Review

NLRP3 Inflammasome and IL-11 in Systemic Sclerosis Pulmonary Fibroblasts

Caya M. McFalls * and Carol M. Artlett

Department of Microbiology & Immunology, College of Medicine, Drexel University, Philadelphia, PA 19129, USA; cma49@drexel.edu (C.M.A.)

* Corresponding author. E-mail: cmcfall6@jh.edu (C.M.M.)

ABSTRACT: Systemic sclerosis (SSc) is an autoimmune disease characterized by widespread fibrosis affecting multiple organ systems. There is clinical heterogeneity among patients with SSc in terms of the organs affected. However, the pathophysiology of the disease remains elusive. The NLRP3 inflammasome is upregulated in SSc and exerts its fibrotic effects through activation of caspase-1, which in turn activates a fibrotic signaling cascade, resulting in increased collagen deposition and myofibroblast transition. Recently, IL-11 has been shown to be elevated in disease and has been shown to participate in downstream signaling via the NLRP3 inflammasome. A significant number of patients with SSc will develop pulmonary involvement, termed interstitial lung disease (SSc-ILD). Though this type of pulmonary involvement is distinct from other types of pulmonary fibrosis (such as idiopathic pulmonary fibrosis), it may be a valuable model to study mechanisms of fibrosis that could apply to other fibrotic diseases. Here, we discuss recent advances in understanding the mechanisms of the NLRP3 inflammasome and IL-11 in SSc pulmonary fibroblasts. We tie together some of the recent findings, such as senescence, the unfolded protein response, and reactive oxygen species, that contribute to fibrotic pathology via modulating NLRP3 activation, possibly leading to IL-11 expression.

Keywords: Systemic sclerosis; Fibrosis; NLRP3 inflammasome; Caspase-1; IL-11; Senescence

1. Introduction

Systemic Sclerosis (SSc) is an autoimmune process that is characterized by widespread fibrosis. Variability in disease expression and severity is observed, ranging from limited organ involvement, including the skin and extremities, to a more diffuse pattern of organ involvement, including the lungs, GI tract, heart, and vasculature [1,2]. The underlying pathophysiology for the progression of SSc is complex and, although somewhat shrouded in mystery, may have important generalizability to a host of other fibrotic diseases, including aging. The development of fibrosis in many disease processes is a fundamental cause of morbidity and mortality in the aging population and, to no surprise, has gained widespread interest among basic translational researchers. It has been estimated that nearly 50% of deaths in Westernized countries can be attributed to fibrosis [3]. Considering the important role that collagen elaboration plays in various disease processes affecting all organs, the development of novel therapies to interrupt this devastating process has significant implications. SSc-associated interstitial lung disease (SSc-ILD) may have a nuanced mechanism. It exhibits a variable clinical course and is associated with high mortality [2]. Much of the variability seen in SSc patient lung involvement has been associated with race [4]. For example, patients of Asian descent have an earlier onset and more severe manifestations of SSc-ILD compared with patients of Caucasian descent, with approximately 80% of Asian patients presenting with SSc-ILD, which was reported to have a rapidly progressing phenotype [4]. SSc-ILD is thought to be the leading cause of death [5]. Correctly diagnosing SSc-ILD is critical to better disease management. Not only is correlating the autoantibody profile important [6], but recently, ultrasounds [7] and high-resolution computed tomography [8] have become valuable tools in diagnosing early SSc-ILD onset.

Advancing our understanding of the mechanisms that lead to collagen formation in fibroblasts isolated from patients with SSc may provide a valuable model for understanding a variety of other fibrotic diseases. SSc is considered

an autoimmune disease, but it shares many similarities with other fibrotic disease states caused by increased collagen deposition and cellular senescence, including those affecting the cardiovascular, pulmonary, and renal systems.

1.1. NLRP3 Inflammasome in SSc

A central player in inflammation seen in pulmonary SSc fibroblasts is the NLRP3 inflammasome. Key studies have shown that disruption of NLRP3 inflammasome signaling via caspase-1 results in the amelioration of collagen deposition and myofibroblast differentiation [9]. Inflammasome activation is part of the innate immune system's defense against invaders and is a long-standing idea that has been shown to be an effective mechanism to protect against non-autologous antigens [10]. There are even indications that certain pathogens exploit this pathway to gain an advantage against the body's immune system, such as hepatitis B [11]. However, the idea that the inflammasomes can be activated by internal stimuli (cellular stress, mitochondrial dysfunction, pharmaceuticals, *etc*.) is a relatively novel idea that has become popular in the investigation of autoinflammatory conditions [12,13].

