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Review Article

Dendritic Cells in Systemic Lupus Erythematosus: From Pathogenic Players to Therapeutic Tools

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System lupus erythematosus (SLE) is a multifactorial systemic autoimmune disease with a wide variety of presenting features. SLE is believed to result from dysregulated immune responses, loss of tolerance of CD4 T cells and B cells to ubiquitous self-antigens, and the subsequent production of anti-nuclear and other autoreactive antibodies. Recent research has associated lupus development with changes in the dendritic cell (DC) compartment, including altered DC subset frequency and localization, overactivation of mDCs and pDCs, and functional defects in DCs. Here we discuss the current knowledge on the role of DC dysfunction in SLE pathogenesis, with the focus on DCs as targets for interventional therapies.

1. Introduction

Systemic lupus erythematosus is a chronic autoimmune inflammatory disease that affects multiple organ systems, prototypically characterized by high levels of circulating autoantibodies and glomerulonephritis. Clinical symptoms also encompass musculoskeletal, dermatological, neuropsychiatric, pulmonary, gastrointestinal, cardiac, vascular, endocrine, and hematologic manifestations. The reported incidence of SLE nearly tripled over the last 40 years due to improved detection of mild disease [1], but SLE prevalence estimates still vary considerably, ranging from 10 to 150 cases per 100,000, depending on geography, race, and gender [2–5]. In the United States, the prevalence of SLE is higher among Asians, African Americans, African Caribbeans, and Hispanic Americans compared with Caucasians [6–9]. Similarly, in European countries SLE prevalence is higher among people of Asian and African descent [5–9]. Interestingly, SLE is reported infrequently in Africa [10]. Mortality rates are relatively low, at 10–50 per 10,000,000 of the general population and show correlation with renal and cardiovascular manifestations as well as infection [11]. Importantly, patients commonly experience profound fatigue and joint pain and a decreased quality of life [12–15].

The precise etiology of SLE remains unclear and likely varies, considering its diverse clinical manifestations. Nevertheless, SLE is believed to result from dysregulated immune responses, loss of tolerance of CD4 T cells and B cells to ubiquitous self-antigens, and the subsequent production of anti-nuclear and other autoreactive antibodies. This dysregulation is associated with high serum levels of type I IFN, observed in greater than 70% of patients [16, 17]. Current "standard of care" treatments encompass high-dose corticosteroids, antimalarials, and immunosuppressive drugs that are associated with significant adverse side effects. As these treatments suppress symptoms and do not cure the disease, new therapies are needed.

Contemporary treatment strategies have been shifting emphasis toward the identification of immunological processes, both soluble and cellular, in order to redirect aberrant immune responses. Dendritic cells have recently been recognized as important players in the induction and progression of autoimmune diseases, including SLE [18]. Human and mouse studies have associated lupus development with

altered DC subset frequency and localization, overactivation of mDCs or pDCs, and functional defects in DCs [19, 20].

However, full dissection of the relative contribution of the causes and the consequences of the dysfunctionality in the different DC subpopulations is needed to understand the processes that govern SLE development, progression, remission, and relapses, in order to design interventional treatments that have the potential to redirect the immune system and eventually lead to a cure for this disease.

2. DC Populations in Humans

DCs are a heterogenous population of professional antigen presenting cells, which bridge innate and adaptive immunity. In the absence of exogenous triggers, DCs contribute to the clearance of dying cells and the maintenance of tolerance. During infection, or in the context of autoimmunity, however, DCs play a pivotal role in the activation of CD4 and CD8 T cells. DCs were initially identified by Ralph Steinman and lack typical lineage markers for T cells (CD3), B cells (CD20), and NK cells (CD56) while expressing high levels of MHC class II [35, 36]. Within this population comparative studies have identified a small number of subsets that have homologues in several mammalian species [37, 38].

2.1. Myeloid DCs: BDCA1$^+$ DCs and BDCA3$^+$ DCs. Myeloid DCs are considered "conventional" or "classical" DCs and are characterized by expression of CD11c and CD11b and lack of CD14 and CD16. Within this population we currently distinguish two populations based on the expression of the markers CD1c/BDCA1 and BDCA3/CD141 [39].

