

Role of dendritic cells in the pathogenesis of systemic lupus erythematosus

Seetha U Monrad,
Karl C Desch &
Mariana J Kaplan[†]

[†]Author for correspondence
University of Michigan,
Division of Rheumatology,
5520 MSRB1, Box 0680,
1150 W Medical Center
Drive, Ann Arbor,
MI 48109, USA
Tel.: +1 734 936 7905;
Fax: +1 734 763 4151;
makaplan@med.umich.edu

Given their crucial role in immunologic tolerance and immune activation, dendritic cells are considered important orchestrators of autoimmunity. Research over the past decade has revealed multiple potential mechanisms by which dendritic cells contribute to the immunopathogenesis of systemic lupus erythematosus. Genetic abnormalities in systemic lupus erythematosus can result in dendritic cells with aberrant uptake, maturation and presentation capabilities. Dysregulated apoptosis in lupus can provide a source of autoantigens for uptake by inappropriately activated dendritic cells. These cells then present autoantigen to autoreactive lymphocytes, stimulating autoantibody and immune complex formation. In addition to depositing in tissues and causing damage, these immune complexes can stimulate plasmacytoid dendritic cells via Toll-like receptors 7 and 9 to synthesize IFN- α . This cytokine exerts a host of pathogenic effects on various effector cells, including myeloid dendritic cells, generating a feedback loop that promotes a persistently and aberrantly activated immune system. Therapies that target dendritic cells may thus allow modulation of numerous immunologic abnormalities in lupus and other autoimmune diseases.

Immunopathogenesis of systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease of unclear etiology, characterized by the presence of autoantibodies (auto-Abs), primarily to nuclear material, and by the deposition of immune complexes (ICs) in various tissues. Studies evaluating the immunopathogenesis of SLE have classically focused on the role of lymphocytes. While a wide range of T- and B-cell abnormalities have been demonstrated [1–3], it is unclear which aspects of lymphocyte dysfunction are intrinsic and which are secondary to external factors. The potential for dendritic cells (DCs) to contribute to aberrant lymphocyte function and the overall abnormal immunologic milieu described in SLE is of great interest. DCs have powerful and widespread effects on all aspects of the immune system. As such, breakdown of DC regulation can lead to loss of tolerance on multiple levels, and thereby promote autoimmune responses. In this review, we will summarize the current evidence implicating a role for DCs in the pathogenesis of SLE.

Biology of human dendritic cells

There are at least two distinct subsets of human DCs, arising from a common CD34⁺ hematopoietic stem cell (reviewed in [4]). Myeloid DCs (mDCs) are thought to derive from a common myeloid progenitor and are CD11c⁺; they reside

in tissues and lymphoid organs, and circulate as monocytic precursors. mDCs are studied *in vitro* by culturing human monocytes or murine bone marrow cells with IL-4 and granulocyte-macrophage colony-stimulating factor. The other major subset of DCs, plasmacytoid (p)DCs, circulates in blood and is thought to derive from a common lymphoid precursor; pDCs are CD11c⁻ and express both the IL-3 receptor and BDCA2. pDCs are considered the primary source of IFN- α , which, as will be discussed below, makes them potentially very relevant to the immunopathology of SLE.

Dendritic cells regulate both innate and adaptive immune effector cells, and are pivotal in maintaining the balance between tolerance and immune response (reviewed in [5]). Tissue and lymphoid DCs reside in an inactive, highly phagocytic state at sites of potential antigen (Ag) exposure. These immature DCs continuously sample the environment, usually encountering self or harmless Ags. They migrate at low levels to regional lymph nodes, where Ag presentation induces tolerance or anergy in resident lymphocytes. Thus, DCs are crucial for generating and maintaining peripheral tolerance, a key component in the prevention of autoimmunity.

Uptake of pathogenic Ags in the presence of a variety of accessory danger signals (such as microbial-derived pathogen-associated molecular patterns [PAMPs], inflammatory products, necrotic cells, heat-shock proteins and oxidation products)

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induces DC maturation, manifested by downregulation of phagocytic receptors, and upregulation of Ag presentation machinery and costimulatory molecules. These activated DCs secrete chemokines that attract innate and adaptive responders to the site of injury. Activated DCs also upregulate the chemokine receptor CCR7, and migrate to lymphoid tissues to trigger secondary specific immune responses, which vary depending on the environment and signals encountered during DC activation. DCs stimulate naïve T cells, generating immunological memory. In addition, DCs present Ag to Ag-specific T cells by classical and non-classical pathways, and can trigger both Th1 and Th2 responses. DCs secrete and express a wide variety of cytokines and surface molecules that help directly control B-cell proliferation, differentiation and isotype switching. DCs can also modulate the functions of nonspecific effectors such as natural killer cells and natural killer T cells.

