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Dendritic Cells: Novel Players in Fibrosis and Scleroderma

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Abstract

Dendritic cells are professional antigen-presenting cells that are most studied for their function in mediating T-cell tolerance and T-cell activation. In addition, recent evidence indicates that dendritic cells can regulate the vasculature and function of fibroblast-type cells. The potential contribution of dendritic cells to scleroderma and fibrosis is not well-understood. In this article, we review recent studies as well as describe our own ongoing work that points toward a role for dendritic cells in scleroderma and fibrosis.

Keywords

Scleroderma; Fibrosis; Dendritic cells; Vascular; Skin; Kidney; Lung; Liver

Introduction

Systemic sclerosis, or scleroderma, in the diffuse form is a disease characterized by skin fibrosis as well as fibrosis of the lungs, gastrointestinal tract, and heart. The skin fibrosis is attributable in part to the accumulation of activated fibroblasts [1] and is characterized by a loss of blood vessels [2–4]. Transforming growth factor (TGF)- β is a key mediator, and new drug therapies have been aimed at targeting this and other biologic candidates [1, 5], but much of the pathophysiology that drives and sustains the fibrosis remains poorly understood.

Dendritic cells are a heterogeneous population of cells that reside in almost all tissues and have potent antigen-presenting properties, but that can also potentially regulate the vasculature and fibroblast-type cells. The contributions of dendritic cells to scleroderma and fibrosis is not well-understood, but studies are emerging that suggest a role for dendritic cells. Here we review recent studies as well as discuss our own ongoing work that examines whether dendritic cells might be novel therapeutic targets in scleroderma and fibrosis.

Dendritic Cells: Possible Players in Scleroderma and Fibrosis?

Broadly, dendritic cells in the steady state can be divided into two categories: 1) lymphoid tissue-resident and migratory dendritic cells and 2) plasmacytoid dendritic cells. Lymphoid

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tissue-resident dendritic cells, also known as “classical” or “conventional” dendritic cells, originate from bone marrow-derived precursors that have recently been established as distinct from monocytes. The precursors circulate and continuously enter lymphoid tissues, where they fully develop into dendritic cells. Migratory dendritic cells are resident in nonlymphoid tissues such as skin and migrate continuously via the afferent lymphatic vessels to the draining lymph node. The lymphoid tissue-resident and migratory dendritic cells present antigen to T cells and mediate T-cell tolerance and activation. In contrast, plasmacytoid dendritic cells can present antigen to T cells but are more often studied for their ability to secrete high levels of interferons and are known as natural interferon-producing cells.

The skin contains several subsets of migratory dendritic cells. The dendritic cells that reside in the epidermis are Langerhans cells. In contrast, the dermis is populated by Langerhans cells that are transiting from the epidermis into the dermal lymphatics, Langerin⁺CD103⁺ dermal dendritic cells that are distinct in lineage from Langerhans cells, and Langerin⁻CD103⁻CD11b^{hi} dendritic cells. In the steady state, dendritic cells in the skin are in a mature but semiactivated state and continuously migrate via afferent lymphatic vessels to the draining lymph node, where they function to mediate T-cell tolerance. Upon activation by an inflammatory “danger” signal, dendritic cells that take up antigen are fully activated and are potent T-cell activators. Dendritic cells that migrate from the skin are able to present to T cells directly within the draining node or pass along the antigen to lymph node-resident dendritic cells. Antigen can also be transported directly from skin via the afferent lymphatics to the draining node, where it can be taken up by the lymph node-resident dendritic cells (reviewed in [6–10]).