The BDCA1$^+$ DCs are the major myeloid DC population and are found in blood, lymphoid organs, and most tissues. BDCA1$^+$ DCs express a wide variety of pattern recognition receptors including TRL1–8, lectins, and cytokines, allowing them responsiveness to a diverse array of environmental cues. BDCA1$^+$ DCs are strong stimulators of naïve CD4 T cell responses, which can be shaped differently depending on which innate stimuli are present [37].

The BDCA3$^+$ DCs make up >10% of the mDCs and have been found in lymphoid and nonlymphoid tissues as well as blood and bone marrow. BDCA3$^+$ DCs express high levels of TLR3, XCR1, and CLEC9 and have been shown to display an increased capacity to phagocytose dying cells and cross-present cell-associated antigens to CD8 T cells compared to other DCs subsets [34, 40, 41].

2.2. Plasmacytoid DCs. pDCs lack the classic mDC markers CD11b and CD11c and express high levels of CD123, CD303 (BDCA2), and CD304 (BDCA4). pDCs are known for their capacity to produce vast amounts of type I IFNs in response to viruses and/or virus-derived nucleic acids predominantly via engagement of TLR7 and TLR9. pDCs have been shown to prime CD4 T cells and cross-prime CD8 T cells, especially in the context of infection [42]. Several studies implicate pDCs in the induction and maintenance of tolerance through the induction of regulatory T cells (Tregs) [43–45].

2.3. Monocyte-Associated DCs. There are currently several populations of DCs that are thought to develop from monocytes rather than common DC precursors. These cells display a variety of phenotypes and functions, but there is no consensus on their exact classification or their role *in vivo*.

CD14$^+$ DCs are observed in several nonlymphoid tissues, including the skin. These cells express CD11c but lack BDCA1 or BDCA3. The CD14$^+$ DCs express low levels of costimulatory molecules or chemokine receptors that promote migration. While these cells have been suggested to be poor at stimulating naïve T cells, they have been found to support the formation of T follicular helper cells and to provide direct help to B cells [46–49].

Inflammatory DCs (iDCs) have been suggested to originate from classic CD14$^+$ blood monocytes under inflammatory conditions. These cells may express some of the myeloid DC markers and seem prone to produce proinflammatory cytokines. *In vitro* studies suggest that different types of inflammatory stimuli give rise to populations with distinct proinflammatory phenotypes. TNFα/iNOS expressing inflammatory DCs have been found in skin lesions of patients with psoriasis and atopic dermatitis [50, 51].

SlanDCs encompass a subset of monocytes with high expression of MHC class II, CD16, and 6-sulpho LacNAc (slan). SlanDCs were shown to express TRL7 and TLR8 and to produce IL-12, IL-23, and TNF, preferentially promoting Th1 and Th17 cell differentiation. This population has been isolated from the inflamed skin of psoriatic patients and SLE patients with cutaneous lupus, the colon, and draining lymph nodes of patients with inflammatory bowel diseases, as well as CSF samples and inflammatory brain lesions of patients with MS [52–55]. Interestingly, SlanDC infiltration in tumors is associated with tolerance and poor prognosis, indicating either diversity within the slanDC population or heterogeneity in its function.

2.4. Tissue DCs. Nonlymphoid tissue resident DCs are present in most tissues in steady state and have been associated initially with induction of tolerance to self-antigens [36–38, 56–58]. These cells migrate at a very low rate to the draining LN under steady state conditions but show significant increased migration under inflammatory conditions. Several studies have identified networks of tissue resident DCs in the skin, lung, gut, and liver [59, 60]. Each of these networks consists of several subpopulations with different capacities for phagocytosis, antigen processing and presentation, migration, and the type of immune response they promote. Due to accessibility, skin DCs, especially Langerhans cells (LC), have been the most studied tissue-DC in the context of SLE.

2.5. DC Activation of T Cells. One of the defining features of DCs is the expression of class I and class II major histocompatibility proteins and the processing and presentation of peptide antigens to T cells. DCs predominantly present self-antigens in low quantities resulting in immunologic tolerance. Once activated, however, DCs mature in a process that usually involves migration to a draining lymph node and the priming of T cells [61–63]. The factors governing the functional result of T cell priming are multifactorial,

Table 1: pDCs in SLE.

