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SYSTEMIC LUPUS ERYTHEMATOSUS (G TSOKOS, SECTION EDITOR)

SLE-associated risk factors affect DC function

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Abstract
Purpose of Review Identification of function and potential pathogenic mechanisms of SLE risk genes in dendritic cells.
Recent findings Functional studies of individual SLE risk factors in dendritic cells were performed, and functional alterations of some risk genes in dendritic cells were observed. Recent studies confirmed the pathogenic function of known risk genes. These findings postulate novel pathogenic mechanisms made by dendritic cells.
Summary SLE is a complex disease and its etiology is not clearly understood. Dendritic cells are innate immune cells and critical for determining immune activation and immune tolerance. Genetic studies identified several new candidate genes which predispose to development of autoimmune diseases, but the mechanism of those genes has not been identified. This report updates functional implications or pathways in dendritic cells which are putatively important for the development or propagation of SLE based on genetic and functional studies performed in both human and animal models.

Keywords Dendritic cells · SLE · genetic risk factors

Introduction

Dendritic cells (DCs) are professional antigen-presenting cells (APCs) and express a range of co-stimulatory molecules and cytokines. DCs continuously uptake and process antigens either from tissue or pathogens, and initiate immune silence (tolerance) or immune activation depending on the source of antigen and their own activation status. DCs consist of heterogeneous populations with different developmental pathways and regulatory functions. Classical (or myeloid) DCs (cDCs) are characterized by expression of CD11c and CD11b and further subgrouped by expression of either BDCA1 (CD1c) for cDC1 or BDCA3 (CD141) for cDC2. Plasmacytoid DCs (pDCs) lack cDC markers but express high levels of CD123, BDCA2 (CD303) and BDCA4 (CD304) [1]. All DC subsets function as professional APCs, but each subset also has specialized functions. CD141+ cDC2 and pDCs have been shown to prime CD4+ T cells and cross-prime CD8+ T cells [2–5]. PDCs secrete high amount of type I IFNs (IFNα and IFNβ) upon stimulation with viral antigens. Type I IFNs production leads to upregulated surface expression of co-stimulatory molecules, making pDCs better APCs and promoting differentiation of B cells to antibody-secreting plasma cells [6, 7]. PDCs are also implicated in the induction and maintenance of tolerance through the induction of regulatory T cells (Tregs) [8].

Whether abnormalities of DCs are causative in SLE is not yet clear. However, several studies have implicated pathogenic roles for DCs in SLE. This report will summarize current genetic and functional studies which attempt to establish the DC as a key pathogenic player in SLE.

DCs in SLE

The systemic immune alterations in SLE suggest that the disease might be driven by alterations of APCs, particularly DCs. The pathogenic roles of DCs in autoimmune disease have long been investigated, and evidence has been observed in both animal models of lupus and SLE patients. Although there are controversial observations from SLE patients, animal studies clearly show that DCs contribute to the maintenance of immune homeostasis. Continuous depletion of DCs (both

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cDCs and pDCs) in wild-type mice increased the frequency of autoimmune lymphocytes and development of autoreactive antibodies [9]. There was also an increased frequency of IFNγ/IL-17-producing autoreactive T cells, partly due to aberrant negative selection in the thymus. Many investigators have found that the frequency, subsets and phenotype of DCs found in the blood are different in SLE patients compared to healthy individuals. Decreased frequencies of cDCs or pDCs are more often associated with active disease, but less with non-active disease [10]. Interestingly, both cDCs and pDCs are decreased in blood but increased in inflamed tissue, such as kidney in SLE patients compared to healthy individuals [11–14]. These data suggest that activated DCs may migrate to the site of inflammation. It is likely that DCs in the circulation and those recruited into affected tissues will display different characteristics. Consequently, it is important to further assess the populations in inflamed tissue and their contribution to disease pathogenesis.

Genetic risk factors for cDC in SLE

Although the exact cause of lupus is not fully understood, strong genetic links have been identified by family and large-scale genome-wide association studies (GWAS). Disease concordance in monozygotic twins is higher than in dizygotic twins (24–57% vs. 2–5%) [15, 16]. A population-based family study tried to examine familial aggregation and heritability of SLE in a Taiwanese population. There is a strong relative risk in the primary relatives of patients (parents or siblings) [17]. There are now more than 80 genetic loci reported to be associated with the susceptibility of SLE, and accumulated data from genetic studies identified newly genetically susceptible areas mostly due to the increased power. Among those genetic loci, several candidates are implicated in the alteration of DCs (Fig. 1A).