Upon inflammation, additional populations of dendritic cells can develop from monocytes that are recruited to lymphoid or peripheral tissues. One well-characterized example of monocyte-derived dendritic cells is the tumor necrosis factor (TNF) and inducible nitric oxide synthase (INOS)-producing dendritic cells. These cells were identified in the spleen of *Listeria*-infected mice and develop from inflammatory monocytes that leave the bone marrow in a CCR2-dependent manner. As their name implies, they express TNF and INOS, leading to the control of *Listeria* in a manner that is independent of antigen presentation to T cells [11, 12]. Recently, murine monocyte-derived DC-SIGN⁺ dendritic cells were characterized that resemble human peripheral blood monocyte-derived DC-SIGN⁺ dendritic cells. These cells differentiate from monocytes that are recruited from the blood to lymph nodes upon stimulation with lipopolysaccharide and show antigen-presenting capabilities on par with those of lymphoid tissue-resident dendritic cells [13].

Dendritic cells present antigen to naïve T cells within lymphoid tissues. In the context of signals provided by co-stimulatory molecules expressed by dendritic cells, T cells recognizing the antigen are activated. In the context of antigen presentation without co-stimulation, T-cell tolerance is promoted. In addition to presenting antigen and providing co-stimulatory signals, dendritic cells can present a third signal that polarizes the T-cell response. Expression of interleukin (IL)-12 and interferon- γ polarizes T cells toward T-helper type 1 (Th1) responses; IL-23 promotes expansion and survival of Th17 cells that have been implicated in scleroderma [14]. Th2 responses involving T-cell expression of

cytokines such as IL-4, IL-5, and IL-13 that have also been implicated in fibrosis [1, 15] are less clearly driven by dendritic cells, but data are emerging that dendritic cells are also likely to shape Th2 responses [16–19]. In addition to stimulating naïve T cells within lymphoid tissues, dendritic cells can potentially stimulate effector and memory T cells within peripheral tissues. Furthermore, some dendritic cells, such as Langerhans cells, are becoming understood to be specialized to negatively regulate T-cell responses (reviewed in [10]). Dendritic cells can thus play crucial roles in shaping T-cell responses in multiple ways.

T cells have been implicated and are being targeted in scleroderma [1, 20], and, given the importance of dendritic cells in orchestrating T-cell responses, alterations in dendritic cell phenotype or activity could potentially shape the fibrotic process. However, there is evidence that innate immunity may be sufficient to drive fibrosis [21–23], and dendritic cells could potentially play a role in fibrosis independent of their T-cell-stimulating properties. Dendritic cells and fibroblasts have been observed to be co-localized, suggesting the possibility of direct cross-talk between the two cell types. In inflamed skin, activated fibroblasts and CD11c dendritic cells co-localize, and fibroblasts could support dendritic cell maturation in culture [24]. Fibroblasts have also recently been shown to support the recruitment of dendritic cells in inflamed lungs [25]. In lymph nodes, dendritic cells are directly attached to fibroblast-type reticular cells, which express α smooth muscle actin (α SMA) and secrete the extracellular matrix components of the stromal scaffold [26–29]. Dendritic cells express CD11c, and CD11c⁻DTR mice expressing diphtheria toxin receptor in CD11c⁺ cells allow for inducible depletion of CD11c⁺ cells by injection of diphtheria toxin [30]. Depletion of CD11c⁺ cells in these mice resulted in disrupted organization of the fibroblastic reticular cells around and near blood vessels (see below) [31] and also reduced fibroblastic reticular cell proliferation [32], suggesting that dendritic cells can modulate the function and activity of fibroblast-type cells. Also worth noting is that dendritic cells can express TGF- β 1 [33, 34], which could potentially act directly on mesenchymal cells to promote fibrogenesis.

