Novel Insights into dendritic cells in the pathogenesis of Systemic Sclerosis

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Short title: Dendritic cells in Systemic Sclerosis

List of abbreviations:
SSc - Systemic sclerosis
DCs - Dendritic cells
TGFβ - Transforming growth factor-β
PDGF - Platelet-derived growth factor
IL - Interleukin
TLRs - Toll-like receptors
NLRP3 - nod-like receptor protein 3
CLRs - C-type lectin receptors
RLRs - RIG-I-like receptors
NLRs Nod-like receptors
SLE - Systemic Lupus Erythematosus
RA - Rheumatoid Arthritis
Th - T helper
Tregs - Regulatory T cells
pDCs - Plasmacytoid dendritic cells
cDCs - Conventional or classical dendritic cells
IFN - Interferon
lcSSc - Limited cutaneous Systemic sclerosis
dcSSc - Diffuse cutaneous Systemic sclerosis
COPD - Chronic obstructive pulmonary disease
BAL - Bronchoalveolar lavage
TNFα - Tumor necrosis factor α
PLD4 - Phospholipase D4
PSGL-1 - P-selectin glycoprotein ligand-1
ILD - Interstitial lung disease
inflDC - Inflammatory dendritic cells
moDC - Monocyte derived dendritic cells
GM-CSF - Granulocyte-macrophage colony-stimulating factor
RUNX3 - Runt-related transcription factor 3
HSCT - Hematopoietic stem cell transplantation
MSCs - Mesenchymal stromal cells
SVF - Stromal vascular fraction
tolDC - Tolerized dendritic cells
Summary
Systemic sclerosis (SSc) is a severe autoimmune fibrotic disease characterized by fibrosis, vasculopathy, and immune dysregulation. Dendritic cells (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 DCs subsets with potential implications in inflammatory conditions. Alterations on 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. Particularly, recent studies have evidenced the importance of plasmacytoid dendritic cells either by their high capacity to produce type I interferon or other inflammatory mediators implicated in SSc pathology such as CXCL4 chemokine. *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 gives the 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 potential use of DC and their mediators as therapeutic targets.

Keywords
Systemic sclerosis, dendritic cells, plasmacytoid dendritic cells, conventional dendritic cells, inflammation, fibrosis.
Introduction

Systemic sclerosis (SSc), also known as scleroderma, is an immune-mediated rheumatic disease characterised 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 like pericytes, vascular smooth muscle cells, fibroblasts and myofibroblasts, but also both innate and adaptive immunity play an important contribution in SSc. Additionally, highly specific circulating autoantibodies are present in nearly all of the patients (2). Immune mediators like transforming growth factor-β (TGFβ), platelet-derived growth factor (PDGF), IL-6, IL-13, endothelin 1, angiotensin II, lipid mediators, reactive oxygen species (RO) 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 CXCL4 also plays an important role in SSc as it was found increased in circulation and in the skin of SSc patients, correlated with the presence and progression of complications, as lung fibrosis and pulmonary arterial hypertension (7, 8).

The role of dendritic cells (DCs) in SSc have gained a particular interest due to their capability to regulate the immune responses, but also the vasculature cell and fibroblast-like cells (9, 10). Significant progresses have been made in comprehending the pathogenesis of SSc, mostly by an increasing number of studies using advanced molecular technologies and a more complete representation of the features of SSc in preclinical mouse models of the disease (11).

Dendritic cells role and function

DCs represent the most potent antigen presenting cells in promoting activation of naïve 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 break of tolerance. For instance, in Systemic Lupus Erythematosus (SLE) or Rheumatoid Arthritis (RA), alteration in numbers of circulating cells, but also in affected tissues have been reported. Additionally, changes in their function, with

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impaired phagocytosis of apoptotic cells, enhanced cross-presentation of autoantigens derived from apoptotic cells and altered cytokine secretion have been also found. Therefore, these functional alterations are responsible for a harmful imbalance between Th type 1 (Th1), Th2, Th17 and regulatory T cells (Tregs). 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).

**Dendritic cells population in human 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 in cDC type 1 (cDC1s) and cDC2 type 2 (cDC2s), since their development depends on 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 better identify and characterize these cells. As summarized by Collin M et al., currently there are markers that perform consistently across species, such as CD141, CLEC9A, CADM1, BTLA and CD26 for cDC1; and CD1c, CD2, FcεR1 and SIRPA for cDC2s. pDCs express CD303, CD304, CD123 in humans and B220, Siglec-H and BST2 in mouse in the absence of other myeloid and lymphoid markers (18).