Genes altering antigen recognition Numerous functionally relevant single nucleotide polymorphism (SNP) variants and copy number (CN) variants have been characterized in the Fc gamma receptor (FCGR) genes. Many of these variants have been shown to associate with the development or progression of SLE [18]. FCRIIIB (CD16) and FCRIIA (CD32) are low affinity receptors for IgG, and variants of both have been correlated with disease in different populations. Genetic risk was associated with *FCRIIIB* in a Japanese population [19], and *FCRIIA* in Caucasians by a family-based study [20]. Strong experimental evidence was observed from the case of a missense mutation at *FCRIIA* [21]. The polymorphism,

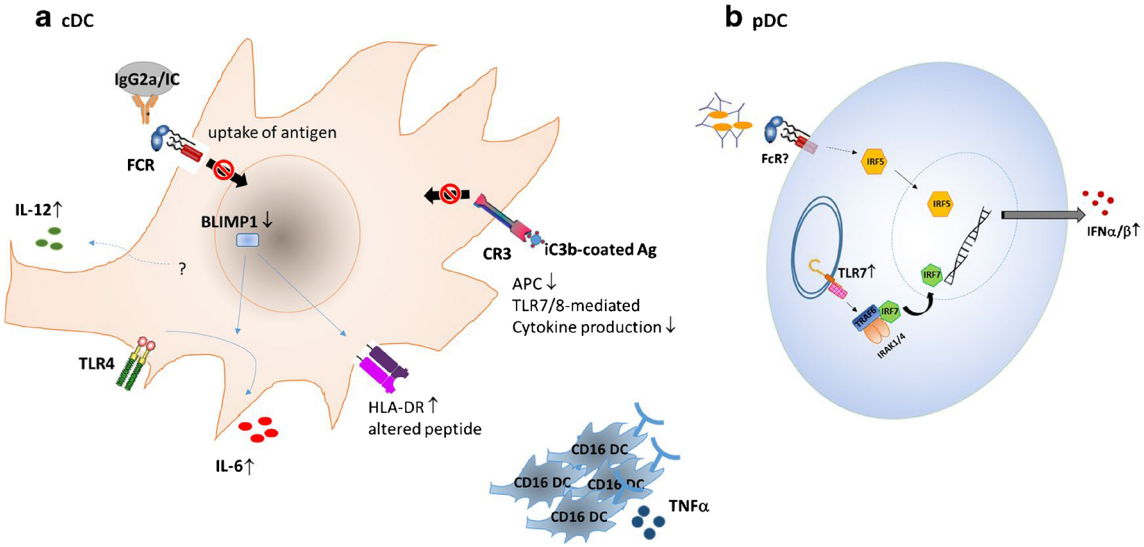

Fig. 1. Molecules which are known to harbor polymorphism associated with SLE are depicted. **A** In cDCs, mutations in antigen binding of FCRs or CR3 are related to the defective phagocytosis of immune-complexes or complement component-coated antigens. A defective clearance of pathogens or immune complexes leads to a chronic inflammation by residual pathogens. Polymorphisms resides in molecules (for example, BLIMP1) which regulate HLA expression and processing of antigenic peptides are associated with SLE. BLIMP1 also regulates pro-inflammatory cytokine, IL-6, production either by suppression of IL-6 promoter activity or by regulating the TLR4 signaling pathway. Increased production of IL-12 is also associated with SLE, but the mechanism is not clearly elucidated. CD16-positive DCs are rare population of DC family in healthy individuals, but an increased frequency of CD16+ DCs contribute to SLE pathogenesis, mainly through their high production of TNFα. **B** Polymorphisms in the endosomal TLR signaling pathway are known to contribute to the pathogenic function of pDCs. Polymorphism in IRF5 leads to the increased translocation of IRF5 into the nucleus followed by immune complexes-mediated FCR engagement, which causes an increased production of type I IFNs. Increased TLR7 signaling pathway leads to an increased IRF7 translocation, subsequently increasing production of type I IFNs

rs1801274, generates a histidine to arginine (H to R) switch at amino acid 131, in its ligand binding domain, significantly lowering affinity to IgG2, and leading to impaired IgG2-mediated phagocytosis [22, 23]. Other studies have demonstrated that a low copy number of FCRIIA is associated with lupus nephritis. A large scale study showed that less than 2 copies is a major risk factor both for lupus nephritis (OR=2.43) and SLE without renal involvement (OR=2.21) [24, 25].