In addition to capillary loss in the affected skin, scleroderma is associated with vascular dysregulation manifesting in Raynaud's phenomenon, pulmonary hypertension, and renal crisis [1, 35]. Our studies of the lymph node vasculature have delineated a role for dendritic cells in vascular growth and regulation, and it is possible that a dendritic cell-vascular axis has relevance for the vascular alterations in scleroderma and fibrosis. Upon immune stimulation, lymph nodes grow, and there is a concomitant proliferative expansion of the blood vasculature followed by a period of vascular quiescence and stabilization whereby endothelial cell proliferation is downregulated and vessels are made less leaky by the reaccumulation of fibroblastic cells around them [36, 37]. We have shown that injected dendritic cells can initiate vascular proliferation even in the absence of T and B cells, and that a late-accumulating population of CD11c^{hi}MHCII^{med} cells bearing the markers of lymph node-resident dendritic cells mediates the period of quiescence and stabilization. Of potential importance is that while depletion of CD11c^{hi}MHCII^{med} cells causes upregulation of endothelial cell proliferation, endothelial cell numbers are not expanded over time, suggesting that CD11c^{hi}MHCII^{med} cells and perhaps the proper reaccumulation of fibroblastic reticular cells around the vessels they mediate may also be required for

endothelial cell survival [31]. Interestingly, Plaks and colleagues [38] have found a similar role for CD11c^{hi} dendritic cells and vascular stabilization in the uterus. These studies raise the possibility that defective CD11c^{hi} dendritic cell-mediated regulation of vascular stabilization or endothelial cell survival could potentially contribute to scleroderma pathogenesis.

Studying Dendritic Cells in Scleroderma: The Challenges

Dendritic cells could potentially play a role in scleroderma and fibrosis in multiple ways. The study of dendritic cells in scleroderma poses several challenges, however. First, dendritic cells are present in relatively small numbers in blood, lymphoid tissues, and peripheral tissues, making them difficult to purify and analyze. Although dendritic cells can be generated in large numbers from cultured mouse bone marrow or human blood monocytes [39–41], and these cultured cells are commonly used as a model for dendritic cells, the cultured dendritic cells may not be representative of a particular endogenous subpopulation. Second, dendritic cells are mostly resident in tissues rather than in the circulation, making them less accessible for translational and clinical studies. Third, identifying dendritic cells and differentiating them from other cell types based on markers can be difficult. All dendritic cells in mice express the integrin CD11c, as well as major histocompatibility complex (MHC)II, although neither marker is specific to dendritic cells, as, for example, CD11c can also be expressed at lower levels on some activated T cells and macrophages, and MHCII can be expressed at lower levels by macrophages and B cells. Other molecules expressed by dendritic cells, such as CD11b, can also be expressed by macrophages or monocytes. Indeed, as understanding of dendritic cell development and function grows, some cells previously identified as dendritic cells are being reclassified as macrophages [10, 42•]. The field of dendritic cell biology is rapidly evolving, and greater understanding of the dendritic cell development and subsets in mice and humans and new tools for identifying and manipulating dendritic cells will enable us to deepen our understanding of how dendritic cells contribute to scleroderma and fibrosis.

Studies of Skin Dendritic Cell Subsets and Localization in Scleroderma and Skin Fibrosis

The idea that dendritic cells might play some type of local role in scleroderma was proposed from observational studies of skin samples. Aiba and colleagues [43] showed a decrease in cells bearing the morphology of dendritic cells and expressing CD34, raising the idea that these CD34⁺ cells might be protective. However, only 2% of these CD34⁺ cells expressed MHCII [44], suggesting that most of these CD34⁺ cells were unlikely to be dendritic cells and may be multipotent precursors or fibrocytes [45]. An additional cell type resembling dendritic cells morphologically expressed factor XIII, and they were observed to accumulate in higher numbers throughout the dermis in morphea samples [46] and in the skin of patients with early nephrogenic fibrosing dermopathy [47, 48]. In nephrogenic fibrosing dermopathy, the factor XIII⁺ cells accumulated along with the increase in TGF- β 1 levels, leading to the proposal that perhaps the factor XIII⁺ dendritic cells expressed TGF- β 1 that could directly stimulate fibroblast activation as well as play other roles in modulating dendritic cell

accumulation and immune function [48, 49]. Factor XIII⁺ cells from human skin recently have been shown to be macrophages, based on their high phagocytic activity and reduced potential for T-cell activation [50], suggesting that the factor XIII⁺ cells in the lesional skin are likely to be macrophages, though the exact identity of the accumulated cells along with the functional role of these cells still warrant more detailed examination.

