Immunology Letters xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Immunology Letters

journal homepage: www.elsevier.com/locate/immlet

Review

The IL-1 family of cytokines. Do they have a role in scleroderma fibrosis?

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ARTICLE INFO

Keywords:
IL-1
IL-18
IL-33
IL-36
Systemic sclerosis
Fibrosis

ABSTRACT

Systemic sclerosis is a profibrotic autoimmune disease mediated by the dysregulation in collagen synthesis, leading to the increased deposition of collagens, primarily type I and III, and the deposition of other extracellular matrix proteins in the skin and internal organs, in a mechanism that is thought to be an over active wound healing process. These patients experience significant morbidity and the mortality rate in this disease is high. Indeed, scleroderma is the most deadly of diseases in the autoimmune spectrum. Recent evidence has placed the assembly and chronic activation of the inflammasome as a central driver of fibrosis. Once assembled, the inflammasome is a large protein complex that regulates the release of IL-1, IL-18, and IL-33, which are thought to play a role in the fibrotic response. IL-36 also belongs to the IL-1 family of cytokines and is a new comer to this field of research. Recent analyses of the IL-1 family of cytokines have demonstrated that many of them play a role in skin inflammation and fibrosis and their corresponding antagonists (IL-1RA and IL-36RA) can abrogate this pathology. Understanding how these cytokines are regulated and how they contribute to fibrosis will be important to understanding this pathology and may shed light in new areas for therapeutic development.

1. Introduction

Systemic sclerosis (scleroderma; SSc) is an autoimmune disease where the etiology is currently unknown. It often manifests as a severe and progressive cutaneous fibrosis that is complicated by internal organ involvement. There are well defined alterations to the microvasculature, as well as several distinct cellular and humoral immunological abnormalities. SSc can present as a very heterogeneous disease, where the manifestation of fibrosis can range from milder forms with limited skin involvement. These patients often present with internal organ involvement later in life. In contrast, in the most severe variant of SSc, patients present with aggressive skin fibrosis with internal organ involvement manifesting shortly after disease onset. The mortality of SSc is very high as there are no truly effective therapeutics that can stop the fibrotic process. In addition, these patients experience a poor quality of life that is directly related to the extent of the dermal fibrosis and microvascular alterations.

Fibrosis is a common end stage pathology observed in many divergent pathological diseases. Thomas Wynn has estimated that about 45% of all deaths in the Western world can be attributed to some type of fibrotic disorder [1]. This reported figure seems to be extraordinarily high, but when diseases such as solid tumors [2–5], pulmonary fibrosis and other interstitial lung diseases [6–8], cardiovascular disease [9,10], liver fibrosis [11,12], SSc [13,14], kidney fibrosis mediated by diabetes or other diseases [15–17], etc., are taken into consideration, this figure is not an exaggeration.

Fibrosis is the abnormal expression of collagens and other extracellular matrix proteins within the tissues and this accumulation of proteins causes scarring and mediates the failure of the organ or tissue. Once the tissue has been damaged, there are milieus of signaling events that can recruit additional cells to the damaged site to aid in “repair” of the tissue and these cells further exacerbate the damage by contributing more collagen and extracellular matrix. Intriguingly, fibrosis occurs more often in the aged than in the young [18]. Recently it was shown that aging induces a profibrotic matrix in the tissues that increases fibrocyte recruitment [19] that further exacerbates the profibrotic microenvironment.

Often the initiating insult driving the fibrotic process in the tissue or organ is unknown, but once fibrosis has been established there are no effective therapies to halt its progression. The FDA recently approved two drugs (perfenidone and tocilizumab) but these drugs only slow collagen deposition. Thus, there is an urgent need to understand the cause and maintenance of fibrosis. A more thorough understanding of the initiating pathways in the cell highlighting pathways that mediate fibrosis could identify therapeutics that halt the abnormal deposition of extracellular matrix.

