Novel insights into dendritic cells in the pathogenesis of systemic sclerosis

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Introduction

Systemic sclerosis (SSc), also known as scleroderma, is an immune-mediated rheumatic disease characterized by vasculopathy, inflammation and fibrosis of the skin and internal organs. The aetiology of SSc is largely unknown, and its pathogenesis is complex and poorly understood [1].

Cell types prominently implicated in the disease process include endothelial cells, platelets, structural cells such as pericytes, vascular smooth muscle cells, fibroblasts and myofibroblasts; both innate and adaptive immunity also play an important contribution in SSc. Additionally, highly specific circulating autoantibodies are present in nearly all the patients [2]. Immune mediators such as transforming growth factor (TGF)-β, platelet-derived growth factor (PDGF), interleukin (IL)-6, IL-13, angiotensin II, lipid mediators and reactive oxygen species (ROS) have been shown to be relevant in SSc pathology, as well as Toll-like receptors (TLRs) and NOD-like receptor protein 3 (NLRP3) inflammasome dysfunction [3–6]. Moreover, the chemokine C-X-C motif ligand 4 (CXCL4) also plays an important role in SSc, as it was found increased in circulation and in the skin of SSc patients and correlated with the presence and progression of complications such as lung fibrosis and pulmonary arterial hypertension [7,8].

The role of dendritic cells (DCs) in SSc is a severe autoimmune fibrotic disease characterized by fibrosis, vasculopathy, and immune dysregulation. DCs are the most potent antigen-presenting cells, specialized in pathogen sensing, with high capacity to shape the immune responses. The most recent technological advances have allowed the discovery of new DC subsets with potential implications in inflammatory conditions. Alterations of DC distribution in circulation and affected tissue as well as impaired DC function have been described in SSc patients, pointing towards a crucial role of these cells in SSc pathogenesis. In particular, recent studies have shown the importance of plasmacytoid DCs either by their high capacity to produce type I interferon or other inflammatory mediators implicated in SSc pathology, such as chemokine C-X-C motif ligand 4 (CXCL4). In-vivo models of SSc have been vital to clarify the implications of DCs in this disease, especially DCs depletion and specific gene knock-down studies. This review provides these new insights into the contribution of the different DCs subsets in the pathogenesis of SSc, as well as to the novel developments on DCs in in-vivo models of SSc and the potential use of DCs and their mediators as therapeutic targets.

Keywords: conventional dendritic cells, dendritic cells, fibrosis, inflammation, plasmacytoid dendritic cells, systemic sclerosis

Summary

Systemic sclerosis (SSc) is a severe autoimmune fibrotic disease characterized by fibrosis, vasculopathy, and immune dysregulation. DCs represent the most potent antigen-presenting cells in promoting activation of naive T cells, being crucial in...
initiating and shaping immune responses. They express an array of pathogen recognition receptors such as TLRs, C-type lectin receptors (CLRs), RIG-I-like receptors (RLRs) and NOD-like receptors (NLRS) to recognize pathogen- or danger-associated molecules in the extracellular and intracellular environment [12]. Besides their important role as effector cells, fighting against pathogens and controlling adaptive immunity, DCs are also important for maintaining peripheral T cell homeostasis and preventing inappropriate T cell activation [13,14].

In autoimmune diseases, it has been shown that DCs have a critical role contributing to the breakdown of tolerance. For instance, in systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA), alteration in numbers of circulating cells and also in affected tissues has been reported. Additionally, changes in their function, with impaired phagocytosis of apoptotic cells, enhanced cross-presentation of autoantigens derived from apoptotic cells and altered cytokine secretion, have been found. Therefore, these functional alterations are responsible for a harmful imbalance between T helper type 1 (Th1), Th2, Th17 and regulatory T cells (Treg). DCs are also able to shape B cell responses through the secretion of B cell stimulatory and survival factors and through the contribution to the formation and maintenance of ectopic lymphoid structures in target tissues [15].

DC population in humans and mice

Despite the low numbers of DCs in circulation of healthy individuals [16], DCs can be broadly subdivided into plasmacytoid DCs (pDCs) and conventional or classical DCs (cDCs). As suggested by Guilliams et al., cDCs can be further subdivided into cDC type 1 (cDC1s) and cDC type 2 (cDC2s), as their development depends upon distinct sets of transcription factors and because they arise from discrete committed precursors [17].

The complexity of these cell subsets leads to a continuous demand for specific cell markers to identify and characterize these cells more clearly. As summarized by Collin et al., currently there are markers that perform consistently across species, such as CD141, C-type lectin domain family 9 (CLEC9A), cell adhesion molecule 1 (CADM1), B and T lymphocyte associated (BTLA) and cadherin-like receptor 3 (CADM3). Additionally, Dutertre et al. data allowed us to identify distinct markers to differentiate monocytes from cDC2s. CD88, together with CD89, were used to identify monocytes, while HLA-DQ and FcεRIα were used for cDC2s, allowing their specific identification in blood and tissues [19,25].