We have been examining the localization of dendritic cells within fibrosed skin in the bleomycin model of scleroderma, in which skin fibrosis is induced upon 4 weeks of subcutaneous bleomycin injection [51]. In control saline-injected mice, CD11c^{bright} cells are distributed throughout the dermis (Tian and Lu, unpublished observations). After 4 weeks of bleomycin, however, CD11c^{bright} cells relocate and accumulate in the deep dermis along with the accumulated α SMA⁺ myofibroblasts (Fig. 1). By flow cytometry, CD11c^{hi} cells are also MHCII⁺ (Tian and Lu, unpublished observations). The localization of the CD11c^{bright} cells near the myofibroblasts suggests the possibility that these cells regulate the development or maintenance of the myofibroblasts that are thought to contribute to the excessive collagen deposition in sclero-derma. We are currently testing this possibility, and the expression of CD11c and MHCII suggests that these cells could be dendritic cells, but further studies will be needed to understand their identity fully.

Functional Evidence for Aberrant Dendritic Cell Function in Scleroderma

Direct functional evidence for dendritic cell involvement in scleroderma is relatively scant but emerging as more is becoming understood about dendritic cell biology. In systemic sclerosis, dendritic cells cultured from blood monocytes expressed higher levels of the Th2 cytokine IL-10 upon Toll-like receptor (TLR)4 stimulation when compared with equivalent cells from unaffected patients [52], suggesting that dendritic cells in scleroderma respond aberrantly to TLR4 stimulation and thus could contribute to the cytokine milieu in the disease. The same group recently expanded on this finding, showing that TLR2 stimulation can also drive increased IL-10 expression by monocyte-derived dendritic cells from scleroderma patients, and, importantly, that upregulated IL-10 was also observed in dendritic cells that were isolated directly from the blood. The blood dendritic cells were isolated based on expression of blood dendritic cell antigen-1 (BDCA-1), a marker of nonplasmacytoid blood dendritic cells in humans that is also expressed by human dermal dendritic cells. Significantly, the investigators also separately examined early and late diffuse and limited scleroderma patients and showed that all subgroups had abnormal TLR responses, with early diffuse and early limited patients expressing the highest levels of the proinflammatory cytokines TNF and IL-6. The basis of the differential TLR responses is unclear, as an initial examination of the cell surface phenotype on the cultured dendritic cells was unrevealing [53•], but these results suggest the interesting possibility that abnormal dendritic cell responses to endogenous TLR ligands in scleroderma patients could skew the cytokine milieu to contribute to disease pathogenesis.

Plasmacytoid dendritic cells also have been implicated in scleroderma. Scleroderma patients can have an interferon signature in peripheral blood cells [54–56], indicating that the cells have been exposed to high levels of type 1 or 2 interferons in the bloodstream or the peripheral tissues. Many cell types can express interferons, but plasmacytoid dendritic cells

were fairly recently discovered to be high expressers of type 1 interferons [57, 58] and have been implicated as a source of elevated type 1 interferons in lupus [59, 60], and it is possible that plasmacytoid dendritic cells contribute to abnormally high levels of type 1 interferon in a subset of scleroderma patients. In support of this theory, Kim and colleagues [61] recently showed that scleroderma sera containing anti-topoisomerase, the autoantibody associated with lung fibrosis in scleroderma, can induce plasmacytoid dendritic cells in peripheral blood mononuclear cells to express high levels of type 1 interferon. This suggested a scenario whereby select circulating autoantibodies can stimulate circulating plasma-cytoid dendritic cell activation, leading to increased type 1 interferon and thus potentially to more autoantibody generation and classical dendritic cell activation [57, 58, 61].