Broadly speaking, two aspects of inflammasome activation appear to be important regardless of disease: priming and triggering. The NLRP3 inflammasome does not typically sit ready, waiting for an inflammatory insult to become activated. There is priming, which increases NLRP3 and pro-inflammatory cytokine gene transcription through the NFκB pathway. Inflammaging, the low-grade and chronic inflammation associated with aging, may be enough for priming [14]. This allows for activation by inflammatory stimuli such as ATP, toxins, ROS, DNA, unfolded proteins, crystals, or other cellular stressors [15]. Priming is responsible for increasing expression via the NFκB pathways to prepare for the insult, which is followed by activation by cellular stressors, resulting in potassium efflux and activation of downstream inflammasome signaling [16,17].

Activation of the inflammasome leads to the cleavage of procaspase-1 to its active form, caspase-1 (Figure 1). Caspase-1 is one of the most well-studied human caspases and goes on to cleave several cytokines into their active forms, most notably IL-1β, IL-18, and IL-33, which are prime targets for activation via this pathway [9,18]. Caspase-1 is also able to cleave and activate itself as well as exert several downstream effects, including cleaving proteins involved in mitochondrial function, cytoskeleton rearrangement, and glycolytic pathways [19,20]. Cytokines activated by caspase-1 exert fibrotic responses such as collagen secretion, crosslinking, and myofibroblast transitions through transcriptional changes [21]. Specifically, blockade of IL-1, IL-33, and IL-36 has been postulated as treatment targets for inflammasome activation [22].
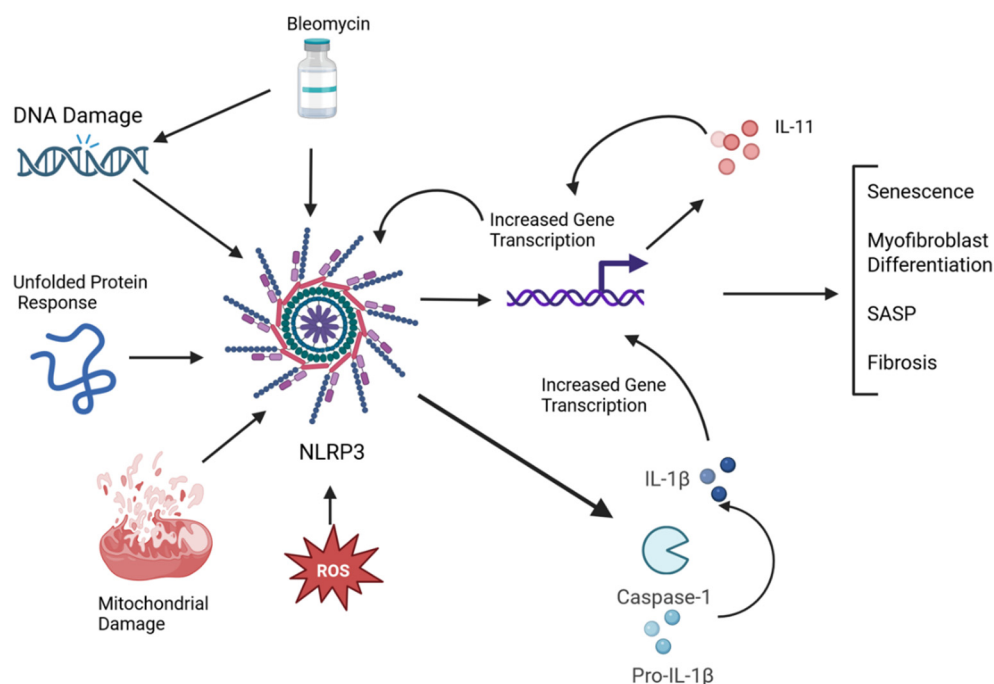

Figure 1. The interplay between the NLRP3 inflammasome and IL-11 in SSc fibrosis. Numerous insults can activate the NLRP3 Inflammasome, which has a pathologic role in collagen deposition in SSc tissues. The maturation of caspase-1 leads to its downstream processing of IL-1β (and other cytokines), which increases the expression of IL-11. This, in turn, upregulates collagen deposition in the tissues and is involved in the differentiation of myofibroblasts, leading to SASP, senescence, and fibrosis. Created in BioRender. Artlett, C. (2025) https://BioRender.com/p83n03i (accessed on 4 April 2025).