These recent findings point towards the necessity of exploring these newly described pDCs and cDC2s subsets in the context of SSc, given their potential inflammatory role, as they were already found disturbed in conditions such as SLE and psoriasis [23,25].

DCs in the affected tissues of SSc patients

The skin is frequently affected in SSc patients and, based on the extent of skin fibrosis, SSc patients can be classified as limited cutaneous SSc (lcSSc) or diffuse cutaneous SSc (dcSSc). In lcSSc, skin fibrosis is restricted to the distal areas of the elbows and knees, while in dcSSc skin fibrosis is more extensive and accompanied by internal organ involvement [26–28]. These patients often present lung fibrosis or interstitial lung disease, as well as pulmonary arterial hypertension. Other affected organs may include the gastrointestinal tract, kidney and heart [1,2].

In barrier tissues such as skin and lung, DCs play a major role in determining the severity of inflammatory response and consequently the severity of inflammatory diseases. The different DCs subsets previously described, cDC1s, cDC2s and pDCs, were not only present in blood but also in different tissues, especially in draining lymph nodes and mucosal sites [29], and these DCs subsets were also found in the lung. Albeit cDC2 proinflammatory role, they have also been associated with tolerogenic properties; for instance, isolated lung CD1c+ DCs from patients with
chronic obstructive pulmonary disease (COPD) benefited the differentiation of IL-10-secreting CD4+ T cells. pDCs are distributed throughout the lung, in the airways, parenchyma and alveolar septa and are essential during antiviral responses for their ability to produce type I IFNs [30,31]. Lung tissues from SSc patients and non-SSc controls were tested for the presence of pDCs, which were detected at low levels in the control lung tissues, while in SSc lungs, pDCs were found to be increased not only in the interstitial tissue and bronchi, but also on their bronchoalveolar lavage (BAL) samples [32].

In skin under steady-state conditions, there are at least three well-described major DC subsets: epidermal Langerhans cells (LCs), dermal cDC1 and dermal cDC2. Under inflammatory conditions, however, additional subtypes of DCs arise in the inflamed skin, such as pDCs, inflammatory myeloid DCs and monocyte-derived DCs [33,34]. In SSc skin samples, CD1a+ survivin+ DCs were shown to infiltrate into dermal lesions [35].

**Plasmacytoid DCs in SSc**

In SSc patients, genetic risk factors studies have found several genes involved in the IFN type I signalling pathway to be highly associated with the risk of SSc [36–39]. Moreover, the IFN signature present in blood and affected skin of SSc patients is indicative of the presence of aberrant pDCs [40,41]. In a proteomic
The frequency of the newly characterized CD14+CD163+ inflDC population has been studied in a small SSc cohort, but was not found to be altered compared to healthy controls [25]. Nevertheless, the scavenger receptor CD163, mainly considered as a marker for M2 macrophages, has been found to be increased in the serum of SSc patients [48–50]. Therefore, the role of CD163+ DCs in SSc could be studied more extensively using a larger patient cohort with distinguished SSc subsets. A new role has been described for phospholipase phospholipase D family member 4 (PLD4), linked to SSc genome-wide association studies [51]. The study by Gavin et al. on PLD4-deficient mice suggested that PLD4 functions as 5′ exonuclease, which breaks down single-stranded oligonucleotide (ODN), thereby limiting TLR-9 stimulatory capacity. Importantly, PLD4-deficient DCs were indirectly responsible for up-regulation of major histocompatibility complex (MHC) class II on macrophages and, in general, enhanced responsiveness to TLR-9 ligands [52]. As TLR-9 signalling has an important role in SSc pathogenesis, aberrant PLD4 activity, specifically in DCs, might contribute to the increased immune responses in SSc.

Another factor which might be involved in the development of SSc is P-selectin glycoprotein ligand-1 (PSGL-1) [53]. Increased expression of PSGL-1 specifically in SSc cDCs was associated with the presence and severity of interstitial lung disease (ILD), although the precise role of DCs in ILD development is not clear. Taken together, the evidence indicates that cDCs do not contribute to SSc only by proinflammatory cytokine production, but also by dysregulated antigen processing, T cell activation and probably other mechanisms to be elucidated further.