Nevertheless, in the recent years highly sensitive and high-throughput technologies at the transcriptional and proteomic level have revealed a remarkable heterogeneity among the DC subsets. DCs are under a continuous process of differentiation that starts in the bone marrow, with common DC progenitors, diverges at the point of emergence of pre-DC and pDC potential, and culminates in maturation of both lineages in the blood and spleen. The pre-DC compartment contains functionally and phenotypically distinct lineage-committed subpopulations, including one early uncommitted CD123+ pre-DC subset and two CD45RA+CD123lo lineage-committed subsets (19).

pDC are characterized by their capacity in the production of type I interferons, mainly in response to TLR7 and TLR9 activation, translated in their importance on antiviral immune responses, on the other hand pDCs have also been implicated in the pathogenesis of autoimmune diseases that are characterized by a type I IFN signature. Moreover, pDCs are also known to induce tolerogenic immune responses (20). Nevertheless, recent studies have highlighted pDC heterogeneity in mice and human (Figure 1) (19, 21-23). Conversely, the integration of high-dimensional single-cell protein and RNA expression become possible to identify several cDC2 subsets in mice and human as well (Figure 1) (21, 24, 25). Additionally, Dutertre et al. data allowed to
identify distinct markers to differentiate monocytes from cDC2s. CD88 together with CD89 were used to identify monocytes, while HLA-DQ and FceRIα were used for cDC2s, allowing their specific identification in blood and tissues (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 like in SLE and psoriasis (23, 25).

**Dendritic cells in the affected tissues of SSc patients**

The skin is very often 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 with internal organs 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, cDC1, cDC2 and pDCs, were not only present in blood, but also in different tissues, especially in draining lymph nodes and mucosal sites (36). In the lung, these DCs subsets were also found. Albeit cDC2 proinflammatory role, they also have been associated to 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 (29, 30). Lung tissues from SSc patients and non-SSc controls were tested for the presence of pDCs, which were low detected in the control lung tissues, while in SSc lungs, pDCs were found to be increased in the interstitial tissue and bronchi, but also on their bronchoalveolar lavage (BAL) samples (31).

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 plasmacytoid DCs, inflammatory myeloid DCs, and monocyte-derived DCs (32, 33). In SSc skin samples CD1a+ survivin+ DCs were shown to infiltrate in dermal lesions (34).
**Plasmacytoid dendritic cells 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 (35-38). Moreover, the IFN signature present in blood and affected skin of SSc patients is indicative of the presence of aberrant pDCs (39, 40). In a proteomic profiling study, CXCL4 has been identified to be largely produced by pDCs from SSc patients. Increased numbers of pDCs co-localized with CXCL4 in the skin of SSc patients indicate that pDCs are also the main source of CXCL4 in the affected tissue (7, 41). In the same study, CXCL4 was shown to induce the production of IFN-α in pDCs stimulated with TLR9. Moreover, blocking CXCL4 abrogated the production of IFN-α in SSc pDCs (7). Another recent study has confirmed that pDCs are largely infiltrating the skin of SSc patients and are releasing high quantities of CXCL4 and IFN-α. It was also reported that the expression of TLR8 is increased in SSc pDCs, and that TLR8 signaling is responsible for the high production of CXCL4 and IFN-α in SSc pDCs (42). Moreover, CXCL4 was shown to potentiate TLR8 and TLR9 activation of SSc pDCs (42). Another study found that CXCL4 forms liquid crystalline complexes with human and bacterial DNA that amplify TLR9-mediated IFN-α production in SSc pDCs. In the same study it was also shown that CXCL4-DNA complexes activates pDCs in TLR9 dependent manner but independent of CXCR3, a known CXCL4 receptor. Interestingly, CXCL4-DNA complexes were found to be present in vivo and to correlate with type I IFN in the blood of SSc patients (41).

*In vivo*, in the bleomycin-induced SSc mouse model, depleting pDCs attenuated fibrosis of the skin and lung, highlighting the importance of pDCs in SSc pathogenesis (31, 42). Furthermore, imatinib treatment in SSc patients reduced pDCs number in the lung and improved skin and lung disease (43, 44).

**Conventional dendritic cells and Inflammatory dendritic cells in SSc**

The role of cDC 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 TNFα in response to TLR2, 4 and 6 activation than the cDC from SSc patients with long disease history or healthy controls (45). This emphasize a possible higher impact of cDCs in the early and progressive phase of the disease.

Recently, it has been shown that cDC2 of lcSSc patients spontaneously produce higher amounts of CXCL10 in vivo than cDC2 from healthy individuals (46). In addition, they also produce more CXCL8 upon in vitro stimulation with LPS plus IFN-γ, which activate signalling pathways involved in SSc pathology. Moreover,
deSSc cDC2 were found to produce more CCL4 than cDC2 from healthy individuals (46). Differences in the cytokine production patterns may suggest differences in the molecular mechanism in two disease subtypes.