Markers used to identify subset	Reference	Frequency	Phenotype	Function
BDCA2$^+$ CD123$^+$	Tucci et al. [82]	↓ in blood, correlated with LN and ↑ in kidney (more than other DC subsets)		
BDCA2$^+$ (blood) and BDCA4$^+$ (kidney)	Fiore et al. [78]	↓ in blood in active disease and ↑ in kidney (more than other DC subsets)	DCs in kidney were immature (DC-LAMP$^-$), localized to tubulointerstitium, in clusters, and lacked dendrites	
BDCA2$^+$ Lin.$^-$ HLA-DR$^+$	Migita et al. [77]	↓ in blood		
CD123^{high} CD11c$^-$ CD16$^-$ HLA-DR$^+$	Henriques et al. [80]	↓ in blood in active disease		
BDCA2$^+$CD123^{high}	Kwok et al. [90]	*Normal* in blood	↓ IFNα production by PBMC per pDC upon CpG stimulation	
BDCA2$^+$ BDCA4$^+$ CD123$^+$	Jin et al. [79]	↑ in blood per total PBMC	*Normal* HLA-DR, CD86, CD83, CCR7	↑ T cell proliferation in MLR
BDCA2$^+$ CD11c$^-$	Gerl et al. [81]	na	*Normal* HLA-DR, CD86, CD83, CCR7, CD40, BAFF, CCR1, and CCR5 and ↓ CMKLR1	↑ basal and CCL19-specific migration
BDCA-2$^+$ CD4$^+$ CD11c$^-$ Lin$^-$	Hagberg and Rönnblom [86]		↓ SLAMF5/CD84, SLAMF7/CRACC/CD319, *normal* SLAMF1, SLAMF2/CD48, SLAMF3/CD229, SLAMF4/CD244, and SLAMF6/CD352	

including the relative concentration of surface peptide/MHC, costimulatory molecule expression, and cytokine release. Ultimately, the combination of these signals will result in either T cell anergy, deletion, or activation, proliferation, and differentiation [64–66].

A wide variety of cell surface costimulatory proteins expressed by DCs can signal both activation (41-BB, CD40, CD70, CD80, CD83, CD86, GITRL, ICOSL, LTBR, and OX40L) and inhibition (PDL1, PDL2) of an engaged T cell (reviewed in [67, 68]). In addition, secretion of pro- and anti-inflammatory cytokines by DCs contributes to the outcome of T cell priming. DCs can produce a wide variety of cytokines; which cytokines are produced depends upon environmental signals as well as upon the DC subtype. Cytokine production is driven by input from paracrine and autocrine cytokine signaling, as well as input from innate pattern recognition receptors (PRRs) including toll-like receptors (TLRs). The combination of these signals not only influences whether a T cell becomes activated, but also plays a key role in directing T cell differentiation toward various effector fates.

3. Role of DCs in SLE Development and Progression

Although it is not certain how immunological tolerance is broken in SLE, DCs are thought to play key roles [30]. Perhaps the most prominent model proposes that the initial injury is due to a build-up of dying cells, a result of either dysregulated apoptosis or insufficient clearance of dying cells by DCs and other phagocytes [22, 23, 69]. Indeed, high levels of apoptotic cells are found in SLE patient serum, germinal centers, and inflamed tissues, such as the skin and kidney [24, 27]. Mounting evidence indicates that self-RNA and self-DNA from these dying cells induce the unremitting output of type I IFN by pDCs [21] via engagement of TLR9 or TLR7 [31, 70] and potentially via other cytosolic nucleotide sensing pathways such as *RIG-I/IPS1* and STING (*TMEM173*) [28, 71, 72]. Type I IFNs produced by DCs promote their own activation and maturation in an autocrine manner, including increased IFN output and increased surface expression of CD80, CD86, and MHC class II, making them better at activating T cells [21, 25, 26, 73]. Furthermore, type I IFNs directly promote B cell activation, antibody production, and T cell survival and expansion [29, 32, 33]. Altogether, these data suggest that DCs are key players in SLE pathogenesis and point to DCs as promising therapeutic targets.

4. DC Abnormalities in SLE Patients

Several reports indicate that the frequency, composition, and phenotype of DCs in SLE patients differ from those of healthy individuals (see Tables 1 and 2). However, it is difficult to compare results between laboratories, given differences in disease activity and manifestations, the effect of various drug treatments on DC development and phenotype, and the variations in analytical parameters.

Table 2: DCs in SLE.