As a result of systemic autoimmune activation in SSc, monocytes are likely to be recruited to the affected lesions, consequently differentiating into inflDC, similar to that described to occur during inflammation [54]. In humans, an in-vitro model of monocyte differentiation into DC (moDC) is often exploited to describe the potential role of inflDC. Importantly, there is a high correlation between cytokine production capacity of cDCs and moDCs of the same SSc patients [46]. Recently, several studies have focused on understanding how SSc-related factors modulate DC differentiation and function. For instance, CXCL4, in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-4, was shown to skew monocytes to differentiate into more proinflammatory and profibrotic moDCs [55–57]. This suggests that under the effect of an inflammatory environment and the presence of CXCL4, monocytes might differentiate into inflDC that could potentially contribute to the fibrotic process. However, the presence of these cells in the affected tissues of SSc patients still needs to be confirmed.

Conventional DCs and inflammatory DCs (inflDCs) in SSc

The role of cDCs is less studied in the pathogenesis of SSc than the role of pDC. It has been shown that cDCs from early limited and diffused patients produce higher amounts of different proinflammatory cytokines, such as IL-6 and TNF-α, in response to TLR-2, -4 and -6 activation than the cDCs from SSc patients with a long disease history or healthy controls [46]. This emphasizes a possibly higher impact of cDCs in the early and progressive phase of the disease.

Recently, it has been shown that cDC2s of lcSSc patients spontaneously produce higher amounts of CXCL10 ex vivo than cDC2s from healthy individuals [47]. In addition, they also produce more CXCL8 upon in-vitro stimulation with lipopolysaccharide (LPS) plus IFN-γ, which activate signalling pathways involved in SSc pathology. Moreover, dcSSc cDC2s were found to produce more CCL4 than CDC2 from healthy individuals [47]. Differences in the cytokine production patterns may suggest differences in the molecular mechanism in two disease subtypes.
The role of DCs in mouse models

The importance of DCs in SSc has been studied in several mouse models for many years [58–65]. Recent studies have focused on the role of DCs in the bleomycin induced-SSc mouse model. The bleomycin model is the most commonly used model to study the pathogenesis of SSc [66]. Using this mouse model, several recent studies have highlighted the importance of pDCs in SSc. pDCs depletion resulted in attenuation of skin fibrosis in two independent studies, but also reduced lung fibrosis, chemotaxis, inflammation and differentiation of DC in the skin and lung of animals [32,43].

Koon et al. have reported high expression of TLR-8 in SSc pDCs, and to understand more clearly whether TLR-8 can directly promote fibrosis in vivo they used bleomycin model in huTLR-8Tg mice (mice with a single copy of the human TLR-8 gene under the control of human TLR-8 genomic regulatory regions). They found that TLR-8 exacerbates skin fibrosis in the bleomycin-induced fibrosis model, leading to an increased number of pDCs in the skin of bleomycin-injected mice, confirming an important role of TLR-8 signalling and pDCs in skin fibrosis developments [43].

A recent study by Affandi et al. focused on the identification of pathways underlying pDCs aberrances in SSc. This study identified down-regulation of runt-related transcription factor 3 (Runx3) in SSc pDCs, which correlated with skin severity in SSc patients. Using mice with DC-specific deletion of Runx3, they showed increased skin inflammation and fibrosis, together with an enhanced pDC infiltration and increased expression of CD86. Low Runx3 expression in SSc pDCs further highlights the pathological role of pDCs in SSc pathogenesis [67].

Conversely, no reports are available on the pathological role of cDCs in SSc pathogenesis. For instance, depletion of non-pDCs worsened bleomycin-induced skin fibrosis. However, further analysis at different stages of the disease is required to identify different roles of DC subsets in the development of fibrosis in SSc [62].

DC-targeted therapies for SSc

The main therapies for SSc involve immunosuppression, treatment of skin and lung fibrosis and separate treatment of other complications. So far, there is no cure to reverse the disease, therefore there is a serious demand for more specific and efficient therapies. Although there are no clinical trials for specifically targeting DCs in SSc, most of the available and potential treatment options affect DC activity.

Autologous haematopoietic stem cell transplantation (HSCT) has been shown to be a promising solution for severe and therapy-refractory forms of SSc. HSCT aims to re-establish the normal immune system, including self-tolerant DCs. Results have been published for several recent clinical trials [68,69], showing better patient long-term survival. The clinical evidence supporting HSCT usage has been recently reviewed by Ng et al. [70]. HSCT has been suggested recently as the standard of care for rapidly progressive dcSSc patients [71,72].

Another promising cellular-based treatment to alter fibrosis is mesenchymal stem cell therapy, recently discussed by Peltzer et al. [73]. Mesenchymal stromal cells (MSCs) possess anti-inflammatory, anti-proliferative, anti-fibrotic and immunomodulatory properties. There is evidence that dermal white adipose tissue DCs could contribute to potentially reversing fibrosis by sustaining the viability of adipose tissue stem cells [62]. In an ongoing clinical trial (NCT03060551 ClinicalTrials.gov), adipose tissue stromal vascular fraction (SVF)-containing stem cells are subjected to subcutaneous injection of SVF in the fingers in SSc.