Though caspase-1 is responsible for the bulk of downstream activity of the NLRP3 inflammasome, caspase-4 and -5 (and -11 in mice) are the remaining so-called "inflammatory" caspases that are involved in non-canonical signaling [23–25]. To this end, the activity of these caspases is ancillary to that of caspase-1, but more work is needed to understand these non-canonical pathways. Interestingly, caspase-5 is expressed to a greater degree than other caspases, including caspase-1, in psoriatic skin lesions [26]. However, no reports of increased caspase-4 or -5 in SSc exist.

Following activation of IL-1β and IL-18 in fibroblasts, there is a response leading to increased collagen deposition and myofibroblast transition [17]. This is also accompanied by increases in the machinery that controls the export of collagen from the endoplasmic reticulum [21]. This activation of the NLRP3 inflammasome leading to increased fibrosis is recapitulated in the in vitro studies on fibroblasts and in vivo mouse models using bleomycin. Collectively, bleomycin exerts diffuse fibrotic effects, which are dependent on the NLRP3 inflammasome [9], and the fibrosis seen in SSc fibroblasts is dependent on the NLRP3 inflammasome [9]. Downstream effects of the NLRP3 inflammasome leading to fibrosis are mediated by TGF-β1 [27], which exerts vast fibrotic impacts that are relevant to the elaboration of pulmonary fibrosis, potentially via IL-11 signaling.

1.2. IL-11 in SSc

Though there are a host of cytokines that are upregulated in diseased SSc fibroblasts, IL-11 specifically has garnered much attention in recent years as a possible modulator of disease. Starting initially with studies in myocardial fibroblasts, Schafer et al. postulated that IL-11 is a mediator of fibrosis through its effect on TGF-β1 [28]. Further studies by this group showed similar mechanisms in pulmonary and hepatic fibroblasts, further strengthening the hypothesis that IL-11 drives fibrosis [29,30]. However, other studies could not replicate this data and suggested that IL-11 effects limit fibrosis in tissues or have no effect at all [31–34]. These studies have been complicated by different effects between human and mouse antibodies, but the conclusions are hazy and suggest a more complicated mechanism [35].

Though the end-points of fibrosis, such as increased collagen deposition, cannot be entirely attributed to IL-11, there is no dispute that its levels are elevated in SSc, with particularly elevated levels in SSc with pulmonary involvement [36]. Although the mechanism underlying enhanced expression of IL-11 in SSc remains elusive, our lab has shown that it is dependent upon caspase-1 activation, which, in turn, is activated by the NLRP3 inflammasome [34]. Inhibition of IL-1β, whose activation in SSc is also dependent on caspase-1 activation, does not demonstrate as great of an effect on IL-11 expression as inhibition of caspase-1 or of TGF-β1 [34]. These data suggest the vital role that the NLRP3 inflammasome plays in the fibrotic process in the lungs of individuals with SSc, potentially via the IL-11 signaling cascade.

1.3. Senescence in SSc

An unanswered question posed by researchers and clinicians alike is how intrinsic functional abnormalities in tissue fibroblasts leads to extensive fibrosis. It has been hypothesized that an initial hit causes a domino effect of cellular abnormalities, as previously discussed. One attractive concept is that cellular senescence, typically associated with aging and cell cycle arrest, leads to a senescence-associated secretory phenotype (SASP) [2]. In a healthy system, SASP contributes to wound healing after a sudden insult, but in a diseased or aged system without a counterregulatory check, it can be unleashed and contribute to chronic inflammation [37]. Senescent cells are characterized by upregulation of the transcription factor p16^{INK4a} or p53-p21, which causes cell cycle arrest, as well as β-galactosidase, monocyte chemotactic protein-1, plasminogen activator inhibitor 1, inflammatory cytokines such as TNF-α and pro-fibrotic cytokines such as TGF-β [38]. Idiopathic pulmonary fibrosis, which is a more aggressive fibrotic disease of the lung, is often studied in conjunction with SSc-ILD, and both show increased markers of senescence [39]. In a comparison study, the expression of hundreds of genes associated with cellular senescence was upregulated in SSC-ILD and idiopathic pulmonary fibrosis compared to controls [40]. The authors show that aging and senescence markers are elevated in both diseases. In addition, dermal fibroblasts from SSc mirror the genetic upregulation of senescent-associated markers seen in the lungs [40]. These dermal fibroblasts have increased oxidative stress and SASP profile that can be ameliorated with reactive oxygen species scavengers, suggesting that senescence is driven by oxidative stress [41].