Dendritic Cells and Fibrosis in the Kidney

In kidneys, dendritic cells have been identified by electron microscopy to be located in the interstitium of the cortex, between the tubules and around arterioles and capillaries, with close interactions with fibroblasts [62–64]. Consistent with these findings, CD11c⁺ cells were also detected primarily in the tubulointerstitium. By flow cytometry, the renal CD11c⁺ cells resembled splenic dendritic cells in the levels of MHCII and CD80 and other co-stimulatory molecules. A large proportion of the renal CD11c⁺ cells were F4/80⁺, which is expressed by a smaller subpopulation of splenic dendritic cells [65, 66]. These cells were able to stimulate T-cell proliferation in mixed leukocyte reactions but did so less well than splenic dendritic cells. Inflammatory stimuli such as injection of nephrotoxin sheep immunoglobulin lead to accumulation of greater numbers of CD11c⁺, upregulation of activation markers, and a capacity to stimulate T cells that is equal to that of splenic dendritic cells. These renal CD11c⁺ cells, then, resembled dendritic cells [65].

Dong and colleagues [67] examined the role of these renal CD11c⁺ cells in a model of renal fibrosis. Unilateral ureteral ligation experimentally leads to immediate renal inflammation and within days to subsequent interstitial fibrosis. The ureteral ligation leads within hours to local upregulation of TNF, which is an important mediator in this model. The investigators showed that the numbers of CD11c⁺ F4/80⁺ and F4/80[−] dendritic cells increased in number by 24 h after ureteral ligation, and both subsets showed upregulation of MHCII and the co-stimulatory molecule CD86. The F4/80⁺ dendritic cells were the predominant population expressing TNF during this time period. Clodronate liposomes, which are taken by and kill macrophages, monocytes, and some dendritic cells, reduced the number of F4/80⁺ dendritic cells, the level of TNF and other inflammatory mediators, and the accumulation of memory/activated T cells at 24 h [67]. This study then was suggestive of a role for renal dendritic cells in the early inflammatory arm of the response, but the effects of clodronate liposomes could have been attributable to macrophage or monocyte depletion.

A second study attempted to deplete dendritic cells more specifically by using CD11c[−]DTR mice and examined the effects on fibrotic parameters. Machida and colleagues [68] depleted CD11c⁺ cells at day −1 and day +3 relative to ureteral obstruction and analyzed TNF and parameters of fibrosis at day +5. At day 5, CD11c⁺ cells were depleted, but there was no effect on type III collagen, αSMA, TGF-β, or TNF levels, suggesting that dendritic cells did not play a role in the inflammatory or fibrotic aspects of the response [68]. However, CD11c

⁺ cells can reaccumulate by 2 days after depletion [30], and an inflammatory stimulus will accelerate this reaccumulation (Lu, unpublished observations), and it is possible that CD11c⁺ cells were not fully depleted between day 1 and day 3. Therefore, these results most clearly indicate that CD11c⁺ cell depletion between day 3 and day 5 did not affect the fibrotic or inflammatory parameters at day 5, but the exact role of CD11c⁺ cells in the early inflammatory response is still not entirely clear. Additional studies ensuring full depletion in this early time period would help clarify whether CD11c⁺ dendritic and other cells have any role in this model of fibrosis.