Thus, there are a number of mechanisms by which aberrant DC function and regulation could have immunologic consequences of relevance to the pathogenesis of SLE. These include imbalances in DC number, subsets and locations; altered uptake and response to benign and harmful antigenic stimuli; dysregulated activation states and altered migratory capacity; and aberrant interactions with other immune effector cells, triggering inappropriate downstream responses.

Dendritic cell phenotype in SLE

Several groups have documented decreased numbers of circulating pDCs and sometimes mDCs in the peripheral blood of SLE patients [6–8]. It has been postulated that this is due to increased migration into peripheral tissues. Indeed, increased numbers of DCs have been found in various tissues and organs of lupus patients. Renal specimens from patients with active SLE nephritis demonstrated accumulation of pDCs in glomeruli [7] and the tubulointerstitium [8]. The onset of proliferative glomerulonephritis and proteinuria in NZB/W lupus-prone mice is associated with infiltration of renal tissue by activated DCs [9]. In addition, lymphoid organs of lupus-prone mice [10,11] and lupus cutaneous lesions [12,13] also demonstrate increased numbers of DCs.

Increased intrinsic migratory capacity of lupus DCs has not been documented. However, as increased migration normally follows activation and maturation of DCs, the maturation status of lupus DCs is important to define. Our group has demonstrated that monocyte-derived DCs from

human SLE patients display an activated, pro-inflammatory phenotype, characterized by: accelerated differentiation from the monocyte to the myeloid DC stage *in vitro* and *in vivo*; increased expression of the maturation markers CD80, CD86 and MHC class II; blunted responses to maturation stimuli; and increased production of the proinflammatory cytokine IL-8. In addition, lupus mDCs promote significantly increased proliferation and activation of allogeneic control T cells, relative to allogeneic DCs from healthy controls [14]. These findings suggest that lupus mDCs are more mature and more stimulatory than DCs from healthy controls. Enhanced baseline lupus DC maturation could potentially result in accelerated migration into lymphoid organs, and thus represents one explanation for the decreased numbers of circulating DCs seen in SLE. Furthermore, mature DCs can break tolerance and induce lupus auto-Abs in normal hosts [15], which is another potential pathologically relevant consequence in SLE. While some groups have corroborated our findings with both human and murine DCs [16,17], other groups have found varying phenotypic abnormalities in lupus mDCs (reviewed in [18]). These differences appear to be highly dependent on the species studied and the method of DC isolation, culture and purification.

These phenotypic abnormalities, at least in part, appear to be intrinsic to the mDCs, as the addition of lupus serum to healthy control or lupus mDCs could not reproduce or increase the aberrant phenotype in our system [14]. Nevertheless, various groups have found that DCs may be activated by factors present in serum, including ICs and cytokines, such as IFN- α (discussed below).

Relationship between type I IFN & dendritic cells in SLE

The association between type I IFNs and SLE was first noted in 1982 [19], but only more recently has the extent of their role in the pathogenesis and perpetuation of disease been investigated. Type I IFNs, which, in humans, include α , β , κ , ω and ϵ IFNs [20], are key mediators in the defense against viral pathogens. IFN- α synthesis is triggered predominantly by viral-associated DNA/RNA that is recognized by a number of different receptors on various cells. Type I IFNs have numerous immunomodulatory effects on many different cell types (Box 1) [21–24]. While many cells can synthesize small amounts of IFN- α , the primary IFN- α -producing cell appears to be the pDC [25].