Markers used to identify subset	Reference	Frequency	Phenotype	Function
BDCA1$^+$	Fiore et al. [78]	↓ blood in active disease and ↑ kidney in active disease	DCs in kidney were immature (DC-LAMP$^-$), localized to tubulointerstitium	
BDCA3$^+$	Fiore et al. [78]	↓↓ blood and ↑ kidney in active disease	DCs in kidney were immature (DC-LAMP$^-$), localized to tubulointerstitium, with elongated processes	
BDCA1$^+$ CD11c$^+$ BDCA4$^-$ CD19$^-$	Jin et al. [91]	↓ in blood per total PBMC	↓ CD83, especially in active disease, *normal* HLA-DR, CD86, and CCR7	
HLA-DR$^+$ Lin$^-$ CD4$^+$	Scheinecker et al. [76]	↓ in blood	↓ CD40$^+$, B7$^+$, and CD11c$^+$	↓ T cell proliferation in MLR
BDCA1$^+$ CD11c$^+$	Tucci et al. [82]	*Normal* in blood, relatively few in kidney		
CD11c$^+$ Lin$^-$	Crispín et al. [83]	↑ in blood (though not significant)	↑ CD86$^+$, CD80$^+$, *normal* HLA-DR$^+$, and CD40$^+$	*Normal* T cell proliferation in MLR, moDCs fail to increase costimulatory molecule expression upon activation
CD11c^{high} CD14$^-$	Gerl et al. [81]	na	↑ CD86, BAFF, *normal* HLA-DR, CD83, CD40, CCR7, CCR1, and CCR5 and ↓ CMKLR1	
Adherent, monocyte-derived DCs (MDDCs)	Ding et al. [93]	na	↑ CD86, CD80, HLA-DR, and CD1a and ↓ CD83 after 5–7 d culture	↑ T cell proliferation in MLR
CD14$^+$ sorted, monocyte-derived DCs (MDDCs)	Köller et al. [92]	na	↓ HLA-DR after 8–10 d culture, *normal* CD86, CD83, CD80, CD40, CD54, and CD33	↑ antigen-specific T cell proliferation and normal MLR
M-DC8 (slanDCs)	Hänsel et al. [53]	↑ in skin of patients with cutaneous LE and "strong inflammation" SLE	*In situ* TNF production in cutaneous LE	↑ TNFα production by healthy donor slanDCs in response to SLE serum compared with control serum

Studies have shown reduced [74–81], normal [80, 82], and increased [83] levels of CD11c$^+$ mDC frequencies in PBMC from lupus patients compared to healthy controls. Similarly, pDC levels were found to be unaffected, reduced [74–78, 84, 85], or increased [79, 86]. Decreased frequencies of pDCs or mDCs were most often associated with active disease and to a lesser degree with nonactive disease [75]. Interestingly, studies showing peripheral pDCs decreases observed a concomitant infiltration of pDCs in nephritic kidneys, suggesting that active pDCs may have migrated to the sites of inflammation [78, 82]. Similarly, Fiore et al. showed that besides pDCs, BDCA1$^+$ DCs and BDCA3$^+$ DCs were increased in the renal tubulointerstitium of patients with lupus nephritis [78]. Increased numbers of pDCs and inflammatory/slanDCs are also found in cutaneous lesions of lupus patients, further suggesting migration of DCs to target organs [87, 88]. It is likely that DCs that reside in or have been recruited into the affected tissues will display different characteristics than those circulating in the periphery. Consequently, these populations should be included in further assessments in order to understand their contribution to disease pathogenesis and allow for a rational design of DC-targeting therapeutics.

5. SLE-Associated Dysfunction in Primary DCs

The few published maturation and functionality studies with primary human DCs have given conflicting results. Earlier reports indicated that DCs from SLE patients have normal or even reduced levels of costimulatory molecules and are poor stimulators of allogeneic T cells in mixed lymphocyte reactions. Scheinecker et al. reported that in SLE patients B7$^+$ and CD40$^+$ DCs were reduced and that DC-enriched APC from SLE patients displayed a diminished T cell-stimulatory capacity in both the allogeneic and the antigen-specific MLR, as compared with healthy individuals [76]. On the other hand, Mozaffarian et al. showed increased CD80/CD86 and

reduced PDL-1 expression on mDC during disease flares and an upregulation of PDL-1 during remission [89]. Similarly, Gerl et al. [81] published that monocytes and mDCs from SLE patients expressed higher levels of CD86 and BAFF, but not CD83 and CD40. Upon further assessment of their migratory capacity, they found that pDCs and mDCs from SLE patients had normal expression of CCR1, CCR5, and CCR7 but reduced expression of the chemokine receptor ChemR23 (CMKLR1). However, pDCs from the SLE patients showed an increased basal and CCL19-specific migration *in vitro*.