Age-related senescence in pulmonary fibroblasts leads to increased NLRP3 inflammasome expression, possibly through increased priming due to inflammaging. In bleomycin studies, aged mice are more likely to die than younger mice [42]. These studies also showed elevated NLRP3 expression with bleomycin in aged mice, which increased the processing of IL-1β and IL-18 and downstream TGF-β mediated effects. Bleomycin injury in the lung also induces

ROS, which exacerbates the fibrotic process seen in the lungs, and this likely occurs through the induction of cellular senescence. Inhibition of NLRP3 inflammasome through CY-09 ameliorates this effect and causes a reduction in markers of cellular senescence [43].

Tying in another factor that contributes to cellular senescence is DNA damage. SSc has long been known to have damaged DNA, and cells feature telomere attrition [44] and chromosomal rearrangements [45]. More recently, studies have expanded on these earliest observations to show that this damage can be extensive [46]. Damage to nuclear and mitochondrial DNA promotes the activation of the NLRP3 inflammasome [47,48], and in turn, NLRP3 activity can promote DNA damage. Intriguingly, the Licondro group found that the deficiency in NLRP3 reduced the overall amount of damage to DNA in cells due to inflammation [49]. Furthermore, the unfolded protein response and senescence are closely related; this feature promotes NLRP3 activation in the lung, leading to fibrosis [50]. It is currently unknown whether these factors directly induce IL-11 expression or whether it is induced secondary to inflammasome activation.

Given the possible relationship between NLRP3 inflammasome and SASP, this begs the question of whether there is a relationship between IL-11 and cellular senescence. Like age-induced senescent cell markers (p16 and p21), IL-11 expression increases in all tissues with age [51]. Further, the direct administration of IL-11 to fibroblasts increased p16 and p21 expression [51]. Supporting this evidence, IL-11-KO mice had longer lifespans compared to controls, and through this work by Widjaja and others, they have postulated that IL-11 could be a regulator of senescence [51,52]. Recent work by Chen et al. investigated the effect of cellular senescence on TGF-β and IL-11 pathways using the Bmi-1-KO mouse model. Bmi-1 plays a role in cellular senescence by inhibiting p16 and maintaining redox balance, while the Bmi-1-KO mouse demonstrates stress-induced premature senescence. IL-11 was increased in Bmi-1-KO, and this was decreased with the reactive oxygen species scavenger NAC by inhibiting the expression of p16. In addition, the inhibition of IL-11 led to decreased p16 expression, suggesting IL-11 plays a role in managing cellular senescence, likely through upregulation of the MEK/ERK signaling cascade [53].

These recent advances in fibrotic diseases and the study of SSc fibrosis have raised an interest in senolytics that specifically cause the death of senescent cells and in senomorphics, which interrupt the senescent signaling cascade. One such compound is dasatinib, a tyrosine kinase inhibitor, which, in conjunction with quercetin, demonstrated a reduction in senescent dermal fibroblasts in SSc [54,55]. However, to date, no studies have investigated the direct effects of senolytics on IL-11 expression. Further studies in senolytics have been performed in other fibrotic and age-related diseases that have an accumulation of senescent cells, with variable results and toxicity profiles [17]. Senolytics are being identified using artificial intelligence screening of existing therapeutics and could open the door to novel treatment strategies in the future, particularly in SSc [56].