Box 1. Effects of IFN- α on target cells.**Dendritic cells**

- Promotes monocyte differentiation into dendritic cells
- Induces immature dendritic cell activation
- Upregulates IFN- γ production
- Autocrine survival factor
- Upregulates B-lymphocyte stimulator and APRIL expression (B-cell survival factors)
- Promotes Th1 skewing phenotype
- Promotes crosspriming of CD8⁺ cells

T cells

- Antiproliferative, proapoptotic (direct effects)

B cells

- Promotes development, proliferation
- Increases survival, resistance to Fas-mediated apoptosis
- Promotes immunoglobulin isotype switching
- Induces plasma cell differentiation
- Enhances antibody responses

Macrophages

- Promotes development and maturation

Natural killer cells

- Enhances cytotoxicity

The exact role of type I IFNs in the induction/perpetuation of autoimmunity in lupus is complex. Microarray analysis has revealed marked overexpression of IFN-related gene expression (the 'IFN signature') in the leukocytes of some SLE patients [26,27], as well as in the glomeruli of patients with lupus nephritis [28]. However, not all patients with SLE exhibit elevated IFN- α levels in serum or IFN gene signatures [24]. Serum levels of type I IFN have been shown to correlate with lupus disease activity and severity [29] and also with auto-Ab levels [30]. A subset of patients receiving type I IFN treatment for other conditions develop a lupus-like condition, with auto-Ab synthesis and organ damage [31]. Furthermore, IFN- α has recently been linked to abnormal vascular repair and, potentially, to atherosclerosis development in SLE [32,33].

Mouse models of lupus present a conflicting picture. The induction of IFN- α in *lpr/lpr* mice aggravated lupus-like disease, an effect that was ameliorated by IFN receptor deletion [34]. Type I IFN receptor deficiency ameliorates disease in NZB lupus-prone mice [35]. Adenovector-mediated delivery of IFN- α to pre-autoimmune NZB/W mice resulted in accelerated disease and mortality [36]. However, IFN- α receptor deficiency in the MRL/*lpr* model of murine lupus worsened clinical, serological and pathological

disease manifestations [37]. In addition, IFN- α blockade also worsened auto-Ab production in the B6.*Sle2* murine lupus model [38]. It has been postulated that some of these disparate findings, in addition to being due to mouse strain-related differences in disease pathogenesis, may also be secondary to differential IFN effects in SLE depending on the stage and severity of ongoing disease [39].

The potential relationship between IFN- α and DCs in lupus, while not fully investigated, appears to be more straightforward. IFN- α in SLE serum induces the transformation of peripheral blood monocytes into DCs and promotes their maturation and allostimulatory capacity [29,40], thereby enhancing their intrinsically aberrant phenotype. IFN-primed mDCs exhibit enhanced chemokine-directed migration *in vitro* via upregulation of CCR7 [41] and matrix metalloproteinase 9 expression [42], suggesting other possible mechanisms by which DCs in SLE could leave the circulation and migrate to peripheral and lymphoid tissues.

In addition, pDCs produce IFN- α upon *in vitro* stimulation with lupus serum [43]. However, depletion of pDCs from SLE blood results in only partial abrogation of type I IFN production capability [40], thereby indicating that other cells might also be responsible for type I IFN synthesis in SLE. These additional cell subsets have not been well characterized, although a monocyte-like circulating cell population has been implicated in one murine model of SLE [44]. The IFN-inducing serum factors include DNA- and RNA-containing ICs composed of auto-Ags from chromatin and other as yet undefined ligands [45–48]; these ICs are also capable of stimulating the production of other chemokines and cytokines implicated in autoimmunity [49].

Aberrant apoptosis, dendritic cells & SLE

Normally, chromatin containing auto-Ags are sequestered in the intracellular compartment and do not stimulate immune responses. Dysregulated apoptosis is a potential source of increased and/or modified self Ag. Lupus patients exhibit increased rates of apoptosis of numerous cells, including lymphocytes [50], neutrophils [51], monocytes and macrophages [52,53]. In addition, they exhibit decreased levels of apoptotic clearance and elevated levels of circulating nucleosomes (reviewed in [54,55]). Our group has shown that increased macrophage apoptosis is sufficient to break tolerance in non-lupus-prone

mice, as well as worsening nephritis and autoimmune responses in lupus-prone mice [56]. Immunostimulatory DCs may take up auto-Ags exposed from the increased apoptotic burden and cross-present them to autologous cytotoxic T lymphocytes in the lymph nodes. Histological analysis of lymph nodes in a subgroup of SLE patients has shown that apoptotic cells are not properly cleared from the germinal centers; consequently, nuclear auto-Ags bind to follicular DCs, possibly providing survival signals for autoreactive B cells [57,58]. In combination with auto-Abs, nucleic acids released by apoptotic cells are efficiently processed by DCs and stimulate Ag-specific T-cell proliferation [59]. Both ICs [47] and purified apoptotic bodies [60] can stimulate IFN- α production by pDCs, which may then promote accelerated monocyte differentiation into mDCs. Bone marrow-derived DCs from lupus-prone NZB/W F1 mice, when pulsed with apoptotic cells, worsened clinical disease in lupus mice, and induced auto-Ab production in non-autoimmune mice [61,62].