Dendritic Cells and Fibrosis in the Lung

Cells bearing the markers of dendritic cells have also been implicated to play a role in lung fibrosis. In lung biopsies from patients with interstitial pulmonary fibrosis, cells bearing the dendritic cell marker DC-SIGN were found to be numerous and often in a perivascular location [69]. Interestingly, DC-SIGN is a C-type lectin that is expressed by dendritic cells cultured from human monocytes and also expressed by a recently identified mouse monocyte-derived dendritic cell population [13], raising the thought that DC-SIGN⁺ cells in the fibrosed lung could be monocyte-derived dendritic cells. Interestingly, Marchal-Sommé and colleagues [70] also identified aggregates of mononuclear cells resembling ectopic lymphoid tissues in lungs from patients with interstitial lung fibrosis. Within the ectopic lymphoid tissues, dendritic cells expressed markers of more mature dendritic cells: CD40⁺, CD86⁺, CD83⁺, and DC-LAMP and were accumulated with T cells [70]. Some of the DC-SIGN⁺ cells found in the fibrotic tissue were around the perimeter of these ectopic lymphoid tissues [69], and the investigators speculated that, potentially, the DC-SIGN dendritic cells migrated from the perimeter into the ectopic lymphoid tissues, which provided a niche that allowed for dendritic cell maturation and subsequent stimulation of pathogenic T cells. In support of this hypothesis, these investigators characterized the dendritic cell infiltrates in the bleomycin-induced lung fibrosis model and found that CD11c⁺MHCII⁺ cells accumulated in large numbers in the lung at day 7 after bleomycin instillation at day 0, after the acute inflammatory process, and during the fibrotic process. These dendritic cells had a mature phenotype and were localized in proximity to T cells bearing an activated/memory phenotype. Treatment of the mice daily from day 0 onward with VAG539, a molecule that inhibits upregulation of co-stimulatory molecules on dendritic cells, perhaps by inhibiting aryl hydrocarbon receptor activation, attenuated the fibrotic sequelae of bleomycin treatment [71•]. Although one interpretation of the VAG539 treatment results could be that the dendritic cell–T-cell interactions were disrupted and thus led to attenuated fibrosis, an alternate interpretation could be that VAG530 disrupted T-cell-independent profibrotic functions of dendritic cells. Further studies will help us understand whether the beneficial effects of VAG539 were specifically due to targeting of dendritic cells, but these findings provide a tantalizing beginning. If the drug does specifically target dendritic cells, altering the timing of drug administration can be used to understand whether dendritic cells are required during the early inflammatory phase or the subsequent fibrotic phase.

Dendritic Cells and Fibrosis in the Liver

Dendritic cells are also being implicated as key orchestrators of the inflammatory process associated with liver fibrosis. Connolly and colleagues [72••] found a potential role for dendritic cells in mediating the proinflammatory environment in a model of liver fibrosis induced by 6 weeks of three-times-weekly injections of thioacetamide and leptin. CD11c⁺ cells accumulated in the fibrosed livers and were a mixed population, but many expressed MHCII and CD40, and isolated CD11c⁺ cells could stimulate natural killer cells and T cells in vivo and in vitro, suggesting that these CD11c⁺ cells were comprised at least in part by bona fide dendritic cells. Depletion of CD11c⁺ cells resulted in remarkable reductions in the levels of TNF- α , IL-6, and other inflammatory cytokines in the cultures of nonparenchymal cells, indicating a role for CD11c⁺ cells initiating or sustaining a proinflammatory environment in the fibrosed liver [72••]. CD11c⁺ cells cultured with hepatic stellate cells, which can adopt a proinflammatory phenotype upon insult or can differentiate into myofibroblasts during fibrosis [73], resulted in increased expression of proinflammatory mediators and increased proliferation of hepatic stellate cells, suggesting that dendritic cells can directly modulate hepatic stellate cell activity. This modulation was in part dependent on TNF- α , presumably from the CD11c⁺ cells [72••]. The requirement for CD11c⁺ cells in fibrosis per se was not tested, but this study suggested that dendritic cells or other CD11c⁺ cells could potentially contribute to the inflammatory aspects of fibrosis. The contribution to the fibrosis-associated inflammation is reminiscent of the proposed role for renal CD11c⁺ cells in the study discussed above [67], and it is possible that the two studies are describing related cells in different organs. Of note, Gr1⁺CD11b⁺F4/80 myeloid cells were found by Karlmark and colleagues [74] to accumulate early after CCl₄-induced injury, as well late during CCl₄-mediated fibrosis. The accumulation of these cells was dependent on whether CCR2 and CCR2^{-/-} mice had attenuated fibrosis that could be rescued by injection of Gr1⁺ cells [74]. Whether these inflammatory monocytes are related to the CD11c⁺ cells in the study by Connolly and colleagues [72••] remains to be examined, and it will also be very interesting to understand whether long-term depletion of CD11c⁺ cells using tools such as the CD11c⁻DTR mice [31, 75] affects parameters of fibrosis.

