 observed deaths) and demonstrated a three-fold increased risk of all-cause mortality in these patients (meta-standardized mortality ratio [SMR] 2.98, 95% confidence interval [CI] 2.32–3.83) when compared with the general population. The risks of death from cardiovascular disease (meta-SMR 2.72, 95% CI 1.83–4.04), infection (meta-SMR 4.98, 95% CI 3.92–6.32), and renal disease (SMR 7.90, 95% CI 5.50–11.00) were significantly increased, but that for malignancy was not (meta-SMR 1.19, 95% CI 0.89–1.59) [55]. Wu et al. also examined the causes of death in a large nationwide database in China involving 10 centers and 29,510 patients with SLE who were hospitalized between 2005 and 2014. They found that infection (65.8%), particularly severe pulmonary infection, was the most common cause of death, followed by lupus nephritis (48.6%), hematological abnormality (18.1%), neuropsychiatric SLE (15.8%), and interstitial pneumonia (13.1%) [56].

Bernatsky et al. examined mortality trends in patients with SLE using a large international SLE cohort that included 9547 patients treated at 23 centers from the 1970s to 2001. They noted a marked decrease in the all-cause standardized mortality ratio, which was demonstrable for specific causes, including death from infection and lupus activity-related diseases (such as renal disease) over the study period. In contrast, there was a slight increase in the frequency of circulatory diseases during this time [57].

6. Risk factors for infection in SLE

Corticosteroids and immunosuppressive medication increase the risk of infection [58–61]. The risk of serious infection, particularly bacterial infection, is similar in new users of mycophenolate mofetil, azathioprine, or cyclophosphamide [62]. However, intrinsic factors related to the pathophysiology of SLE are implicated in susceptibility to infection in patients with SLE. For example, relapse of lupus nephritis [63] and exacerbation of SLE [64] were demonstrated to be risk factors for infection. Zonana-Nacach et al. investigated the risk factors for infection in 200 outpatients with SLE over an average follow-up period of 22 months [65]. The only variable associated with infection in the multivariate analyses was a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score of $\geq 4$, although univariate analyses revealed that the dose of prednisone and administration of intravenous cyclophosphamide were significantly associated with infection. Torres-Ruiz et al. recently developed a novel index for prospective prediction of the 12-month risk of severe infection in patients with SLE, including immunophenotyping data based on multiparametric flow cytometry, which is comprised of increased numbers of peripheral Th17 cells, B-cell lymphopenia, and lower TLR2 expression in monocytes, as well as use of cyclophosphamide [66]. Therefore, immunological abnormalities related to high SLE disease activity could also predispose patients with SLE to a higher risk for infection independently of therapeutic interventions.

6.1 Hypocomplementemia

Patients with active SLE, especially lupus nephritis, have low serum complement levels because of consumption of complement by the immune complexes. The main function of the complement system is to protect the host from infection by opsonizing invading microorganisms, including encapsulated bacteria such as Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitidis, and Salmonella typhi [67,68]. Therefore, it is possible that hypocomplementemia in active SLE may lead to defective opsonization and reduced clearance of foreign invaders [69].

6.2 MBL deficiency

Circulating serum MBL is involved in host defense against infection. As described elsewhere, the phenotype of MBL single nucleotide polymorphisms associated with susceptibility to SLE is a low serum MBL level, which predisposes patients with SLE to infection [70–72], and particularly bacterial infection [64].
6.3 Lymphopenia

Ng et al. reviewed the case records of 91 patients with SLE and a disease duration of less than 12 months to delineate the role of lymphocytopenia in the development of infection in patients with SLE. They identified 48 major infections during 260 patient-years of follow-up and found that lymphopenia at presentation was a risk factor for major infection but that the SLEDAI score and use of corticosteroids or immunosuppressive medication were not [73]. Merayo-Chalico et al. also performed a retrospective analysis of 167 patients who had SLE with and without severe infections (including diverse microorganisms, not only opportunistic infections) over a 5-year period. Of the many risk factors identified in univariate analysis, including lymphopenia, a high SLEDAI score, treatment with a corticosteroid or mycophenolate mofetil, and low levels of C3 and C4, multivariate analysis revealed that only lymphopenia, corticosteroid use, and low serum C3 levels were independent risk factors for severe infection in SLE [69].