Assessment of peripheral monocytes, total DCs, $BDCA1^{+}$ DCs, and $CD14^{-/low}CD16^{+}$ DCs by Henriques et al. showed that a higher percentage of SLE monocytes and $CD14^{-/low}CD16^{+}$ DCs produced proinflammatory cytokines as well as a higher amount of cytokines produced per cell, particularly in active disease. Data from Kwok et al. [90] seemed to indicate that type I IFN production by pDC upon TLR9 engagement was diminished in SLE patients, leading them to hypothesize that the persistent presence of endogenous IFNα-inducing factors induces TLR tolerance in pDCs of SLE patients, resulting in impaired production of IFNα. Studies by Jin et al. [79, 91] also suggested deficiencies in TLR9 recruitment/signaling and production of proinflammatory cytokines in pDCs from SLE patients; however, they also showed that SLE pDC had an increased ability to stimulate T cells. Importantly, while pDCs from healthy donors induced suppressive T regulatory cell features (Foxp3 expression) in T cell cultures upon addition of apoptotic PMNs, SLE pDCs failed to do so.

These studies indicate that SLE is associated with phenotypic and functional changes in DCs and that these changes can affect different aspects of the DCs' functional program in distinct and divergent ways.

6. SLE-Associated Dysfunction in *In Vitro* Generated DCs

Due to the paucity of DCs in leukopenic SLE patients, many studies have used *in vitro* generated monocyte-derived DCs (moDCs) to gain insight in DC generation, phenotype, and function in the context of SLE.

Initial studies suggest that monocyte-derived DCs had a reduced proinflammatory and T cell stimulatory activity [92] while later studies suggested accelerated differentiation and maturation concomitant with increased activity to maturation stimuli [93]. MoDCs from SLE patients expressed higher levels of HLA-DR and activating FcγRs, but decreased expression of inhibitory FcγR and expression levels correlated with disease severity [92, 94]. In addition, moDCs spontaneously overexpressed activating costimulatory molecules including CD40, CD80, and CD86 and showed increased production of stimulatory cytokines (IL-6, IL-8, and BAFF/BlyS), eventually resulting in an increased capacity to activate T cells in an MLR [93, 95]. Similarly, Nie et al. [96] demonstrated substantial phenotypic and functional aberrations in DCs generated from Flt3-ligand and GM-CSF/IL-4 stimulated bone marrow aspirates. Both immature and mature DCs from SLE donors expressed higher levels of CCR7, CD40, and CD86 and induced stronger T cell proliferation.

7. Nature versus Nurture

Drawing causative relationships between DCs frequencies, maturation status, functionality, and disease is complex as it is not clear whether aberrations in DC frequency and functionality are the driver or a result of the disease. It is likely that genetic alterations in DCs predispose to the development of accelerated maturation and abnormal behavior. Evidence for this intrinsic defect is supported by the observations that moDCs from SLE patients, generated from either PBMC or bone marrow, display accelerated maturation and increased proinflammatory status compared to moDC from healthy donors. On the other hand, serum of SLE patients has been shown to contain pro- and anti-inflammatory stimuli like type I IFN, type I IFN-inducing factors, and IL-10 that alter DC differentiation, maturation, and functionality, even in DCs from healthy donors [97–99]. This raises the question whether the aberrant behavior of DCs in SLE patients is a result from an intrinsic defect, a result of their development in an inflammatory environment, or a combination of these two [97]. To further confound the interpretation of human clinical data, various classic SLE treatments, including antimalarials, corticosteroids, and immunosuppressive drugs significantly affect DC number, maturity, and functionality [100].

8. Mouse Models to Dissect Role of DCs in SLE Pathogenesis

The availability of mouse models provides an exciting opportunity to gain cellular and molecular insight in the role of different DC populations in the development and progression of SLE. There are a variety of spontaneous models, including the F1 hybrid between the New Zealand Black (NZB) and New Zealand White (NZW) strains (NZB/W F1) and its derivatives, the MRL/lpr and BXSB/Yaa strains, as well as inducible models such as the pristane-induced model and chronic graft-versus-host-disease models (cGVHD) [101–104]. In recent years the number of models has been expanded with genetically modified mice, targeted in genes that can promote, resist, and modify lupus susceptibility [105, 106]. All of these models display their own variation of lupus-like disease reminiscent of symptoms observed in patients, including autoantibody production, lymphoid activation and hyperplasia, lupus nephritis, and skin manifestations. Although all of these models have been instrumental in the identification of several main concepts in this diseases, none of the models can completely recapitulate the complexity and variety of human disease. However, careful pairing of models with patient groups with the similar clinical manifestations can ensure the translational relevance of these preclinical models.