Recent evidence suggests that tolerized dendritic cells (tolDC) could become a treatment option for autoimmune conditions [74]. This includes differentiating autologous monocytes into DCs, loading them with disease-specific autoantigens and injecting them back into the patients. A small-scale clinical trial has been conducted to treat patients with inflammatory arthritis, with promising data of autoantigen-loaded tolDCs stability and effect on disease symptoms when injected into the inflamed knee [75]. No study has yet been conducted in SSc; however, considering the more recognized role of DCs in SSc pathogenesis, it might be a particularly beneficial treatment approach for early SSc in which the immune disbalance plays a bigger role than in the fibrosis phase.

A few biologicals targeting DC–T cell interactions and DC-produced cytokines have been or are being tested in clinics [76,77] (NCT01284322 ClinicalTrials.gov). For instance, Abatacept, an immune checkpoint inhibitor, cytotoxic T lymphocyte antigen 4 (CTLA-4) and Ig fusion protein binds to co-stimulatory molecules CD80/CD86 on DCs and thereby inhibits DC–T cell interaction and T cell activation [76]. Targeting IL-6 by tocilizumab has been shown to moderately improve skin and fibrosis in SSc patients; however, it is accompanied by an augmented risk for severe infections [77,78]. Targeting IL-23/IL-17 axis by ustekinumab, also implicated in SSc pathogenesis [79,80], has been shown to be promising in other autoimmune diseases [81,82].

In addition, results from clinical trials in other autoimmune diseases, in-vitro experiments and mouse models support the idea of inhibiting certain signalling pathways downstream from PRR and cytokine receptor activation of DCs and other immune cells, such as the Janus kinase–signal transducer and activator of transcription (JAK–STAT) pathway by tofacitinib (clinical trial, Phase I/II,
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Fig. 2. Plasmacytoid dendritic cells (pDCs) and conventional dendritic cells (cDCs) have a crucial role in the inflammatory and fibrotic processes in systemic sclerosis (SSc). pDCs produce a large amount of type I interferon (IFN)-α and chemokine C-X-C motif ligand 4 (CXCL4) due to dysregulated mechanisms such as runt-related transcription factor 3 (RUNX3) and Toll-like receptor (TLR)-8 signalling. IFN-α has a strong capacity to induce inflammation and to activate other innate immune cells such as cDCs. Exacerbated TLR activation in SSc cDCs lead to an increased production of cytokines and chemokines as, for example, CXCL10, chemokine (C-C motif) ligand 4 (CCL4), IL-6, TNF-α and cell adhesion molecules such as P-selectin glycoprotein ligand 1 (PSGL-1). Activated cDCs display a higher ability to induce T cell activation. Additionally, exacerbated CXCL4 production by pDCs might modulate monocytes differentiation into monocyte-derived inflammatory DCs (inflDC) with an enhanced cytokine production capacity upon TLR (Toll-like receptor) stimulation, a superior T cell stimulation and a profibrotic phenotype. As a result of these dysregulated mechanisms, DCs promote inflammation, myofibroblast transformation and extracellular matrix (ECM) deposition in the affected tissue of SSc patients.

Fig. 3. In-vivo models of systemic sclerosis (SSc) have been fundamental in unravelling the role of dendritic cells (DCs) in systemic sclerosis. In the bleomycin-induced SSc mouse model, plasmacytoid DC (pDC) depletion has improved the clinical score, skin and lung fibrosis [32,43]. Therefore, these findings point towards a crucial role for DCs on SSc pathogenesis and makes DCs potential targets in this disease.
NCT03274076 ClinicalTrials.gov) and mitogen-activated protein kinase (MAPK) p38 inhibition [56,83].

Conclusion and future perspectives

SSc pathogenesis is currently perceived as a complex condition with a strong link between impaired inflammatory and fibrotic processes. In this study, we show that DCs are an essential link between these processes. In disturbed conditions such as SSc, different DC subsets have the capacity to produce a large array of inflammatory mediators with the ability either to activate other immune cells or to skew different structural and stromal cells towards activated myofibroblasts (Fig. 2). The role of DCs in SSc pathology has recently been reinforced by several studies using in-vivo models of SSc (Fig. 3). Nevertheless, more studies will be imperative to unveil the role of the most recent described DCs subsets in SSc and their potential use as therapeutic targets.

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Disclosures

All authors have no conflicts of interest to declare.

Author contributions

T. C., M. Z. and W. M. performed the literature review, wrote the manuscript and prepared the figures. T. R. D. J. R. critically reviewed and discussed the manuscript content. All authors edited and approved the final version of the manuscript.

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