The frequency of newly characterized, CD14^+CD163^+ inflammatory DC population has been studied in a small SSc cohort, but was not found to be altered compared to HC (25). Nevertheless, the scavenger receptor CD163, mainly considered as a marker for M2 macrophages, have been found to be increased in the serum of SSc patients (47-49). Therefore, the role of CD163^+ DCs in SSc could be studied more extensively using larger patient cohort with distinguished SSc subsets. A new role has been described for phospholipase PLD4, linked to SSc genome-wide association studies (50). The study of Gavin et al on PLD4 deficient mice suggested that PLD4 functions as 5’ exonuclease that break down single-stranded ODN, thereby limiting TLR9 stimulatory capacity. Importantly, PLD4-deficient DC were indirectly responsible for upregulation of MHC class II on macrophages and in general, enhanced responsiveness to TLR9 ligands (51). As TLR9 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, that might be involved in the development of SSc, is P-selectin glycoprotein ligand-1 (PSGL-1) (52). Increased expression of PSGL-1 specifically in SSc cDCs was associated with the presence and severity of ILD, although the precise role of DCs in ILD development is not clear.

All in all, the evidences indicate that cDCs do not contribute to SSc only by proinflammatory cytokine production but also by dysregulated antigen processing, T cell activation and likely other mechanisms further to be elucidated.

As a result of systemic autoimmune activation in SSc, monocytes are likely to be recruited to the affected lesions, consequently differentiating into inflammatory dendritic cells (inflDC), similarly as described to occur during inflammation (53). In humans, an in vitro model of monocyte differentiation into DC (moDC) is often exploited to describe potential role of inflDC. Importantly, there is a high correlation between cytokine production capacity of cDC and moDC of the same SSc patients (45). Recently, several studies have been focusing on understanding how SSc-related factors modulate DC differentiation and function. For instance, CXCL4, in combination with GM-CSF and IL-4 was shown to skew monocytes to differentiate into more pro-inflammatory and pro-fibrotic moDC (54-56). This suggests that under the effect of an inflammatory environment and presence of CXCL4, monocytes might differentiate into inflDC that could potentially contribute to fibrotic processes. However, the presence of these cells in the affected tissues of SSc patients still needs to be confirmed.
The role of dendritic cells in mouse models

The importance of DCs in SSc has been studied in several mice models over the years (57-64). Recent studies, have focused on the role of DCs in bleomycin induced-SSc mouse model. Bleomycin model is the most commonly used model to study the pathogenesis of SSc (65). Using this mouse model, several recent studies 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 (31, 42).

Kioon et al reported high expression of TLR8 in SSc pDCs, and to better understand whether TLR8 can directly promote fibrosis in vivo, they used bleomycin model in huTLR8Tg mice (mice with a single copy of the human TLR8 gene under the control of human TLR8 genomic regulatory regions). They found that TLR8 exacerbates skin fibrosis in bleomycin-induced fibrosis model, leading to increased number of pDCs in the skin of bleomycin-injected mice, confirming an important role of TLR8 signaling and pDCs in skin fibrosis developments (42).

A recent study by Affandi et al focused on identification of pathways underlying pDCs aberrances in SSc. This study identified downregulation 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 in 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 (66).

On the contrary, there are no reports available on the pathological role of cDC 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 (61).

Dendritic cell 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 targeting specifically DCs in SSc, most of the available and potential treatment options affect DC activity.
Autologous hematopoietic stem cell transplantation (HSCT) has shown to be a promising solution for severe and therapy-refractory forms of SSc. HSCT aims to re-establish normal immune system including self-tolerant DCs. Results have been published for several recent clinical trials (67, 68), showing better patient long-term survival. The clinical evidences supporting HSCT usage has been recently reviewed in (69). HSCT has been lately suggested as standard of care for rapidly progressive dcSSc patients (70, 71).

Another promising cellular based treatment to alter fibrosis is mesenchymal stem cell therapy, recently discussed in (72). Mesenchymal stromal cells (MSCs) possess anti-inflammatory, antiproliferative, antifibrotic, and immunomodulatory properties. There is evidence that dermal white adipose tissue DC could contribute to potentially reversing fibrosis by sustaining the viability of adipose tissue stem cells (61). Adipose tissue stromal vascular fraction (SVF) containing stem cells are subjected to subcutaneous injection of SVF in the fingers in SSc in an ongoing clinical trial (NCT03060551 ClinicalTrials.gov).

