



# Role of type I interferons and innate immunity in systemic sclerosis: unbalanced activities on distinct cell types?

Franck J. Barrat<sup>a,b,d</sup> and Theresa T. Lu<sup>a,c,d</sup>

## Purpose of review

The role of type I IFNs (IFN-I) in the promotion of autoimmunity has been well established. However, its role in the skin fibrosis of systemic sclerosis (SSc) is less clear. IFN-I can participate to tissue repair, and, here, we will consider the extent to which IFN-I's role in SSc skin fibrosis may reflect in part IFN-I functions during wound healing.

## Recent findings

Studies are beginning to delineate whether IFN-I has a protective or pathogenic role and how IFN-I affects tissue biology. Recent support for a pathogenic role came from a study depleting plasmacytoid dendritic cells during bleomycin-induced skin fibrosis. The depletion reduced the bleomycin-induced IFN-I-stimulated transcripts and both prevented and reversed fibrosis. Additionally, two recent articles, one identifying SSc endothelial cell injury markers and one showing repressed IFN signaling in SSc keratinocytes, suggest the possibility of unbalanced IFN-I activities on distinct cell types.

## Summary

Recent results support a pathogenic role for IFN-I in skin fibrosis, and recent studies along with others suggest a scenario whereby SSc skin damage results from too much IFN-I-activity driving vasculopathy in combination with too little IFN-I-mediated epidermal integrity and antifibrotic fibroblast phenotype.

## Keywords

lupus, scleroderma, skin, type I interferon, wound healing

## INTRODUCTION

The contribution of innate immunity to the pathogenesis of systemic sclerosis (SSc) has been well established both using patients' samples and using multiple mouse models. However, the precise role of innate cells, and in particular macrophages and plasmacytoid dendritic cells (pDCs), in disease and how they regulate the subsequent adaptive response in SSc patients is still unclear. One of the mediators of innate immune activation, type I IFN (IFN-I), has been associated with the development of fibrosis but also with many other autoimmune diseases that are not fibrotic. We will focus on the role that IFN-I can play and will consider the extent to which IFN-I's role in SSc skin fibrosis may reflect in part IFN-I functions in tissue repair.

## IMPACT OF TYPE I INTERFERONS IN IMMUNITY AND DISEASES

The key role of IFN-I in immunity is to participate in the antiviral response and the pleiotropic activity of IFN-I has been well described. The IFN-I are comprised

of 17 different proteins including 13 IFN- $\alpha$  subtypes, IFN- $\beta$ , IFN- $\omega$ , IFN- $\kappa$ , and IFN- $\epsilon$ . The need for such a large number of proteins, all of which share the same receptor, in immunity is unclear and could result from evolutionary pressure on the IFN pathway. It is also possible that these are differentially expressed by different cells, immune or not, and are associated with distinct functions of specific cell types [1].

The contribution by IFN-I to autoimmunity has first been described in systemic lupus erythematosus (SLE) but has since been reported in many other autoimmune diseases, including SSc [2], because of

<sup>a</sup>Autoimmunity and Inflammation Program, HSS Research Institute, <sup>b</sup>David Z. Rosensweig Genomics Research Center, <sup>c</sup>Division of Pediatric Rheumatology, Department of Medicine, Hospital for Special Surgery and <sup>d</sup>Department of Microbiology and Immunology, Weill Cornell Medical College of Cornell University, New York, New York, USA

Correspondence to Franck J. Barrat, Hospital for Special Surgery, HSS Research Institute, 535 East 70th Street, New York, NY 10021, USA. E-mail: barratf@hss.edu

**Curr Opin Rheumatol** 2019, 31:569–575

DOI:10.1097/BOR.0000000000000659

## KEY POINTS

- IFN-I can both promote wound healing by promoting epithelial barrier integrity and disrupt wound healing by inhibiting proliferation or survival of endothelial cells, and its activities may be dose-dependent and context-dependent.
- Recent results support a pathogenic role for IFN-I in skin fibrosis.
- Recent results also show endothelial injury that could be IFN-I-mediated and suppressed IFN-I-stimulated genes in SSc keratinocytes.
- We speculate that the skin damage of SSc skin fibrosis may reflect, in part, excessive IFN-I effects on endothelial combined with too little on keratinocytes and fibroblasts, resulting in vascular damage, disruption of the epidermal integrity, and profibrotic fibroblasts.