Conclusions

The understanding of whether and how dendritic cells might play a role in scleroderma and fibrosis is still in its infancy. The evidence thus far supports the idea that dendritic cells may contribute to a proinflammatory cytokine environment, that they may express abnormally high levels of IL-10 that echo the elevated IL-10 in scleroderma patients [76, 77], and that they may also directly modulate the activity of fibroblast-type cells (Fig. 2). The proinflammatory role may be a double-edged sword, as inflammation begets fibrosis but may also be required for resolution of fibrosis, and IL-10 may potentially have both profibrotic and antifibrotic roles [15, 78]. Other potential roles for dendritic cells remain to be explored (Fig. 2). The exact role of dendritic cells, then, is still to be determined. Critical will be functional studies that ask about the effects of depleting dendritic cells or deleting molecules specifically from dendritic cells on fibrosis models, and also detailed phenotypic analysis to help us understand the identity and subset of the putative dendritic cell. Understanding whether and how we should target dendritic cells in scleroderma and other

states of fibroses will help provide new directions for the development of therapeutics but may also help us make better use of the drugs that are already available or in the pipeline (eg, abatacept [cytotoxic T-lymphocyte antigen-4-Ig] binds the co-stimulatory molecule CD86 on dendritic cells and is thought to work at least in part by blocking antigen-presenting cell–T-cell interactions, but it also has been shown to directly downmodulate antigen-presenting cell expression of TNF- α , IL-6, and TGF- β [79], raising the possibility that it could be used as a direct dendritic cell modulator). Modulating dendritic cell function could offer a new approach to treating scleroderma and other fibrotic conditions that are in need of better therapeutic options.

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CD11c
αSMA

Fig. 1.

Bleomycin-induced skin fibrosis is associated with accumulation of CD11c^{bright} cells with myofibroblasts. Mice received 60 µg of subcutaneous bleomycin in the lower back 5 days per week starting at day 0. Skin was harvested at 28 days and stained for CD11c (*blue*) and α smooth muscle actin (αSMA) (*brown*). Note the CD11c^{bright} cells intermingled with the scattered brown αSMA⁺ myofibroblasts in the deep dermis directly above the panniculus carnosus muscle. Photo was taken at 60× magnification

Fig. 2.

Possible roles of dendritic cells (DCs) in scleroderma and fibrosis. Nonplasmacytoid dendritic cells (*blue*) could potentially modulate fibrosis by *a*) expressing proinflammatory cytokines that can activate fibroblastic cells and that contribute to the inflammatory milieu, which may help to drive fibrosis or recovery from fibrosis; *b*) expressing interleukin (IL)-10 that could potentially contribute to skewing of T-cell responses toward a profibrotic T-helper type 2 (Th2) phenotype and to plasma cell differentiation, but that could also have antifibrotic effects; *c*) expressing transforming growth factor (TGF)- β that promotes myofibroblast differentiation; and *d*) modulating vascular growth and function. Plasmacytoid DCs (*green*) may also contribute via *e*) expression of type 1 interferons, which can stimulate nonplasmacytoid DCs and plasma cell development. The plasma cells lead to the generation of more autoantibodies, which, in conjunction with Toll-like receptor (TLR) ligands, can be stimulatory for DCs. The *thicker lines* delineating possibilities *a*, *b*, and *e* indicate those that are supported by recent studies. *TNF* tumor necrosis factor