2. Conclusions

In this review, we have outlined some important features of lung fibrosis that overlap and suggest a central mechanism relating to the NLRP3 inflammasome and IL-11. Our laboratory has shown that IL-11 may play an essential role in the process of fibrosis via caspase-1 activation [34]. However, one attractive hypothesis involving pulmonary fibrosis in individuals with SSc is that the NLRP3 inflammasome causes cellular senescence and independently induces IL-11 in SSc fibroblasts. Furthermore, a better understanding of the role of p53 and p21 expression in SSc [57] and their relationship to senescent fibroblasts found in this disease is warranted. Is senescence found in SSc fibroblasts dependent on the activation of the NLRP3 inflammasome, and can it be inhibited via caspase-1? The second hypothesis is that the NLRP3 inflammasome activates IL-11, and then this cytokine promotes cellular senescence. However, it is also possible that both are merely markers of a senescent phenotype induced by an unknown factor. Given that the NLRP3 inflammasome operates to maintain cellular homeostasis and is activated by several intra- and extra-cellular signals, it is critical to decipher how it regulates IL-11 and SASP in SSc pulmonary fibroblasts. Given the recent interest in IL-11, it has been postulated by others that targeting this cytokine could ameliorate age-related diseases [58–60]. Further teasing out these specific factors that upregulate mechanisms related to SSc fibrosis may be generalizable to a host of age-related fibrotic diseases.

Author Contributions

Writing—Original Draft Preparation, C.M.M.; Writing—Review & Editing, C.M.M., C.M.A.

Ethics Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Funding

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Denton CP, Khanna D. Systemic sclerosis. *Lancet* **2017**, *390*, 1685–1699. doi:10.1016/S0140-6736(17)30933-9.
2. Abraham DJ, Black CM, Denton CP, Distler JHW, Domsic R, Feghali-Bostwick C, et al. An international perspective on the future of systemic sclerosis research. *Nat. Rev. Rheumatol.* **2025**, *21*, 174–187. doi:10.1038/s41584-024-01217-2.
3. Wynn TA. Cellular and molecular mechanisms of fibrosis. *J. Pathol.* **2008**, *214*, 199–210. doi:10.1002/path.2277.
4. Jaeger VK, Tikly M, Xu D, Siegert E, Hachulla E, Airò P, et al. Racial differences in systemic sclerosis disease presentation: a European Scleroderma Trials and Research group study. *Rheumatology* **2020**, *59*, 1684–1694. doi:10.1093/rheumatology/kez486.
5. Tyndall AJ, Bannert B, Vonk M, Airò P, Cozzi F, Carreira PE, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann. Rheum. Dis.* **2010**, *69*, 1809–1815. doi:10.1136/ard.2009.114264.
6. Volkmann ER, Assassi S, Denton CP, Simonovska R, Sambevski S, Alves M, et al. Outcomes in Systemic Sclerosis-Associated Interstitial Lung Disease Based on Serological Profiles: Focus on Anti-Centromere and Anti-RNA Polymerase III Antibodies. *J. Rheumatol.* **2025**, *in press*. doi:10.3899/jrheum.2024-1063.
7. Hughes M, Bruni C, Cuomo G, Delle Sedie A, Gargani L, Gutierrez M, et al. The role of ultrasound in systemic sclerosis: On the cutting edge to foster clinical and research advancement. *J. Scleroderma Relat. Disord.* **2021**, *6*, 123–132. doi:10.1177/2397198320970394.
8. Distler O, Assassi S, Cottin V, Cutolo M, Danoff SK, Denton CP, et al. Predictors of progression in systemic sclerosis patients with interstitial lung disease. *Eur. Respir. J.* **2020**, *55*, 1902026. doi:10.1183/13993003.02026-2019.
9. Artlett CM, Sassi-Gaha S, Rieger JL, Boesteanu AC, Feghali-Bostwick CA, Katsikis PD. The inflammasome activating caspase 1 mediates fibrosis and myofibroblast differentiation in systemic sclerosis. *Arthritis. Rheum.* **2011**, *63*, 3563–3574. doi:10.1002/art.30568.
10. Schroder K, Tschopp J. The inflammasomes. *Cell* **2010**, *140*, 821–832. doi:10.1016/j.cell.2010.01.040.
11. Yu X, Lan P, Hou X, Han Q, Lu N, Li T, et al. HBV inhibits LPS-induced NLRP3 inflammasome activation and IL-1β production via suppressing the NF-κB pathway and ROS production. *J. Hepatol.* **2017**, *66*, 693–702. doi:10.1016/j.jhep.2016.12.018.
12. Artlett CM. Inflammasomes in wound healing and fibrosis. *J. Pathol.* **2013**, *229*, 157–167. doi:10.1002/path.4116.
13. Bulte D, Rigamonti C, Romano A, Mortellaro A. Inflammasomes: Mechanisms of Action and Involvement in Human Diseases. *Cells* **2023**, *12*, 1766. doi:10.3390/cells12131766.
14. Gritsenko A, Green JP, Brough D, Lopez-Castejon G. Mechanisms of NLRP3 priming in inflammaging and age related diseases. *Cytokine Growth. Factor. Rev.* **2020**, *55*, 15–25. doi:10.1016/j.cytogfr.2020.08.003.
15. Bauernfeind FG, Horvath G, Stutz A, Alnemri ES, MacDonald K, Speert D, et al. Cutting Edge: NF-κB Activating Pattern Recognition and Cytokine Receptors License NLRP3 Inflammasome Activation by Regulating NLRP3 Expression. *J. Immunol.* **2009**, *183*, 787–791. doi:10.4049/jimmunol.0901363.