Mouse models have several advantages: (i) the relative homology between human and mouse DCs, (ii) the opportunity to genetically or pharmacologically eliminate specific DC populations during specific stages of disease, (iii) access to all target tissues for the assessment of tissue associated or infiltrating DCs, (iv) the opportunity to assess the effects of common treatments on the parameters, and (v) a plethora of biological and pharmacological tools to dissect the relative

contribution of specific molecules and mediators to the development and progression of disease.

9. Similarities between Mouse and Human DCs

Recent genomic, proteomic, and functional analyses of mouse and human DCs have identified high homology between the most abundant DC populations [107]. Like in human DCs, mouse DCs lineages encompass conventional DCs, pDCs, $CD14^+$ DCs, tissue DCs, and monocyte-derived/inflammatory DCs [38, 108].

Conventional mouse DCs encompass three main subpopulations which are found in circulation as well as in secondary lymphoid organs [109]: (1) $CD11c^{high}MHCII^+CD8\alpha^-33D1^+Sirp\alpha^+CD11b^+$ (CD11b DCs), which express most TLRs except Tlr3, display a preference for activation of CD4 T cells, and have high homology with the human $BDCA1^+$ DCs; (2) $CD11c^{high}MHCII^+CD8\alpha^+CD205^+Sirp\alpha^-CD11b^-$ (CD8α DCs), which express Xcl1, CD141, and Clec9A and express mRNAs coding for most TLRs except Tlr5 and Tlr7, and are characterized by high Tlr3 expression; and (3) $CD11c^{high}MHCII^+$ cells that lack CD8α, CD4, and CD11b (generally termed "double" or "triple" negative) DCs that, like CD8a DC, express Xcl1, CD141, Clec9A, and Tlr3 [110–113]. These latter two populations have a high capacity to phagocytose dying cells and cross-present cell-associated or particulate antigens to CD8 T cells. Based on their genomic and functional analysis these two populations are considered to be homologues to the human $BDCA3^+$ DCs.

Like human pDCs, mouse pDCs produce vast amounts of type I IFN in response to viruses via TRL7/9 mediated pathways. Compared to their human counterparts, mouse pDCs show relatively poor capacity for phagocytosis and antigen presentation. However, both populations have been implied in the maintenance of peripheral tolerance [45, 114–116].

Various types of inflammatory and monocyte-derived DCs have been identified in mice as well. Tissue infiltrating $CD14^+$ DC-like cells have been found under inflammatory conditions [117, 118]. Inflammatory DCs have been shown to arise after a wide variety of immunological insults, including pathogenic infection, experimental sterile inflammation, and models of inflammatory diseases such as RA, colitis experimental autoimmune encephalomyelitis, and allergic asthma (reviewed in [119]).

10. The Role of DCs in Mouse SLE Models

Recent studies indicate an important role for DCs in the development and progression of SLE-like disease in mouse models. Similar to human disease, DCs from lupus-prone mice display a range of alterations in their numbers and their functionality [120–123]. Splenic DCs from NZB/W F1 showed enhanced maturation and a stronger ability to attract B cells and present antigens to T cells than DCs from control mice. pDCs from SLE-prone mice showed increased type I IFN producing capacity upon TLR9 stimulation and increased cell survival compared to pDCs from C57BL/6 mice. Enhanced mDC and pDC activity has also been reported in male BXSB/Mp mice that express an extra copy of Tlr7 on the Y chromosome.