2. Is fibrosis caused by a wound healing mechanism gone awry?

Many of the pathological features that occur during fibrosis are also observed in normal wound healing. While normal wound healing is a critical, and yet tightly regulated process, that causes the transient

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https://doi.org/10.1016/j.imlet.2017.11.012
Received 15 June 2017; Received in revised form 27 November 2017; Accepted 27 November 2017
0165-2478/ © 2017 Published by Elsevier B.V. on behalf of European Federation of Immunological Societies.

proliferation of fibroblasts, and the upregulation of collagen and other extracellular matrix proteins to close the wound, it is a mechanism that down regulates itself once the wound has closed. Collagen synthesis and extracellular matrix deposition then declines and the collagens become cross-linked/remodeled and some of it is resorbed. In contrast, fibrosis is thought to be a wound healing mechanism that has gone awry. It was proposed that fibrosis can occur due to a dysregulation in the wound healing process at either the proliferative or remodeling stages [20]. However, fibrosis that occurs in an organ may not be a result of overt damage and indeed, in many instances, the cause of the fibrosis remains unknown. Furthermore, fibrosis can result from a bona fide inflammation such as that observed in the liver with Hepatitis B viral infections or can occur without any obvious inflammation as that which occurs in stiff skin syndrome [21]. Thus, it is crucial to understand the differences between inflammation-mediated fibrosis and fibrosis that is driven in the absence of apparent inflammation. Recently, an innate immune signaling mechanism has been identified that is driven by the inflammasome has been implicated in fibrosis leading to the release of interleukin (IL)-1, IL-18 and IL-33.

3. What are the key cellular players in fibrosis?

Fibroblasts are a heterogeneous population of cells that are able to differentiate into highly activated myofibroblasts. Myofibroblasts are crucial to the wound healing process, mediate wound closure and control many of the wound healing events. Many resident or migratory cells are also capable of differentiating into myofibroblasts, and these include tissue residential cells such as hepatic stellate cells [22], bile duct fibroblasts [23], mesangial cells [24], mesenchymal cells [25–27], epithelial cells [28], and endothelial cells [29]. Furthermore, it has been suggested that pericytes and fibrocytes, cells that are found in the circulation, can differentiate into myofibroblasts contributing to fibrosis in organs [30–33]. Once differentiated into the highly activated myofibroblast, these cells then directly participate in the deposition of collagen and extracellular matrix proteins into the skin or organs.

Currently, it is thought that the fate of the myofibroblast is central to the normal process of tissue repair and various microRNAs mediate downstream responses in myofibroblasts to drive fibrosis [34]. Intriguingly, once the wound is closed, myofibroblasts are believed to undergo apoptosis [35] or revert to a quiescent fibroblast phenotype via dedifferentiation [36,37]. The mechanism(s) that cause myofibroblasts to do this when wound healing is complete are not fully understood however, it has been shown prostaglandin E_2 may play a role [35]. In contrast, during fibrosis, myofibroblasts appear to be resistant to apoptosis and the mechanism(s) promoting this resistant phenotype have not been well described, either. To confound this data, human myofibroblasts seem to be naturally more resistant to apoptosis than their mouse myofibroblast equivalents [38].

4. What are the inflammasomes and how might are they involved in fibrosis?

Inflammasomes are specialized proteins that contain the NOD-like receptor (NLR). NLRs recognize via a leucine rich repeat, a wide range of molecular motifs that are found on bacteria, viruses, and parasites [39]. However, inflammasomes are not just sensors for pathogens leading to a mounted immune response against invaders. The NLRP3 inflammasome senses the overall well-being of the cell and perturbations in reactive oxygen species and perhaps other endogenous danger signals such as potassium efflux [40,41] and can become activated. Inflammasomes can be found in a diverse range of cell populations; including immune cells such as neutrophils [42], NK cells [43], macrophages [44], and T cells [45] and they can found in stromal and parenchymal cells such as myofibroblasts/fibroblasts [36], keratinocytes [46,47], microglial cells [48], endothelial cells [49], and hepatic stellate cells [50]. Because non-immune cells containing inflammasomes are found in all organs and systems of the body, we propose that these cells are often involved in the initiation of inflammation via inflammasome activation that enhances the recruitment of inflammatory cells by the release of cytokines to the sites where there is infection or damage [51]. These non-immune cells may also be involved in sterile inflammation [52–54].