However, other groups have reported that apoptotic cell uptake by human DCs does not result in DC maturation or cross-presentation [63,64], and that DCs exposed to necrotic, but not apoptotic, cells are involved in the induction of autoimmunity in susceptible mouse strains [65]. These discrepancies may be due to what type of apoptotic cell is used and the variable effects of early- and late-stage apoptotic cells on DC maturation [66]; the apoptotic burden [61]; and the surrounding cytokine milieu (reviewed in [54]). In addition, the differing *in vitro* findings may not necessarily be mutually exclusive *in vivo* in SLE. In the absence of a fully functional clearance system, secondary necrosis of uncleared apoptotic material may generate a proinflammatory milieu that enhances DC maturation, activation and migration. In addition, repeated challenge of the chronically primed and activated SLE immune system with a large apoptotic burden could eventually generate an environment capable of breaking normal processing of apoptotic material. This could potentially allow for the generation of an immune response to apoptotic material, even in the absence of other signals such as necrosis.

Toll-like receptors, type I IFNs & dendritic cells in SLE

Autoimmune responses against chromatin, the hallmark of SLE, are often triggered by infections, which are well-known triggers of lupus flares. Indeed, clinical SLE will often first manifest after

a viral infection [67]. Thus, autoimmunity may result when imperfect discrimination of self from nonself occurs. This discriminatory function is assisted by the functioning of several innate pathogen-recognition systems that respond to PAMPs, including the Toll-like receptors (TLRs) [68]. There are ten of these highly conserved type I transmembrane receptors in humans, with a variety of viral, bacterial and fungal ligands (reviewed in [69]). Upon engagement of a TLR with its ligand, a signal transduction cascade is triggered, ultimately activating downstream transcription factors required for the production of various mediators, including type I IFNs.

In recent years there has been great interest in the relationship between TLRs and IFN- α in the immunopathogenesis of SLE (reviewed in [24,70]). TLR 7 and 9 are thought to be of particular importance. Their distribution appears to be limited to B cells and pDCs in humans [71]; they are localized intracellularly and require endosomal acidification to trigger immune responses. pDCs treated with chloroquine, a blocker of endosomal acidification, are unable to synthesize IFN- α and other activation-related cytokines upon stimulation with DNA-containing lupus ICs [72,73]. In addition, treatment of NZB/W mice with a TLR7/9 inhibitor resulted in reduced auto-Ab production and diminished nephritis [74]. Thus, a unifying hypothesis has been proposed whereby self nucleic acid-containing ICs, generated through dysregulated apoptosis and internalized via Fc γ RIIa [72], and, potentially, other uptake receptors, engage TLR7 and/or 9 to stimulate IFN- α production and thereby promote and perpetuate SLE [75–77] (the ‘interferon/Toll hypothesis’).

Several recent studies have attempted to elucidate the specific contribution of TLR7 versus 9. The ribonucleoprotein auto-Ags Ro and Sm/RNP stimulate DC maturation and IFN production via TLR7 [78–80]. The Y chromosome-linked ‘autoimmune accelerator’ locus (*Yaa*) in lupus-susceptible mice is a duplication of a segment of X-chromosomal DNA that doubles 17 gene dosages, including that of *TLR7* [81,82]. This effect was subsequently confirmed to be specific to TLR7, as lowering the *TLR7* dosage ablated the hyper-responsiveness caused by the *Yaa* allele, and *TLR7* transgenic mice developed a lupus-like disease with proliferation of highly activated DCs [83]. Furthermore, compared with male-control pDCs, female-control pDCs produce significantly higher IFN- α upon TLR7 engagement, suggesting an

intriguing mechanism for the higher prevalence of lupus in women [84]. However, other studies have documented decreased IFN- α production in response to certain stimuli, with the use of TLR7 ligands [85,86].