6.4 Decreased production of IL-2

IL-2 is a cytokine that is mainly produced by activated T-cells and is essential for growth and differentiation of T-cells (immunostimulatory function) and homeostasis of regulatory T-cells (immunoregulatory function). Previous studies have demonstrated that production of IL-2 is defective in patients with SLE [74,75] and in some lupus-prone mouse strains [76,77], leading to impaired growth and survival of regulatory T-cells and failure to control autoimmunity [78]. However, IL-2 also plays a key role in cytotoxic T-cell responses that defend the host against infection. Lieberman et al. recently demonstrated that lupus-prone mice fail to raise antigen-specific T-cell responses to intracellular infection. They infected lupus-prone mice (B6.lpr and BXSB) with Toxoplasma gondii, an intracellular parasite, and demonstrated that both strains succumbed rapidly to infection and that the increased parasite burden was correlated with a defective antigen-specific IFN-gamma response. Furthermore, in vitro coculture experiments revealed the presence of an intrinsic T-cell defect that was responsible for the decreased antigen-specific response [79]. It was also demonstrated that selective loss of a certain subset of T-cells (i.e., signaling lymphocyte activation molecule family member 4 [SLAMF4]+ CD8+ T-cells) in patients with SLE contributes to the reduced ability of T-cells to fight infection [80], and that activation of SLAMF7 restores the defective effector CD8+ T-cell function in response to viral antigens [81]. Therefore, impaired production of IL-2 and decreased cytotoxicity of CD8+ T-cells might contribute to the increased rate of infection in patients with SLE [82].

6.5 Conclusions

Patients with SLE succumb to infections as a result of humoral and cellular immunodeficiency because of intrinsic immunologic deterioration in addition to the adverse effects of immunosuppressive drugs. In daily clinical practice, it is important to differentiate between actual infections and flares of SLE and to be aware that there are patients in whom infection causes deterioration of SLE such that infection and active SLE can coexist.

Low-dose IL-2 therapy that decreases SLE disease activity by expanding the Treg population has been shown by Zang et al. to enhance the virus-specific cytotoxic CD8 T-cell response in patients with SLE, which could be potentially valuable in terms of protecting against infection in SLE [83]. Further studies of the immunological abnormalities spanning autoimmunity and immunocompromise (e.g., IL-2) with the aim of developing novel SLE therapies with less severe adverse effects are warranted.

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References

[1] Ziegler JB, Ballow M. Primary immunodeficiency: new approaches in genetic diagnosis, and constructing targeted therapies. J Allergy Clin Immunol Pract. 2019;7:839–841.
[2] Lawrence JS, Martins CL, Drake GL. A family survey of lupus erythematosus 1. Heritability. J Rheumatol. 1987;14:913–921.
[3] Kuo CF, Grainge MJ, Valdes AM, et al. Familial aggregation of systemic lupus erythematosus and coaggregation of autoimmune diseases in affected families. JAMA Intern Med. 2015;175:1518–1526.
[4] Barturen G, Beretta L, Cervera R, et al. Moving towards a molecular taxonomy of autoimmune rheumatic diseases. Nat Rev Rheumatol. 2018;14:180.
[5] Deng Y, Tsao BP. Updates in lupus genetics. Curr Rheumatol Rep. 2017;19:68.
[6] Tsuchiya N. Genetics. In: Hirohata S, editor. Neuropsychiatric systemic lupus erythematosus-pathogenesis, clinical aspects and treatment. New
Ramos PS, Brown EE, Kimberly RP, et al. Genetic factors predisposing to systemic lupus erythematosus and lupus nephritis. Semin Nephrol. 2010;30:164–176.

Yamamoto K. Possible mechanisms of autoantibody production and the connection of viral infections in human autoimmune diseases. Tohoku J Exp Med. 1994;173:75–82.

Lech M, Anders HJ. The pathogenesis of lupus nephritis. J Am Soc Nephrol. 2013;24:1357–1366.

Picard C, Bobby Gaspar H, Al-Herz W, et al. International Union of Immunological Societies: 2017 primary immunodeficiency diseases committee report on inborn errors of immunity. J Clin Immunol. 2018;38:96–128.

Kopecky O, Lukesova S. Genetic defects in common variable immunodeficiency. Int J Immunogenet. 2007;34:225–229.

Salzer U, Warnatz K, Peter HH. Common variable immunodeficiency: an update. Arthritis Res Ther. 2012;14:223.

Cunningham-Rundles C. Autoimmune manifestations in common variable immunodeficiency. J Clin Immunol. 2008;28:42–45.

Azizi G, Kiaee F, Hedayat E, et al. Rheumatologic complications in a cohort of 227 patients with common variable immunodeficiency. Scand J Immunol. 2018;87:e12663.