Importantly, depletion studies have now shown causal relationships between DC subsets and disease manifestations. Constitutive depletion of pDCs in lupus-prone mice either through genetic ablation of IRF8, a transcription factor required for pDC and CD8αDC development, or by diphtheria toxin treatment of mice expressing the diphtheria toxin receptor on pDCs resulted in markedly reduced type I IFN production, a reduced IFN signature, reduced autoantibody production, and reduction in the severity of kidney pathology glomerulonephritis [124–126]. Importantly, transient pDC depletion during the early stages of disease was sufficient to significantly alter the course of the disease, suggesting a more prominent role for pDCs in the induction of the disease than in disease pathogenesis at later stages of disease [125]. Diphtheria toxin treatment of CD11c-DTA MLR.Fas^{lpr} mice resulted in reduced T cell differentiation, plasmablast numbers, and autoantibody levels. Interestingly, these mice developed interstitial kidney infiltrates but failed to progress to glomerular or interstitial nephritis, suggesting that DCs play a role in the development of tissue damage [127]. In line with this observation, this group also showed that CD11c depletion, but not LC depletion, resulted in significantly reduced dermatitis, demonstrating that DCs other than LCs control dermatitis in this model [127].

Besides the opportunity to assess the relative and temporal contribution of different DC populations to the development of specific disease manifestations, mouse models also allow for the identification of specific processes in DCs which affect disease development. Targeted deletion of regulatory molecules associated with SLE susceptibility in humans, including Shp1, A20, Blimp-1, Lyn, or Eat-2, specifically in $CD11c^+$ cells resulted in increased DC activity and development of inflammatory and autoimmune phenotypes characterized by the production of autoreactive antibodies and several manifestations of SLE, including severe glomerulonephritis [128–132].

Together these observations indicate that mouse models provide a useful platform for the identification, dissection, and targeting of DC intrinsic and extrinsic processes that facilitate the development, progression, and possibly a cure for SLE.

11. DC Targeted Therapies for SLE

Based on the general role of DC in the regulation of peripheral tolerance to self-antigens, the dysregulation of DCs observed in SLE, and the emerging evidence of the contribution of DCs in the initiation and perpetuation of SLE pathogenesis, it is not surprising that DC-targeting therapeutic strategies have become a topic of interest. Particularly, strategies that would promote self-antigen presentation in a tolerogenic context could be promising for the generation of an abortive or suppressive environment for the autoreactive T and B cells and restoration of peripheral tolerance [133, 134].

In recent years several *ex vivo* models have been established for the generation of human DCs with stable tolerogenic functions (reviewed in [135]). Generally, these resulting tolerogenic monocyte-derived DCs express low levels of positive costimulatory molecules and high levels of immune suppressive mediators (PDL-1, IL-10, etc.). Upon pulsing with specific antigens these DCs are anticipated to promote antigen-specific tolerance via the induction of T cell anergy, T cell apoptosis, skewing of T cell phenotypes to more Th2 or regulatory phenotypes, and the expansion of regulatory T cells.

Tolerogenic DC therapy is still in its infancy and little data is available on its *in vivo* potential. The first studies showed that transfer of antigen-loaded tolerogenic DCs could induce antigen-specific regulatory CD8 T cells and inhibit effector functions in antigen-specific CD8 T cells [136, 137]. A clinical trial in patients with type I diabetes using DCs treated with antisense oligonucleotides to silence costimulatory molecules was less successful, and although the treatment was well tolerated, only very limited tolerance outcomes were reported [138]. A subsequent trial in T1D patients indicated that transfer of IL-10 and TFGβ1 generated tolerogenic DCs pulsed with pancreatic islet cells induced antigen-specific T cell hyporesponsiveness and was associated with better glycemic control [139]. Similarly, transfer of a single dose of tolerogenic DCs, derived by *ex vivo* treatment with NF-κB inhibitors, into patients with active RA resulted in a modest improvement in disease activity 3 and 6 months after injection [140]. Currently there are several trials addressing the therapeutic potential of tolerogenic DCs in multiple sclerosis, rheumatoid arthritis, type I diabetes, and allergic asthma [141].

To date no tolerogenic DC transfer studies have been published in preclinical models or SLE patients. However, *in vitro* data indicate that tolerogenic DCs can be generated from SLE patients [83, 142, 143] and that apoptotic cells can be used as source to load the DCs with autoantigens [143]. The insight obtained from currently ongoing tolerogenic DC treatment strategies in other chronic inflammatory diseases will help to identify critical parameters such as dose, route, and duration of treatment leading to the most efficacious outcome [144, 145]. However, a better understanding of the role of DCs in disease pathogenesis is critically needed in order to select the type of tolerogenic DC that can successfully counteract the dysfunctional adaptive immune responses that maintain the disease.

Competing Interests

The authors declare that they have no competing interests.

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