16. Song N, Liu ZS, Xue W, Bai ZF, Wang QY, Dai J, et al. NLRP3 Phosphorylation Is an Essential Priming Event for Inflammasome Activation. *Mol. Cell.* **2017**, *68*, 185–197.e186. doi:10.1016/j.molcel.2017.08.017.

17. Lelarge V, Capelle R, Oger F, Mathieu T, Le Calve B. Senolytics: from pharmacological inhibitors to immunotherapies, a promising future for patients' treatment. *NPJ Aging.* **2024**, *10*, 12. doi:10.1038/s41514-024-00138-4.

18. Schmitz J, Owyang A, Oldham E, Song Y, Murphy E, McClanahan TK, et al. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. *Immunity* **2005**, *23*, 479–490. doi:10.1016/j.immuni.2005.09.015.

19. Keller M, Rüegg A, Werner S, Beer HD. Active caspase-1 is a regulator of unconventional protein secretion. *Cell* **2008**, *132*, 818–831. doi:10.1016/j.cell.2007.12.040.

20. Shao W, Yeretssian G, Doiron K, Hussain SN, Saleh M. The caspase-1 digestome identifies the glycolysis pathway as a target during infection and septic shock. *J. Biol. Chem.* **2007**, *282*, 36321–36329. doi:10.1074/jbc.M708182200.

21. Connolly LM, McFalls CM, McMahon IG, Bhat AM, Artlett CM. Caspase 1 Enhances Transport and Golgi Organization Protein 1 Expression to Promote Procollagen Export From the Endoplasmic Reticulum in Systemic Sclerosis Contributing to Fibrosis. *Arthritis. Rheum.* **2023**, *75*, 1831–1841. doi:10.1002/art.42535.

22. Gronberg C, Rattik S, Tran-Manh C, Zhou X, Rius Rigau A, Li YN, et al. Combined inhibition of IL-1, IL-33 and IL-36 signalling by targeting IL1RAP ameliorates skin and lung fibrosis in preclinical models of systemic sclerosis. *Ann. Rheum. Dis.* **2024**, *83*, 1156–1168. doi:10.1136/ard-2023-225158.

23. Kayagaki N, Warming S, Lamkanfi M, Vande Walle L, Louie S, Dong J, et al. Non-canonical inflammasome activation targets caspase-11. *Nature* **2011**, *479*, 117–121. doi:10.1038/nature10558.

24. Schmid-Burgk JL, Gaidt MM, Schmidt T, Ebert TS, Bartok E, Hornung V. Caspase-4 mediates non-canonical activation of the NLRP3 inflammasome in human myeloid cells. *Eur. J. Immunol.* **2015**, *45*, 2911–2917. doi:10.1002/eji.201545523.

25. Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. *Mol. Cell.* **2002**, *10*, 417–426. doi:10.1016/s1097-2765(02)00599-3.

26. Salskov-Iversen ML, Johansen C, Kragballe K, Iversen L. Caspase-5 expression is upregulated in lesional psoriatic skin. *J. Invest. Dermatol.* **2011**, *131*, 670–676. doi:10.1038/jid.2010.370.