The specific role of TLR9 signaling in SLE is also unclear [87]. pDCs from NZB lupus-prone mice express high levels of TLR9 mRNA and IFN- α upon TLR9 engagement [88]. In addition, TLR9-deficient mice are unable to produce anti-dsDNA Abs in MRL/lpr mice [89]. TLR9 signaling in an Fc γ RIIB-deficiency antinucleosome knock-in model is needed for auto-Ab production [90]. Certain *TLR9* polymorphisms have been associated with increased risk of SLE in Japanese patients [91], although there is no difference in TLR9 expression on peripheral blood mononuclear cells from SLE patients and healthy controls [92]. However, several groups have found that TLR9 deficiency worsened lupus-like disease manifestations in several different MRL strains, with varying effects on auto-Ab production [93,94]. Again, some of these disparate results appear to be due to strain differences in the various murine lupus models, with differing cellular requirements for disease manifestation in different genetic backgrounds.

SLE genetics & dendritic cells

A number of studies have attempted to identify genetic risk factors in SLE, and have been well reviewed [95–97]. In the past, researchers performed genome-wide linkage studies in families whose prevalence of SLE was high, while another technique involved a candidate gene approach and population-association studies. Although biased towards the gene variants present in the families under linkage investigation or the group of candidate genes in an association study, these studies provided evidence of several susceptibility loci. Among them, several genes with potential relevance to DC phenotype and function showed strong associations with SLE. These include the *HLA DR-B1* in the HLA class II locus, *FCGR2A/2B*, *FCGR3A/3B*, *STAT4*, *CRP*, and the *TLR5* genes on chromosome 1. Genes in the type I interferon pathway have recently been associated with SLE. Among them are the IFN regulatory factor 5 (*IRF5*) gene on chromosome 7, as well as the *IRF3* and *TYK2* genes on chromosome 19 [98,99]. *IRF5* is expressed on pDCs and appears to be very important for TLR7 signaling [100]. As yet, there is no functional association between the *IRF5* risk haplotype and type I IFN production.

Recently, several genome-wide association studies have confirmed previously identified risk alleles and discovered new risk alleles in specific patient populations with SLE [101–103]. These studies are important because they provide the first genome-wide analysis of risk alleles without the bias inherent in candidate gene and linkage study approaches. Interestingly, in addition to the previously identified HLA class II locus, *FCGR2A* and the *IRF5* gene, several new susceptibility regions have now been reported. Among them is the *ITGAM* gene, which encodes integrin- α M (also known as CD11b, CR3 or Mac-1). This gene product is expressed on numerous cell types, including DCs, and aberrancies can result in a host of functional impairments, potentially even contributing to the accelerated vascular damage seen in SLE.