the presence in blood cells of highly expressed genes that are regulated by IFN-I and form the so-called IFN-signature. IFN-I can be produced by most cells in the body and multiple receptors sensing pathogens can induce its production. During an immune response, pathogens are recognized by multiple layers of sensors that will trigger an inflammatory response. However, in autoimmunity, it is likely that the inability to control the response to nucleic acids plays a central role [3], even though the identity of the sensors and the cell types involved is still debated. Recent studies are pointing to a key role for the nucleic acid sensing toll-like receptor (TLR)7, TLR8, and TLR9 in promoting autoimmunity with a particular role for TLR8 in controlling the development of fibrosis [4<sup>\*\*\*</sup>]. Although the activation of pDCs through TLR7 and TLR9 has been well documented in lupus [5–8], the expression of TLR8 by pDCs of SSc patients and the functional consequences on disease using a mouse model of skin fibrosis was unexpected and stresses not only the key role played by nucleic acid recognition in autoimmunity but also the induction of fibrosis.

One of the mediators of nucleic acid recognition and innate cell stimulation is IFN-I. The inflammatory response that follows tissue injury and that is required for tissue repair can, in some cases lead to fibrosis. In particular, macrophages and the nature of their activation can sway the balance between tissue repair and fibrosis [9]. In addition, IFN-I is associated with fibrosis in SSc patients [10,11], but also with many nonfibrotic autoimmune diseases, such as SLE [12–15]. How IFN-I may contribute to SSc skin fibrosis is unclear. Here we will briefly discuss the roles of IFN-I in SLE, wound healing,

and SSc, and then highlight recent findings that suggest a role for pDCs and unbalanced IFN-I activities on skin stromal cells in fibrosis.

## TYPE I INTERFERONS IN LUPUS

The first observation that IFN-I may contribute to the pathogenesis of SLE were described about 40 years ago [16,17]. Patients can now be characterized by measuring the levels of IFN-inducible genes, which are chronically elevated and can correlate with some of the clinical features of patients [12–15]. The cells responsible for the high presence of IFN-I are believed to be the pDCs, although it is likely that other cells may participate to the overall IFN response over time in patients [8,18]. The role played by pDCs and IFN-I is complex as the key findings rely on measuring interferon-stimulated genes (ISGs) in the blood, not tissues. Blood constitute a heterogeneous population of cells and the dependence of ISGs on certain IFN is still unclear and whether specific ISGs can be linked to specific symptoms is still undefined. Recent findings show that depleting or attenuating pDCs can prevent disease in lupus-prone mice [19,20] and can reduce the IFN-I response in the skin of SLE patients with encouraging signs of clinical efficacy in the skin [21<sup>\*\*\*</sup>]. These data suggest that IFN-I produced by pDCs may have a critical role in generating lesions in the skin whereas its contribution to the overall disease is less clear. IFN-I can also be produced by other cells as well such like epithelial cells [22], which adds complexity to our understanding of how IFN-I impacts the disease. Cutaneous diseases including lichen planus, dermatomyositis, lichen sclerosis, and cutaneous GVHD that share the common pathological feature named ‘interface dermatitis’ [23] all have IFN-signature in the skin but are not associated primarily with fibrosis. These findings may reflect the different tissue microenvironmental contexts of each disease.

Although SLE is not generally considered a fibrosing disease, Putterman and colleagues recently published that nonresponder lupus nephritis patients can have a high IFN-I signature and a fibrotic signature in kidney tubular epithelial cells [24<sup>\*</sup>]. The fibrotic signature was not associated with frank, histological fibrosis, suggesting that these signatures are pointing to an early event and is a harbinger of things to come. The results suggest the possibility of a functional interaction between IFN-I and fibrosis, especially at early stages, and support a potential role for type I IFN in driving fibrosis.

## TISSUE REPAIR

Type I IFN can promote wound healing in the skin [25,26]. Repair of epidermal tissues, such as skin and

gut involves epithelial closure to reform a protective barrier, and the protective role of IFN-I in wound healing in part reflects its contributions to epithelial barrier formation or maintenance. In a tape stripping injury model whereby tape is applied and then pulled off the skin a number of times, IFN- $\alpha$ , likely from pDCs [27], was upregulated within a day after injury, and mice deficient in the IFN alpha/beta receptor (IFNAR) were less able to induce a protective keratinocyte activation response [25]. Similarly, mice lacking TLR3 failed to close skin wounds [28], and, in the gut, IFNAR has a similar function in promoting barrier integrity of the intestinal epithelium [29]. Consistent with these observations, overexpression of IFN-I promoted, via myeloid cells, epithelial proliferation, and repair [26]. Together, the data point to a protective role for IFN-I in promoting epithelial integrity during wound healing.