27. Martínez-Godínez MA, Cruz-Domínguez MP, Jara LJ, Domínguez-López A, Jarillo-Luna RA, Vera-Lastra O, et al. Expression of NLRP3 inflammasome, cytokines and vascular mediators in the skin of systemic sclerosis patients. *Israel. Med. Assoc. J.* **2015**, *17*, 5–10.

28. Schafer S, Viswanathan S, Widjaja AA, Lim WW, Moreno-Moral A, DeLaughter DM, et al. IL-11 is a crucial determinant of cardiovascular fibrosis. *Nature* **2017**, *552*, 110–115. doi:10.1038/nature24676.

29. Ng B, Dong J, D'Agostino G, Viswanathan S, Widjaja AA, Lim WW, et al. Interleukin-11 is a therapeutic target in idiopathic pulmonary fibrosis. *Sci. Transl. Med.* **2019**, *11*, eaaw1237. doi:10.1126/scitranslmed.aaw1237.

30. Widjaja AA, Singh BK, Adami E, Viswanathan S, Dong J, D'Agostino GA, et al. Inhibiting Interleukin 11 Signaling Reduces Hepatocyte Death and Liver Fibrosis, Inflammation, and Steatosis in Mouse Models of Nonalcoholic Steatohepatitis. *Gastroenterology* **2019**, *157*, 777–792.e714. doi:10.1053/j.gastro.2019.05.002.

31. Allanki S, Strilic B, Scheinberger L, Onderwater YL, Marks A, Günther S, et al. Interleukin-11 signaling promotes cellular reprogramming and limits fibrotic scarring during tissue regeneration. *Sci. Adv.* **2021**, *7*, eabg6497. doi:10.1126/sciadv.abg6497.

32. Tan Y, Mosallanejad K, Zhang Q, O'Brien S, Clements M, Perper S, et al. IL11-mediated stromal cell activation may not be the master regulator of pro-fibrotic signaling downstream of TGFbeta. *Front. Immunol.* **2024**, *15*, 1293883. doi:10.3389/fimmu.2024.1293883.

33. Obana M, Maeda M, Takeda K, Hayama A, Mohri T, Yamashita T, et al. Therapeutic activation of signal transducer and activator of transcription 3 by interleukin-11 ameliorates cardiac fibrosis after myocardial infarction. *Circulation* **2010**, *121*, 684–691. doi:10.1161/circulationaha.109.893677.

34. McFalls CM, Connolly LM, Fustakgi AG, Artlett CM. IL-11 Expression in Systemic Sclerosis Is Dependent on Caspase-1 Activity but Does Not Increase Collagen Deposition. *Rheumato* **2024**, *4*, 163–175. doi.org/10.3390/rheumato4040013.

35. Cook SA. Understanding interleukin 11 as a disease gene and therapeutic target. *Biochem. J.* **2023**, *480*, 1987–2008. doi:10.1042/bcj20220160.

36. Steadman T, O'Reilly S. Elevated interleukin-11 in systemic sclerosis and role in disease pathogenesis. *J. Dermatol.* **2023**, *50*, 1255–1261. doi:10.1111/1346-8138.16854.

37. Lopes-Paciencia S, Saint-Germain E, Rowell MC, Ruiz AF, Kalegari P, Ferbeyre G. The senescence-associated secretory phenotype and its regulation. *Cytokine* **2019**, *117*, 15–22. doi:10.1016/j.cyto.2019.01.013.

38. Schafer MJ, White TA, Iijima K, Haak AJ, Ligresti G, Atkinson EJ, et al. Cellular senescence mediates fibrotic pulmonary disease. *Nat. Commun.* **2017**, *8*, 14532. doi:10.1038/ncomms14532.

39. DePianto DJ, Heiden JAV, Morshead KB, Sun KH, Modrusan Z, Teng G, et al. Molecular mapping of interstitial lung disease reveals a phenotypically distinct senescent basal epithelial cell population. *JCI Insight.* **2021**, *6*, e143626. doi:10.1172/jci.insight.143626.

40. Yang MM, Lee S, Neely J, Hinchcliff M, Wolters PJ, Sirota M. Gene expression meta-analysis reveals aging and cellular senescence signatures in scleroderma-associated interstitial lung disease. *Front. Immunol.* **2024**, *15*, 1326922. doi:10.3389/fimmu.2024.1326922.