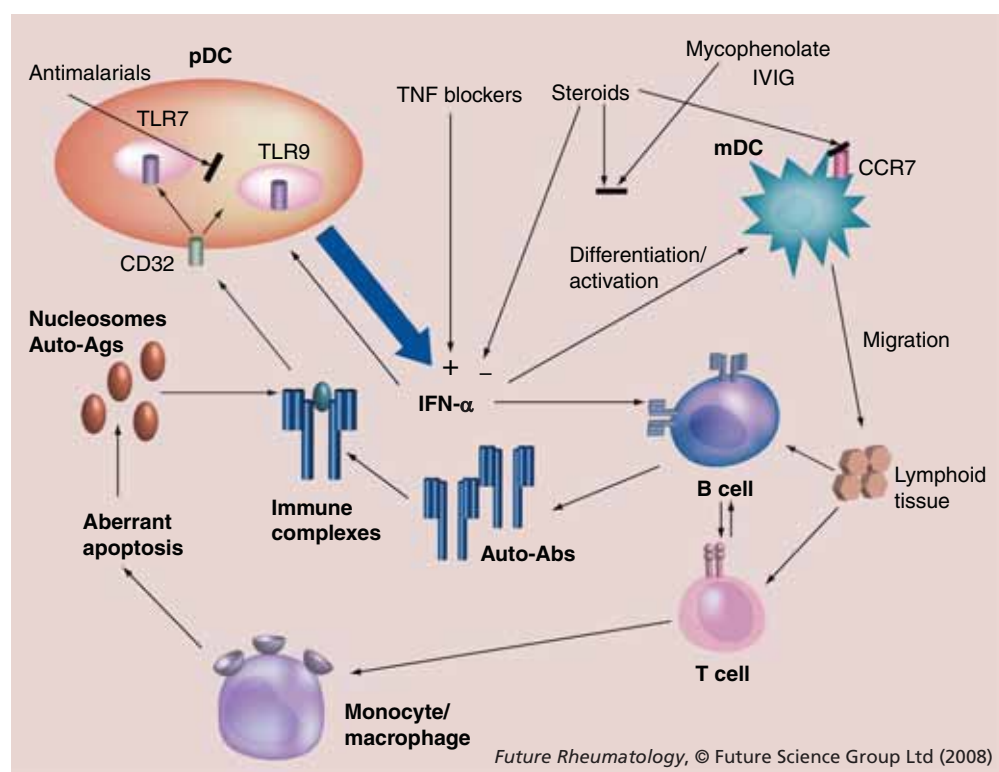
Other mediators

A number of other mediators have been implicated as potential DC modulators and/or contributors to aberrant DC functioning in SLE, including prolactin [104], vitamin D [105] and estrogen [106,107]. In addition, there are plausible rationales for how other contributory agents (UV light, genetic predisposition and so on) could mediate their effects, at least in part, via DC modulation [13,81,108].

Dendritic cells & immunomodulatory drugs in SLE

A number of medications used in the therapy of SLE and other autoimmune conditions exert effects on DCs. The best studied are glucocorticoids, which downregulate the IFN signature [26] via effects on pDCs [109]. Dexamethasone downregulates *CCR7* expression, resulting in decreased migration *in vitro* [110]. Both glucocorticoids and mycophenolate mofetil cause impaired differentiation and maturation of monocytes into mDCs, although there are varying reports as to their effects on subsequent T-cell interactions [111,112]. Antimalarials, commonly used in SLE, block lysosomal acidification, thereby potentially interfering with MHC antigenic peptide loading in DCs. It is postulated that this might result in diminished presentation of low-affinity self peptides and thus diminished autoimmunity [113]. Impaired endosomal acidification impairs TLR7/9 signaling [114], suggesting that another potential mechanism of antimalarial action in SLE may be related to their effects on IFN pathways. One of the postulated mechanisms by which anti-B-cell-directed therapy with

Figure 1. Role of dendritic cells in the immunologic milieu of SLE and how immunosuppressive medications may exert effects on dendritic cells.



Auto-Ab: Autoantibody; Auto-Ag: Autoantigen; IVIG: Intravenous immunoglobulin; mDC: Myeloid dendritic cell; pDC: Plasmacytoid dendritic cell; SLE: Systemic lupus erythematosus; TLR: Toll-like receptors.

rituximab might work is through DC modulation [115]. *In vitro* treatment with intravenous immunoglobulin also interferes with DC differentiation and maturation in the presence of lupus serum, and inhibits nucleosome uptake [116].

TNF- α antagonists are used in the treatment of rheumatoid arthritis and other autoimmune diseases. It is well documented that a subset of treated patients can develop serological and clinical manifestations of SLE [117]. A potential mechanism for this phenomenon is through the alteration of the balance between TNF- α and IFN- α . Neutralization of TNF- α results in sustained IFN- α release by pDCs, and patients treated with TNF- α blockade exhibit increased IFN signatures [118].

Conclusion

There are multiple mechanisms by which DCs can trigger and promote autoimmunity, including their interactions with effector cells, their functions in apoptosis and their role in critical cytokine production (Figure 1). While our understanding of the role of DCs in SLE pathogenesis

has greatly increased, there are still many areas that are not fully clarified. While type I IFNs are implicated in the aberrant phenotype of DCs in lupus, other mechanisms are likely to be involved in this abnormality, including intrinsic genetic defects that are only recently being elucidated, as well as extrinsic environmental and/or infectious factors. It is also necessary to determine the other cytokines that contribute to the autoimmunity-promoting milieu influencing DCs during their activation and maturation. Identifying other DC receptors involved in the inappropriate processing of apoptotic material and the aberrant secretion of autoimmunity-promoting cytokines will be very important. In addition, while a compelling body of evidence supports a potential pathogenic role for type I IFNs, the contradictory mouse model reports and the absence of a documentable IFN signature in a significant number of adult lupus patients warrant further exploration. Clarifying these issues will be crucial to moving forward in the age of cell-specific and cytokine-directed therapies.