The NLRP3 inflammasome is the most frequently studied and best understood inflammasome and its activation has been found to be involved in many different disease pathologies, including fibrosis and cancer [36,55]. However, to complicate this understanding, it can also signal via NLRP3-independent mechanisms as well [56,57]. The critical role for the activation of the inflammasome is the cleavage and the resulting activation of caspase-1 [58]. Once caspase-1 has been activated, it is then able to process an enormous variety of protein precursors and many of them are involved in wound healing [59].

The events that initiate fibrosis are complex and generally unknown, however the NLRP3 inflammasome does play a role in this complex signaling process and its activation possibly occurs via reactive oxygen species as this molecule has been shown to be central to fibrosis. Several cytokines and growth factors (e.g. TGF-β, IL-1 and angiotensin II) are involved in fibrosis and promote reactive oxygen species synthesis [60–62] in what might be a feed forward mechanism. The sensing of PAMPs or DAMPs can increase reactive oxygen species release and activating the NLRP3 inflammasome causing release of IL-1, IL-18, and IL-33. IL-1, IL-18, and IL-33 play crucial roles in the development and amplification of the immune response. However, the abnormal production of these cytokines has been associated with many chronic inflammatory and autoinflammatory disorders suggesting that targeting one or more of these cytokines may resolve disease. Depending on the cell making the cytokine and the receptors on their cell surface such as in the case of fibroblasts, we believe that autocrine signaling could promote continual synthesis and secretion of growth factors leading to more reactive oxygen species that further enhances inflammasome activation. Considering this hypothesis, this autoinflammatory response could be difficult to control.

5. The IL-1 family of cytokines

The IL-1 family of cytokines comprises of 11 cytokines that amplify and modulate the immune response. Members of this family have been associated with some fibrotic diseases suggesting that the cells that secrete the cytokines, or respond to them, have different downstream responses that drive various pathological disorders. The IL-1 family of cytokines and their fibrotic or anti-fibrotic properties are outlined in Table 1. The focus of this review is to discuss how this family drives cellular responses leading to fibrosis. To date, it is unknown as to whether IL-37 and IL-38 are able to promote fibrosis as very little is

Table 1
The IL-1 Cytokine Family.

Name	IL-1 Family Name	Receptor[a]	Co-receptor[a]	Fibrotic/Anti-Fibrotic
IL-1α	IL-1F1	IL-1R1	IL-1R3	Fibrotic
IL-1β	IL-1F2	IL-1R1	IL-1R3	Fibrotic
IL-1RA	IL-1F3	IL-1R1	None	Anti-fibrotic
IL-18	IL-1F4	IL-1R5	IL-1R7	Fibrotic
IL-33	IL-1F11	IL-1R4	IL-1R3	Fibrotic/anti-fibrotic
IL-36α	IL-1F6	IL-1R6	IL-1R3	Fibrotic
IL-36β	IL-1F8	IL-1R6	IL-1R3	Unknown
IL-36γ	IL-1F9	IL-1R6	IL-1R3	Unknown
IL-36RA	IL-1F5	IL-1R6	None	Unknown
IL-37	IL-1F7	IL-1R5	IL-1R8	Unknown
IL-38	IL-1F10	IL-1R6	Unknown	Unknown

Modified from [155,156] and updated based on the current literature and new IL-1 family nomenclature.

[a] IL-1R3 was previously called IL-1RAcP; IL-1R4, ST2; IL-1R5, IL-18Rα; IL-1R6, IL-1rp2; and IL-1R7, IL-18Rβ.

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