Gutierrez MI, Sullivan KE, Fuleihan R, et al. Phenotypic characterization of patients with rheumatologic manifestations of common variable immunodeficiency. Semin Arthritis Rheum. 2018;48:318–326.

Arumugakani G, Wood PM, Carter CR. Frequency of Treg cells is reduced in CVID patients with autoimmunity and splenomegaly and is associated with expanded CD21lo B lymphocytes. J Clin Immunol. 2010;30:292–300.

Melo KM, Carvalho KI, Bruno FR, et al. A decreased frequency of regulatory T cells in patients with common variable immunodeficiency. PLoS One. 2009;4:e6269.

Chapel H, Lucas M, Lee M, et al. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. Blood. 2008;112:277–286.

Park J, Munagala I, Xu H, et al. Interferon signature in the blood in inflammatory common variable immune deficiency. PLoS One. 2013;8:e74893.

Warnatz K, Voll RE. Pathogenesis of autoimmunity in common variable immunodeficiency. Front Immunol. 2012;3:210.

Goyal R, Bulua AC, Nikolov NP, et al. Rheumatologic and autoimmune manifestations of primary immunodeficiency disorders. Curr Opin Rheumatol. 2009;21:78–84.

Anderson MS, Venanzi ES, Klein L, et al. Projection of an immunological self shadow within the thymus by the aire protein. Science. 2002;298:1395–1401.

Gamberini E, Torgerson TR, Ochs HD. Immune dysregulation, polyendocrinopathy, enteropathy, and X-linked inheritance (IPEX), a syndrome of systemic autoimmunity caused by mutations of FOXP3, a critical regulator of T-cell homeostasis. Curr Opin Rheumatol. 2003;15:430–435.

Arkwright PD, Abinun M, Cant AJ. Autoimmunity in human primary immunodeficiency diseases. Blood. 2002;99:2694–2702.

Fu Q, Zhao J, Qian X, et al. Association of a functional IRF7 variant with systemic lupus erythematosus. Arthritis Rheum. 2011;63:749–754.

Wang S, Wen F, Wiley GB, et al. An enhancer element harboring variants associated with systemic lupus erythematosus engages the TNFAIP3 promoter to influence A20 expression. PLoS Genet. 2013;9:e1003750.

Das T, Chen Z, Hendriks RW, et al. A20/tumor necrosis factor alpha-induced protein 3 in immune cells controls development of autoinflammation and autoimmunity: lessons from mouse models. Front Immunol. 2018;9:104.

Almlof JC, Nystedt S, Leonard D, et al. Whole-genome sequencing identifies complex contributions to genetic risk by variants in genes causing monogenic systemic lupus erythematosus. Hum Genet. 2019;138:141–150.

Tsokos GC, Lo MS, Costa Reis P, et al. New insights into the immunopathogenesis of systemic lupus erythematosus. Nat Rev Rheumatol. 2016;12:716–730.

Crow YJ, Chase DS, Lowenstein Schmidt J, et al. Characterization of human disease phenotypes associated with mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR, and IFIH1. Am J Med Genet A. 2015;167A:296–312.

Juptrén M, Flachsbart F, Caliebe A, et al. Low copy numbers of complement C4 and homozygous deficiency of C4A may predispose to severe disease and earlier disease onset in patients with systemic lupus erythematosus. Lupus. 2018;27:600–609.

Macedo AC, Isaac L. Systemic lupus erythematosus and deficiencies of early components of the complement classical pathway. Front Immunol. 2016;7:55.

Truedsson L, Bengtsson AA, Sturfelt G. Complement deficiencies and systemic lupus erythematosus. Autoimmunity. 2007;40:560–566.

Davies KA, Erlendsson K, Beynon HL, et al. Splenic uptake of immune complexes in man is complement-dependent. J Immunol. 1993;151:3866–3873.

Walport MJ. Complement. Second of two parts. N Engl J Med. 2001;344:1140–1144.

Carroll MC. A protective role for innate immunity in systemic lupus erythematosus. Nat Rev Immunol. 2004;4:825–831.

Loos C, Gullstrand B, Truedsson L, et al. C1q inhibits immune complex-induced interferon-alpha production in plasmacytoid dendritic cells: a novel link between C1q deficiency and systemic lupus erythematosus pathogenesis. Arthritis Rheum. 2009;60:3081–3090.
[40] Turner MW. The role of mannose-binding lectin in health and disease. Mol Immunol. 2003;40:423–429.