How exactly IFN-I promotes wound healing and epithelial closure is less clear. With tape stripping, IFNAR-/- mice showed reduced IL-6, IL-17, and IL-22 responses, suggesting that a lack of inflammatory responses contribute to reduced wound healing [25,27]. However, the importance of the reduced inflammatory cytokines was not directly tested. IFN-I also had a protective role upon skin injury with subacute ultraviolet radiation (UVR) [30], as IFNAR-/- mice showed greater skin inflammation compared with controls. Although these studies were apparently at odds with each other with regard to the effect on skin inflammation, IFNAR clearly had a beneficial role in both models. Elkon and colleagues proposed that differences in levels, source, and inducers of IFN (higher, by pDCs, and dependent on TLR7 and TLR9 for tape stripping, whereas UVR produced lower levels of IFN in the absence of pDCs and the IFN was dependent on TLR3 and STING) could potentially account for differences in inflammation. Potentially, some of the differences could be because of direct dermal damage by UVR but not tape stripping, that leads to inflammation that is controlled by IFNAR, perhaps via effects on epidermal integrity. IFNAR can also act on myeloid cells to promote their ability to stimulate healing. IFNAR on myeloid cells has been shown to promote keratinocyte proliferation [26], and IFNAR will modulate pDC expression of cytokines, potentially contributing to the inflammatory cytokines that were lost in IFNAR-/- mice with tape stripping [25].

In addition to a role for IFNAR in epithelial barrier function, IFN-I can affect immunity at the skin level, which could have implications for wound healing. For example, IFN-I produced by keratinocytes activates dendritic cells in the skin [31]. This causes them to be better antigen-presenting cells

and presumably to migrate toward the draining lymph node to activate the immune system. IFNAR can also activate accumulation of effector T cells in a tissue by activating macrophages [32] and can initiate tissue inflammation by promoting macrophage necroptosis [33]. Regulatory T cells, which have tissue repair properties [34], are also directly regulated by IFNAR to promote their development and function [35]. Cumulatively, the data suggest that IFNAR can promote wound healing by acting on local cells to repair tissue and also by stimulating immune cells to control infectious agents.

In some settings involving an excess of cytokine, however, IFN-I can also impede wound healing. For example, injection of IFN- $\alpha$  into wound edges delayed wound closure [36]. This was associated with an antiproliferative effect of IFN- $\alpha$  on the capillaries that normally grow into the wound, as well as on fibroblasts and keratinocytes. These results are in line with the sensitivity of endothelial cells to IFN- $\alpha$  *in vitro* [37], an ehrlichial infection model whereby infection-induced IFN-I signaling on nonhematopoietic cells is detrimental to the host [38] and a skin viral infection model that was associated with lymphatic dysfunction [39]. Whether excessive IFN combined with an unrepaired wound (versus excessive IFN in the absence of a wound) leads eventually to fibrosis would be interesting to investigate.

The idea that IFN-I effects are context-dependent is supported in considering the role of IFN-I in bacterial infection secondary to viral infections [40]. Here, the timing of type I IFN seems to be a critical parameter that determines its exact effect. IFN expressed at high levels prior to secondary infection can suppress the host response, including neutrophil recruitment, Th17 generation, and expression of antibacterial peptides, leaving the host less able to control the secondary infection. This is similar to the role of IFN-I in suppressing a protective Th1 response with *Mycobacterium tuberculosis* and *Mycobacterium leprae*. On the other hand, IFN at 14 days after the start of viral infection reduces the risk of secondary infections. The reasons for a protective role later after a viral infection is unclear, but it is interesting to speculate that IFN-I-mediated remodeling of the affected tissue or of the secondary lymphoid organs where immune responses are initially generated after the initial infection contributed to better protection.

In wound healing then, IFN-I can have different functions in different contexts and has effects in addition to effects on immunity. Overall, IFN-I is protective in promoting epidermal barrier integrity during wound healing, but excessive IFN-I can disrupt vascular function.

## TYPE I INTERFERONS IN SYSTEMIC SCLEROSIS

In SSc, there is an association between IFN-I and disease. An IFN signature is found in the blood of about 50% of SSc patients, and it is apparent even early in disease [41–43]. Importantly, an IFN signature is also found in skin, again in association with early disease [44–46]. Polymorphisms of IFN regulatory genes *IRF-4,5,7,8* and *STAT4* have been found to be associated with SSc [41], further suggesting the possibility of a pathogenic role for IFN-I. As in SLE, there is also anecdotal evidence that IFN-I used for treating other diseases was associated with development of SSc [41]. Intriguingly, anti-IFNAR (Anifrolumab) in phase I trials led to suppression of IFN signature and TGF $\beta$  signaling in SSc skin [47] and further trials to assess clinical efficacy could help us understand the extent to which IFN-I contributes to pathogenesis.