Executive summary

Immunopathogenesis of SLE

- Systemic lupus erythematosus (SLE) research has focused primarily on adaptive immunity.
- There is a growing body of literature implicating a role for dendritic cells (DCs) in many of the disease manifestations.

Biology of dendritic cells

- There are two major subsets of DC: myeloid and plasmacytoid.
- DCs generate peripheral tolerance by presenting harmless or self antigen to lymphocytes in the absence of other signals.
- In the presence of danger signals, DCs mature/activate and migrate to lymphoid tissue, where they stimulate naive and antigen-specific T cells as well as other effector cells.

Dendritic cell phenotype in SLE

- Circulating DCs are decreased in SLE; this is thought to be due to enhanced migration into peripheral affected tissues.
- While there is variability between *in vitro* studies, SLE DCs exhibit an aberrantly mature and activated phenotype.

Relationship between type I IFN & dendritic cells in SLE

- IFN- α is produced primarily, but not exclusively, by plasmacytoid DCs.
- IFN- α exerts numerous immunomodulatory effects on many cell types of potential relevance in SLE. A subset of SLE patients exhibit overexpression of the IFN signature in various tissues.
- IFN- α is implicated in the development of accelerated atherosclerosis in SLE patients.
- Mouse models have generated conflicting reports as to the role of IFN- α in SLE.

Aberrant apoptosis, dendritic cells & SLE

- There is strong evidence for dysregulated apoptosis in SLE. This provides a potential source of circulating nuclear auto-Ag which may promote autoantibodies and immune complex generation.
- Immunostimulatory DCs can take up immune complexes and present them to autoreactive T cells.

Toll-like receptors & dendritic cells in SLE

- Toll-like receptors (TLRs) are pathogen recognition systems that identify highly conserved molecular patterns that help distinguish self from non self.
- Immune complexes can stimulate IFN- α production from plasmacytoid DCs via TLR7 and 9.

SLE genetics & dendritic cells

- Recent powerful genome-wide association studies have confirmed previously reported susceptibility genes in SLE and identified several new ones, some of which could potentially alter DC functioning. These include *IRF5* and *ITGAM*.

Other mediators

- Hormones, vitamin D, and other mediators may exert some of their effects in SLE via DCs.

Dendritic cells & immunomodulatory drugs in SLE

- Steroids decrease maturation, activation and migration of DCs, and downregulate the IFN signature in SLE.
- Antimalarials may modulate disease by inhibiting TLR7/9 signaling.
- TNF- α blockade may trigger/exacerbate SLE by disrupting the TNF- α /IFN- α balance.

Future perspective

Given our current understanding of normal DC biology and aberrant DC function in SLE, there are a number of future directions possible, including:

- Development of a rapid and inexpensive assay screening for the presence of a strong interferon signature or other cytokine-related gene upregulation on an individual level. This could help determine which patients might benefit from specific anticytokine therapy;
- Assessing the effect of anti-IFN- α therapy in human SLE patients. There are ongoing Phase I trials utilizing anti-IFN- α monoclonal antibodies [119];
- Generation of 'tolerizing' DCs by *ex vivo* manipulation with peptides and anti-inflammatory cytokines;
- Development of receptor- and surface molecule-blocking and stimulating antibodies for use in patients. Anti- β -lymphocyte stimulator therapy is already undergoing extensive study. Future targets could include BDCA-2 (involved in downregulation of IFN- α production by pDCs [120,121]) and TLR7 and 9;
- Identifying specific genotype–phenotype correlations with newly identified genetic risk loci. Further genetic investigations will likely involve resequencing efforts to identify

rare gene variants at the identified risk loci and examination of possible copy-number variation to understand gene dosage effects.

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Affiliations

- Seetha U Monrad, MD
University of Michigan, Division of Rheumatology, 5520 MSRB, Box 0680, 1150 W Medical Center Drive, Ann Arbor, MI 48109, USA
- Karl C Desch, MD
F5790 Mott Children's Hospital/0254, Department of Pediatrics, Division of Neonatal–Perinatal Medicine, 200 East Hospital Drive, Ann Arbor, MI 48109-0254, USA
- Mariana J Kaplan, MD
University of Michigan, Division of Rheumatology, 5520 MSRB, Box 0680, 1150 W Medical Center Drive, Ann Arbor, MI 48109, USA
Tel.: +1 734 936 7905
Fax: +1 734 763 4151
makaplan@med.umich.edu