[41] Davies EJ, Snowden N, Hillarby MC, et al. Mannose-binding protein gene polymorphism in systemic lupus erythematosus. Arthritis Rheum. 1995;38:110–114.

[42] Ip WK, Chan SY, Lau CS, et al. Association of systemic lupus erythematosus with promoter polymorphisms of the mannose-binding lectin gene. Arthritis Rheum. 1999;41:1663–1668.

[43] Panda AK, Parida JR, Tripathy R, et al. Low pro-

[44] [46] Lee YH, Witte T, Momot T, et al. The mannose-binding lectin gene: polymorphisms in Japanese patients with systemic lupus erythematosus and Sjögren syndrome. Hum Immunol. 2001;72:516–521.

[45] Tsutsumi A, Sasaki K, Wakamiya N, et al. Mannose-binding lectin gene: polymorphisms in Japanese patients with systemic lupus erythematosus, rheumatoid arthritis and Sjögren’s syndrome. Genes Immun. 2001;2:99–104.

[46] Lee YH, Witte T, Momot T, et al. The mannose-binding lectin gene polymorphisms and systemic lupus erythematosus: two case-control studies and a meta-analysis. Arthritis Rheum. 2005;52:3966–3974.

[47] Takahashi R, Tsutsumi A, Ohtani K, et al. Association of mannose binding lectin (MBL) gene polymorphism and serum MBL concentration with characteristics and progression of systemic lupus erythematosus. Ann Rheum Dis. 2005;64:311–314.

[48] Horiuchi T, Tsukamoto H, Morita C, et al. Mannose binding lectin (MBL) gene mutation is not a risk factor for systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) in Japanese. Genes Immun. 2000;1:464–466.

[49] Piao W, Liu CC, Kao AH, et al. Mannose-binding lectin is a disease-modifying factor in North American patients with systemic lupus erythematosus. J Rheumatol. 2007;34:1506–1513.

[50] Perazzio SF, Granados A, Salomao R, et al. High frequency of immunodeficiency-like states in systemic lupus erythematosus: a cross-sectional study in 300 consecutive patients. Rheumatology (Oxford). 2016;55:1647–1655.

[51] Saiki O, Saeki Y, Tanaka T, et al. Development of selective IgM deficiency in systemic lupus erythematosus patients with disease of long duration. Arthritis Rheum. 1987;30:1289–1292.

[52] Jessar RA, Lamont-Havers RW, Ragan C. Natural history of lupus erythematosus disseminatus. Ann Intern Med. 1953;38:717–731.

[53] Cathcart ES, Idelson BA, Scheinberg MA, et al. Beneficial effects of methylprednisolone "pulse" therapy in diffuse proliferative lupus nephritis. Lancet. 1976;1:163–166.

[54] Scheinberg M. The history of pulse therapy in lupus nephritis (1976–2016). Lupus Sci Med. 2016;3:e000149.

[55] Yurkovich M, Vostretsova K, Chen W, et al. Overall and cause-specific mortality in patients with systemic lupus erythematosus: a meta-analysis of observational studies. Arthritis Care Res (Hoboken). 2014;66:608–616.

[56] Wu XY, Yang M, Xie YS, et al. Causes of death in hospitalized patients with systemic lupus erythematosus: a 10-year multicenter nationwide Chinese cohort. Clin Rheumatol. 2018;38(1):107–115.

[57] Bernatsky S, Boivin JF, Joseph L, et al. Mortality in systemic lupus erythematosus. Arthritis Rheum. 2006;54:2550–2557.

[58] Gladman DD, Hussain F, Iban D, et al. The nature and outcome of infection in systemic lupus erythematosus. Lupus. 2002;11:234–239.

[59] Feldman CH, Hiraki LT, Winkelmayr WC, et al. Serious infections among adult Medicaid beneficiaries with systemic lupus erythematosus and lupus nephritis. Arthritis Rheumatol. 2015;67:1577–1585.

[60] Bosch X, Guilabert A, Pallares L, et al. Infections in systemic lupus erythematosus: a prospective and controlled study of 110 patients. Lupus. 2006;15:584–589.

[61] Noel V, Lortholary O, Casassus P, et al. Risk factors and prognostic influence of infection in a single cohort of 87 adults with systemic lupus erythematosus. Ann Rheum Dis. 2001;60:1141–1144.

[62] Feldman CH, Marty FM, Winkelmayr WC, et al. Comparative rates of serious infections among patients with systemic lupus erythematosus receiving immunosuppressive medications. Arthritis Rheumatol. 2017;69:387–397.