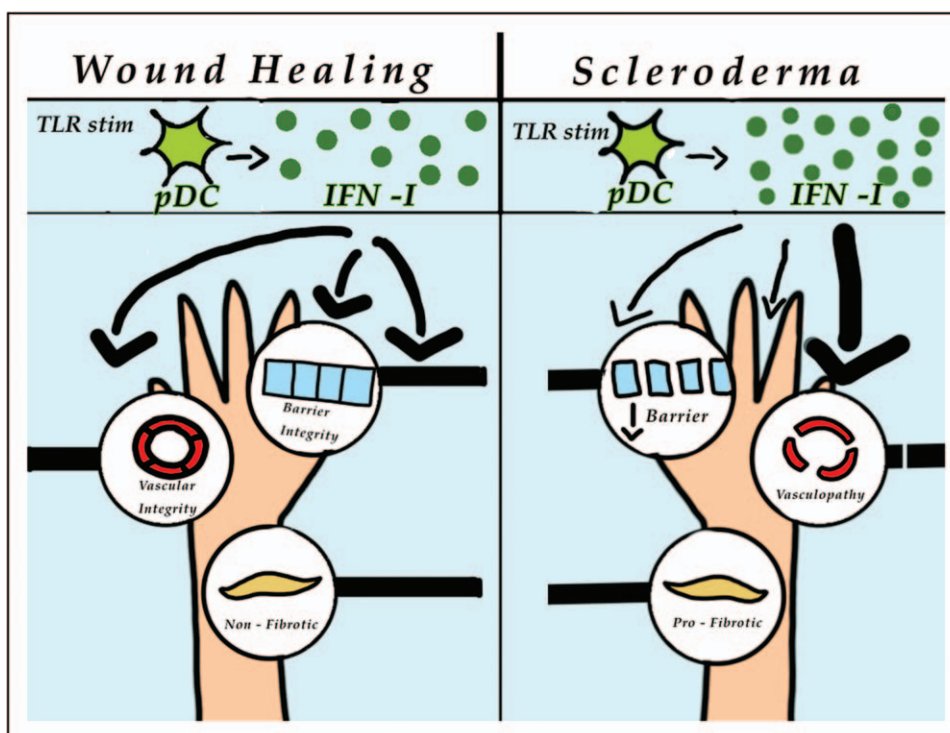
A pathogenic role for IFN-I in skin fibrosis was further supported by two recent studies. Delaney *et al.* [49] treated a graft-versus-host disease (GVHD) model that is characterized by skin inflammation and fibrosis and used as an SSc model [48] with anti-IFNAR. The GVHD model showed upregulated IFN-I stimulated gene expression in the skin and anti-IFNAR reduced the IFN-I signature as well as fibrosis development, suggesting that IFN-I drove fibrosis development. In 2018, Ah Kioon *et al.* [4<sup>00</sup>] examined the role of pDCs in scleroderma that can express very large quantities of IFN-I. They found that pDCs accumulate in SSc skin and express higher levels of IFN- $\alpha$  than cells from healthy controls spontaneously in culture. Although the pDCs also expressed additional cytokines, such as CXCL4, pDC depletion reversed the upregulated IFN-associated genes seen in the bleomycin-induced skin fibrosis model and improved fibrosis. Both these studies in different models [4<sup>00</sup>,49], then, supported the idea that IFN-I overall promotes skin fibrosis, presumably via a local mechanism.

How IFN-I affects skin biology during fibrosis is critical for insight into the role of IFN-I, but understanding is currently limited. Interferon alpha expression in human scleroderma skin has been attributed to pDCs or other types of immune cells that are located near blood vessels and associated with capillary rarefaction [50]. This suggests a scenario whereby high levels of IFN-I and its antiangiogenic effects on endothelial cells may contribute to the pathogenesis of scleroderma skin fibrosis. The Delaney *et al.* [49] study treating the GVHD model with anti-IFNAR also showed that the reduced fibrosis development was associated with prevention of endothelial cell injury, supporting the idea that IFN-I-mediated vascular injury contributed to fibrosis.

Single-cell RNA sequencing of SSc skin has not reported the finding of an IFN-I signature per se in endothelial cells [51<sup>00</sup>], but endothelial cells were found to express higher levels of vWF [51<sup>00</sup>], a marker of endothelial cell damage, and vWF has been shown to have downregulated anifrolumab in SLE patients [52]. Potentially, then, excessive IFN-I contributes to the endothelial cell damage in scleroderma skin.