The association of *FCRIIA*, *FCRIIIB* and *ITGAM* (CD11b) with susceptibility to SLE suggest that the early response of the innate immune response is critical for pathogenesis. FCGRIIA and FCGRIIIB are low-affinity receptors for IgG and ITGAM, which encodes the integrin alpha M protein that dimerizes with integrin β2 to form the cell surface receptor known as complement receptor 3 (CR3) or MAC-1. CD32 and ITGAM are expressed primarily on neutrophils, monocytes and DCs, but the expression of CD16 on DCs is not clearly observed. CD16 expression is known to be limited to neutrophils and a subset of monocytes. There are several reports suggesting that $CD16^{hi}$ monocytes (HLA-DR+CD19-CD3-CD56-CD14-) are a novel subset of DCs in human, and defined as either SLAN-DC or DC4 [26–28]. Transcriptome analysis suggest that the CD16+ DC is distinct from the CD14+CD16+ monocyte and exhibits an inflammatory DC signature (CD14-$CD11c^{hi}CD11b^{lo}$CCR2-CX3CR3+) [29]. Indeed, CD16+ DCs secrete greater amounts of inflammatory cytokines, especially TNFα, upon stimulation with toll-like receptor (TLR) agonists compared to BDCA1 DCs [30]. Therefore, expansion or functionally altered CD16+ DCs could contribute to the pathogenesis of SLE. Autoantibody-DNA complexes isolated from SLE patients can be recognized by and activate DCs through cooperation of FCRII and TLR9 [31]. Tumor cell-loaded DCs induce strong tumor-specific CD8+ T cell activation, which can be suppressed by pre-treatment of DCs with FCR-blocking antibodies [32]. In SLE patients, disease activity is associated with an altered expression of FCRII and costimulatory molecules on DCs [33]. These studies strongly suggest that FCRs provide efficient uptake and presentation of antigens in DCs.

The functional significance of ITGAM has been investigated in monocytes but not in DCs. The SLE-associated rs1143679 (R77H) variant showed a reduced phagocytosis of an inactive product of the complement cleavage fragment C3b (iC3b)-opsonized sheep red blood cells. There was also reduced activation of TLR7/8-induced pro-inflammatory cytokine production in monocytes expressing the risk variant [34]. It would be interesting to investigate whether the rs1143679 risk variant confers similar functional alterations in DCs. A recent mouse study found that CD11b-mediated signaling positively regulated TLR4-induced signaling in DCs but not in macrophages [35]. In this study, CD11b-mediated signaling promoted endocytosis of TLR4, and CD11b deficiency dampened DC activation and impaired T cell activation in vivo.

Genes altering antigen process and presentation Strong association between SLE and variants in the human leukocyte antigen (HLA) region has been known for many years, and significant progress has been made in the recent past [36]. The first genetic signal within the HLA genome region was identified in European SLE families, containing *HLA-DRB1*, *HLA-DQA1*, and *HLA-DQB1* [37]. Mechanisms of how HLA risk variants confer the pathogenesis of SLE could be made in multiple ways. The haplotype AH8.1 in European populations carries multiple variants which have been associated with SLE, including *DRB1*0301* (DR3), the *TNF-308A* allele and the *C4A* complement null allele [37, 38]. Another study found *HLA-DRB1*0301* dosage to be correlated with SLE pathogenesis and the production of anti-Lo/ La autoantibodies. Another study also found that a positive correlation between dosage of HLA-DRB1*0301 and anti-Ro/La positivity in European SLE patients [39]. However, direct evidence is not available as to whether specific HLA-DRB1*0301 preferentially presents self-antigens or functional alteration of DCs, which have yet to be investigated.

The *PRDM1-ATG5* intergenic region has multiple risk SNPs associated with SLE [40], which have been confirmed by meta-analysis [41]. B lymphocyte-induced maturation protein 1 (BLIMP1) (encoded by gene *PRDM1*) is a key factor for plasma cell differentiation, and positive correlation between the level of BLIMP1 and circulating plasma cells in SLE patients has been reported [42]. This study, however, did not show whether the polymorphism of *PRDM1* directly leads to the increased frequency of plasma cells in SLE patients. A study from Zhou and colleague indeed found alteration of autophagy-related 5 (*ATG5*) expression, but not *BLIMP1* expression in B lymphocytes of risk SNP-carrying SLE patients. In contrast, the *PRDM1-ATG5* risk SNP exhibited significant effects on *PRDM1,* but not on *ATG5,* in DCs. MO-DCs carrying the rs548234 risk SNP had a decreased level of BLIMP1, and displayed functional alterations, including increased HLA expression and IL-6 induction upon TLR4 stimulation [43]. Point mutation of the rs548234 risk SNP generates a Kruppel-like factor 4 (KLF4)-binding consensus sequence, and KLF4 binding to the rs548234 SNP recruits chromatin remodeling factors, histone deacetylases (HDAC) 4/6/7, suppressing PRDM1 transcription in MO-DCs [44•]. Interestingly, loss of BLIMP1 expression in $CD11c^{hi}$ cDCs or in thymic epithelial cells induces lupus-like phenotypes in these mice [45, 46]. These data suggest a cell-type-dependent function of BLIMP1, and suggests that genetic variation effects could differ depending on the cell type.