Recent evidences suggest that tolerized dendritic cells (tolDC) could become a treatment option for autoimmune conditions (73). This includes differentiating autologous monocytes into DCs, loading them with disease-specific autoantigens and injecting them back to the patients. A small-scale clinical trial has been conducted to treat patients with inflammatory arthritis with promising data of autoantigen-loaded tolDC stability and effect on disease symptoms when injected into inflamed knee (74). No study has been conducted yet in SSc, however considering the more recognized role of DCs in SSc pathogenesis, it might be particularly beneficial treatment approach for early SSc in which the immune disbalance plays a bigger role than in the fibrosis phase.

A few biologics targeting DC and T cell interactions and DC produced cytokines have been or are being tested in the clinics (75, 76) (NCT01284322 ClinicalTrials.gov). For instance, Abatacept, an immune checkpoint inhibitor CTLA4 and Ig fusion protein binds to co-stimulatory molecules CD80/CD86 on DCs and thereby inhibits DC-T cell interaction and T cell activation (75). Targeting IL-6 by tocilizumab have been shown to moderately improve skin and fibrosis in SSc patients, however it is accompanied by augmented risk for severe infections (76, 77). Targeting IL-23/IL-17 axis by ustekinumab, implicated also in SSc pathogenesis (78, 79), has been shown to be promising in other autoimmune diseases (80, 81).

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 DC and other immune cells, such as JAK-STAT pathway by tofacitinib (clinical trial, I/II phase, NCT03274076 ClinicalTrials.gov ) and MAPK p38 inhibition (55, 82).
Conclusion and future perspectives

SSc pathogenesis is currently perceived as a complex condition with a strong link between an impaired inflammatory and fibrotic processes. Here we show that DCs are an essential link between these processes. In disturbed conditions, such as SSc, different DCs subsets have the capacity to produce a large array of inflammatory mediators with the ability either to activate other immune cells or / and to skew different structural and stromal cells towards activated myofibroblasts (figure 2). The role of DCs in SSc pathology has recently been reinforced by several studies using in vivo models of SSc (figure 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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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 the authors edited, and approved the final version of the manuscript.

Disclosures

All authors have no conflicts of interest to declare.
References


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Figure legends

Fig. 1. Plasmacytoid dendritic cells (pDCs) and type 2 conventional dendritic cells (cDC2s) heterogeneity. Recently two subsets of mature pDCs were described: conventional pDCs and a small subset of pDC-like cells. Although both subsets secreted type I IFNs in response to CpG-A stimulation, pDC-like cells were unable to do it when stimulated with CpG-B (22). This pDC-like cell population has also been described in human circulation (19, 21). Additionally, it was reported that the activation of human pDCs with a single microbial or cytokine stimulus triggers pDC diversification into three stable subpopulations that were described as P1, P2 and P3 –pDC (23). Recently two different cDC2 subsets were identified in mice: cDC2A and cDC2B. These findings were extended to humans, but the cDC2B population was only present in blood, whereas cDC2A population found in mice were also present in human spleen. Interestingly bone marrow DC progenitors lacked the expression of T-bet and RORγt suggesting that cDC2s acquire expression of the respective transcription factors in response to environmental signals (24). In other cDC2 were subdivided into different subsets based on CD5, CD163, and CD14 expression, which were phenotypically and functionally different (25) and related to previously described DC3s (22). Nevertheless, the role of the new DC subsets needs still to be clarified in the pathogenesis of SSc.

Fig. 2. Plasmacytoid dendritic cells (pDCs) and conventional dendritic cells (cDCs) have a crucial role in the inflammatory and fibrotic processes in systemic sclerosis. pDC produce a large amount of type I interferon (IFN-α) and CXCL4 due to dysregulated mechanisms such as RUNX3 and TLR8 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 leads to an increased production of cytokines and chemokines, as for example CXCL10, CCL4, IL-6, TNF-α, and cell adhesion molecules like PSGL-1. Activated cDC 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 pro-fibrotic phenotype. As a result of these dysregulated mechanisms, DCs promotes inflammation, myofibroblast transformation and extracellular matrix (ECM) deposition in the affected tissue of SSc patients.

Fig. 3. In vivo models of SSc have been fundamental in unravelling the role of dendritic cells in systemic sclerosis. In the bleomycin-induced SSc mouse model, pDC depletion has improved the clinical score, skin and lung fibrosis (31, 42). Therefore, these findings point towards a crucial role for DCs on SSc pathogenesis and makes DCs potential targets in this disease.
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non-pDCs depleted DCs

worsen of skin fibrosis

pDCs depleted DCs

amelioration of skin and lung fibrosis

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