In contrast, however, short-term primary cultures of keratinocytes from SSc skin have shown repressed IFN-I signaling when compared with transcriptome of healthy control keratinocytes [53<sup>00</sup>]. This echoes the repressed IFN-I signaling found in cultured SSc skin and lung fibroblasts [46,54]. Whether the repression in keratinocytes and, potentially, fibroblasts reflects the in-vivo fibroblast state or is a result of culturing remains to be further sorted out. Interesting, recent work by Browning and colleagues showing some increased VCAM-1 expression by perivascular but not other fibroblasts in SSc skin [55], which could potentially reflect increased IFN-I signaling [49,56]. This study points to the heterogeneity of fibroblasts in all tissues that is becoming better understood [57,58<sup>00</sup>–61<sup>00</sup>,62] and demonstrates the potential for specific regulation of a subset of cells that may not be detected in bulk sequencing of a particular cell type or that may be lost upon culturing. In the study of scleroderma, the results from single-cell RNA sequencing analyses of fibroblasts and keratinocytes directly from SSc skin will likely be illuminating.

Despite the likely heterogeneity there is in any given cell type, however, the surprising results of Kahlenberg and colleagues raise the interesting possibility that the high levels of IFN-I in the skin in SSc may not signal to all cell types in a balanced way; some cell types, such as keratinocytes and fibroblasts, may be ‘nonresponders’ whereas others, such as endothelial cells, may be very sensitive to IFN-I [53<sup>00</sup>]. Interestingly, Varga and colleagues have shown that IFN- $\beta$  induces an antifibrotic phenotype in cultured fibroblasts, raising the possibility that reduced IFN-I signaling in SSc fibroblasts may be pathogenic [46,63]. Similarly, given the role of IFN-I in promoting epidermal barrier integrity, repressed IFN-I responses in keratinocytes in SSc has the potential to disrupt barrier integrity, thus contributing to the wound healing phenotype of the epidermis [64] and skin damage in SSc. Potentially, the high levels of IFN-I in SSc is meant to be a protective response to a perceived ‘wound’, but the unbalanced response to IFN-I results in damage to the skin, thereby contributing to the fibrotic phenotype.



**FIGURE 1.** Model of type I interferon activities on skin stromal cells during wound healing and in scleroderma. Left panel: during wound healing, IFN-I from toll-like receptor (TLR)-stimulated pDCs acts on the epithelium to promote skin barrier integrity, the vasculature to promote normal function, and fibroblasts to maintain an antifibrotic phenotype. Right panel: in scleroderma skin fibrosis, the excess IFN-I has an imbalanced effect on different stromal compartments. The vasculature is sensitive to the IFN-I, leading to vasculopathy, whereas the epidermis and fibroblasts have repressed IFN-I signaling, leading to disrupted barrier function and a profibrotic phenotype, respectively. IFN-1, type I interferon.

## CONCLUSION

Although high IFN-I levels are associated with SSc and recent data support the idea that high IFN-I is overall pathogenic in SSc skin fibrosis, we propose here that understanding how IFN-I is pathogenic may require us to consider that an imbalance in the non-hematopoietic ‘stromal’ response to IFN-I may be a contributing factor. Potentially, the sensitive endothelial cell response to IFN-I is driving a vasculopathy whereas the repressed responses in keratinocytes and fibroblasts drives epidermal dysfunction and a profibrotic fibroblast phenotype (Fig. 1). In an attempt to repair the ‘wound’ that is not healing, IFN-I levels are driven up, further exacerbating the skin damage. It is also possible that the stromal responses reflect also indirect responses whereby IFN-I acts on myeloid and other immune cells to mediate the distinct endothelial, keratinocyte, and fibroblast responses. Here, more detailed understanding of the effects of IFN-I on the stromal elements in SSc patients or scleroderma models and of the direct and indirect IFN-I-responding cells will help us better understand how IFN-I should be therapeutically targeted in SSc skin fibrosis, and potentially in wound healing and other autoimmune and inflammatory conditions.

## Acknowledgements

The authors thank Charlotte Black for the figure illustration.

## Financial support and sponsorship

This work was supported by grants from the NIH (1R01AI132447 to F.J.B.; NIH R01AI079178 to T.T.L.), from the Scleroderma Research Foundation (F.J.B.), Scleroderma Foundation (T.T.L.), the Lupus Research Alliance (T.T.L.), St. Giles Foundation (T.T.L.), and A Lasting Mark Foundation (T.T.L.).

## Conflicts of interest

F.J.B. has been acting as a consultant for Astra Zeneca, Jansen, Biogen, and EMD Serono but otherwise has no other conflicts. T.T.L. has no conflicts of interest.

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