Genes altering DC activation Compared to the number of known molecules or factors affecting the function of DCs, little genetic evidence of association with risk is available. The association between signal transducer and activator of transcription factor 4 (*STAT4*) variation and SLE was reported from a case–control study and confirmed in GWAS [47]. STAT4 is a signal transducer by cytokine/cytokine receptor such as type I IFNs or IL-12/23 [48]. Increased STAT4 mRNA and protein was observed in PBMCs from SLE patients carrying the rs7574865 risk variant compared to non-risk-carrying SLE patients [49]. It is not clear, however, whether polymorphism directly leads to altered transcription or due to the altered PBMC populations in SLE compared to healthy individuals, since the study did not measured the STAT4 levels in isolated cell types. *IL-12A* (p35) is a relatively new identified genetic loci in both European and Asian populations [50, 51]. IL-12 is known to be a critical cytokine for TH1 differentiation. Recent in vitro studies found that IL-12 is also critical for follicular helper T (TFH) cells in human but not in mice [52], and that DCs play a role in this process by secretion of IL-12 [53]. IL-12 can induce TH1 as well as TFH differentiation, and increased IRF4 skews the differentiation program toward to TFH rather than TH1 [54•]. It has yet to be investigated whether IL-12 genetic risk induces IL-12 production in DCs.

Genetic risk factors for pDC in SLE

The major function of pDCs that is relevant in terms of SLE is most likely production of type I IFNs (IFNα or IFNβ) (Fig. 1B). PDCs also participate in the induction of regulatory T cells, but their function as APCs is still debatable.

Genes affecting IFNα production A functional SNP located in the 3' untranslated region of *TLR7* was associated with SLE [55]. The SNP is a target of microRNA-1348 and the risk allele confers decreased TLR7 mRNA levels, thereby increasing the level of TLR7 in myeloid cells including pDCs.

Interferon regulatory factor 5 (IRF5) and IRF7 are members of the IRF family of transcription factors. SLE-associated variants of *IRF5* and *IRF7* have functional impacts on increased serum IFNα and those functions depends on the presence of specific autoantibodies [56] [57] [58]. IRF5 was identified and characterized as a transcriptional regulator of pro-inflammatory cytokines or type I IFNs after TLR stimulation [59] [60]. The *IRF5* genetic locus carries multiple functional polymorphisms which potentially associate with SLE [61]. An *IRF5* risk haplotype was associated with anti-Ro antibody positivity in asymptomatic individuals and progression to SLE [62]. Barnes and colleagues observed higher levels of IRF5 in PBMCs from SLE patients compared to healthy controls, and higher transcript and protein in the risk haplotype (rs10488631 and CGGGG indel) carriers [63]. IRF5 activation can be induced by serum autoantibody-containing immune complexes, which leads to the translocation of IRF5 to the nucleus and the production of type I IFNs in human monocytes [64]. Early studies showed that IRF5 participates in IFNβ production, but not IFNα production, upon TLR7/8 stimulation through the MYD88/IRAK1/TRAF6 signaling pathway in murine monocytic cells [65]. Consistent observations were made from IRF7 risk variants in which increased levels and/or activity of IRF7 were found in myeloid cells, leading to an increase in IFNα production.

Protein tyrosine phosphatase non-receptor type 22 (PTPN22) is expressed in lymphocytes and myeloid cells [66]. A coding polymorphism in the *PTPN22* gene is a susceptibility allele for SLE [67]. In myeloid cells, PTPN22 positively regulates TLR signaling upon stimulation with TLR agonist and the expression of IFNα via the ubiquitination of TRAF3. SLE patients expressing the PTPN22 variant R620W have pDCs that exhibit impaired production of IFNα upon TLR7 stimulation compared to non-risk control individuals [68]. How an impaired TLR7–IFNα axis contributes to SLE pathogenesis is not fully understood. Inefficient production of IFNα results in delayed clearance of viral infection, and subsequent over-activation of the innate immune system might lead to SLE development. IFNα signaling is also required for optimal regulatory function of Treg cells. A study of Treg-specific conditional IFNA receptor knockout mice ($Ifnr^{fl/fl}$ x *Foxp3*-CRE) suggest that IFNα signaling negatively regulates Treg function during chronic viral infection [69]. However, it has not yet been investigated whether IFNα signaling has a similar function in human Tregs.

Conclusions

Tremendous amounts of information have been obtained regarding genetic variants in human diseases during recent decades. From family or case-based studies, we now know that genetic contribution can be one of the key triggers contributing to the development of SLE. Compared to the amount of information made in genetic studies, there are fewer studies that identify functional relevance in disease pathogenesis. As we review the progress made in both genetic and functional immunology, it is intriguing to identify the causal variants and their mechanisms in immune system.

Compliance with Ethical Standards

Conflict of Interest Dr. Kim has nothing to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors

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- •• Of major importance

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