[63] Lim CC, Liu FY, Tan HZ, et al. Severe infections in patients with lupus nephritis treated with immunosuppressants: a retrospective cohort study. Nephrology (Carlton). 2017;22:478–484.

[64] Mok MY, Ip WK, Lau CS, et al. Patients with systemic lupus erythematosus. J Rheumatol. 2007;34:1270–1276.

[65] Zonana-Nacach A, Camargo-Coronel A, Yanez P, et al. Infections in outpatients with systemic lupus erythematosus: a prospective study. Lupus. 2001;10:505–510.

[66] Torres-Ruiz J, Mejia-Dominguez NR, Zentella-Dehesa A, et al. The systemic Lupus Erythematosus Infection Predictive Index (LIPI): a clinical-immunological tool to predict infections in lupus patients. Front Immunol. 2018;9:3144.

[67] Mitander A, Fei Y, Trysberg E, et al. Complement consumption in systemic lupus erythematosus leads to decreased opsonophagocytosis in vitro. J Rheumatol. 2018;45:1557–1564.

[68] Audemand-Verger A, Descloux E, Ponard D, et al. Infections revealing complement deficiency in adults: a French Nationwide Study enrolling 41 patients. Medicine (Baltimore). 2016;95:e3548.

[69] Merayo-Chalico J, Gomez-Martin D, Pinerua-Menendez A, et al. Lymphopenia as risk factor for development of severe infections in patients with systemic lupus erythematosus: a case-control study. QJM. 2013;106:451–457.

[70] Tsutsumi A, Takahashi R, Sumida T. Mannose binding lectin: genetics and autoimmune disease. Autoimmun Rev. 2005;4:364–372.

[71] Garred P, Madsen HO, Halberg P, et al. Mannose-binding lectin polymorphisms and susceptibility to infection in systemic lupus erythematosus. Arthritis Rheum. 1999;42:2145–2152.

[72] Garred P, Voss A, Madsen HO, et al. Association of mannose-binding lectin gene variation with
disease severity and infections in a population-based cohort of systemic lupus erythematosus patients. Genes Immun. 2001;2:442–450.

[73] Ng WL, Chu CM, Wu AK, et al. Lymphopenia at presentation is associated with increased risk of infections in patients with systemic lupus erythematosus. QJM. 2006;99:37–47.

[74] Comte D, Karampetsou MP, Kis-Toth K, et al. Brief report: CD4+ T cells from patients with systemic lupus erythematosus respond poorly to exogenous interleukin-2. Arthritis Rheumatol. 2017;69:808–813.

[75] Linker-Israeli M, Bakke AC, Kitridou RC, et al. Defective production of interleukin 1 and interleukin 2 in patients with systemic lupus erythematosus (SLE). J Immunol. 1983;130:2651–2655.

[76] Wofsy D, Murphy ED, Roths JB, et al. Deficient interleukin 2 activity in MRL/Mp and C57BL/6J mice bearing the lpr gene. J Exp Med. 1981;154:1671–1680.

[77] Altman A, Theofilopoulos AN, Weiner R, et al. Analysis of T cell function in autoimmune murine strains. Defects in production and responsiveness to interleukin 2. J Exp Med. 1981;154:791–808.

[78] von Spee-Mayer C, Siegert E, Abdirama D, et al. Low-dose interleukin-2 selectively corrects regulatory T cell defects in patients with systemic lupus erythematosus. Ann Rheum Dis. 2016;75:1407–1415.

[79] Lieberman LA, Tsokos GC. Lupus-prone mice fail to raise antigen-specific T cell responses to intracellular infection. PLoS One. 2014;9:e111382.

[80] Kis-Toth K, Comte D, Karampetsou MP, et al. Selective loss of signaling lymphocytic activation molecule family member 4-positive CD8+ T cells contributes to the decreased cytotoxic cell activity in systemic lupus erythematosus. Arthritis Rheumatol. 2016;68:164–173.

[81] Comte D, Karampetsou MP, Yoshida N, et al. Signaling lymphocytic activation molecule family member 7 engagement restores defective effector CD8+ T cell function in systemic lupus erythematosus. Arthritis Rheumatol. 2017;69:1035–1044.

[82] Suarez-Fueyo A, Bradley SJ, Tsokos GC. T cells in systemic lupus erythematosus. Curr Opin Immunol. 2016;43:32–38.

[83] Zhang R, He J, Sun X, et al. AB0052 increased peripheral CD8+ T cell responses in sle by low-dose IL-2 treatment. Ann Rheum Dis. 2017;76:1065.