41. Kizilay Mancini O, Acevedo M, Fazez N, Cuillerier A, Fernandez Ruiz A, Huynh DN, et al. Oxidative stress-induced senescence mediates inflammatory and fibrotic phenotypes in fibroblasts from systemic sclerosis patients. *Rheumatology* **2022**, *61*, 1265–1275. doi:10.1093/rheumatology/keab477.

42. Stout-Delgado HW, Cho SJ, Chu SG, Mitzel DN, Villalba J, El-Chemaly S, et al. Age-Dependent Susceptibility to Pulmonary Fibrosis Is Associated with NLRP3 Inflammasome Activation. *Am. J. Respir. Cell. Mol. Biol.* **2016**, *55*, 252–263. doi:10.1165/rcmb.2015-0222OC.

43. Feng J, Liu H, Jiang K, Gong X, Huang R, Zhou C, et al. Enhanced oxidative stress aggravates BLM-induced pulmonary fibrosis by promoting cellular senescence through enhancing NLRP3 activation. *Life Sci.* **2024**, *358*, 123128. doi:10.1016/j.lfs.2024.123128.

44. Artlett CM, Black CM, Briggs DC, Stevens CO, Welsh KI. Telomere reduction in scleroderma patients: a possible cause for chromosomal instability. *Br. J. Rheumatol.* **1996**, *35*, 732–737.

45. Artlett CM, Black CM, Briggs DC, Stephens C, Welsh KI. DNA allelic alterations within VNTR loci of scleroderma families. *Br. J. Rheumatol.* **1996**, *35*, 1216–1222.

46. Vijayraghavan S, Blouin T, McCollum J, Porcher L, Virard F, Zavadil J, et al. Widespread mutagenesis and chromosomal instability shape somatic genomes in systemic sclerosis. *Nat. Commun.* **2024**, *15*, 8889. doi:10.1038/s41467-024-53332-z.

47. Hasegawa T, Nakashima M, Suzuki Y. Nuclear DNA damage-triggered NLRP3 inflammasome activation promotes UVB-induced inflammatory responses in human keratinocytes. *Biochem. Biophys. Res. Commun.* **2016**, *477*, 329–335. doi:10.1016/j.bbrc.2016.06.106.

48. Shimada K, Crother TR, Karlin J, Dagvadorj J, Chiba N, Chen S, et al. Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. *Immunity* **2012**, *36*, 401–414. doi:10.1016/j.immuni.2012.01.009.

49. Licandro G, Ling Khor H, Beretta O, Lai J, Derks H, Laudisi F, et al. The NLRP3 inflammasome affects DNA damage responses after oxidative and genotoxic stress in dendritic cells. *Eur. J. Immunol.* **2013**, *43*, 2126–2137. doi:10.1002/eji.201242918.

50. Li Z, Jiao Y, Wu Z, Liu H, Li Y, Cai Y, et al. The role of quercetin in ameliorating bleomycin-induced pulmonary fibrosis: insights into autophagy and the SIRT1/AMPK signaling pathway. *Molec. Biol. Rep.* **2024**, *51*, 795. doi:10.1007/s11033-024-09752-7.

51. Widjaja AA, Lim WW, Viswanathan S, Chothani S, Corden B, Dasan CM, et al. Inhibition of IL-11 signalling extends mammalian healthspan and lifespan. *Nature* **2024**, *632*, 157–165. doi:10.1038/s41586-024-07701-9.

52. O'Loghlen A. IL-11 as a master regulator of ageing. *Nat. Rev. Molec. Cell. Biol.* **2024**, *25*, 956–956. doi:10.1038/s41580-024-00793-1.

53. Chen H, Chen H, Liang J, Gu X, Zhou J, Xie C, et al. TGF-beta1/IL-11/MEK/ERK signaling mediates senescence-associated pulmonary fibrosis in a stress-induced premature senescence model of Bmi-1 deficiency. *Exp. Mol. Med.* **2020**, *52*, 130–151. doi:10.1038/s12276-019-0371-7.

54. O'Reilly S. Senescence in diffuse systemic sclerosis is elevated and may play a role in fibrosis. *Clin. Exp. Immunol.* **2023**, *2019*, uxad077. doi:10.1093/cei/uxad077.

55. Martyanov V, Whitfield ML, Varga J. Senescence Signature in Skin Biopsies From Systemic Sclerosis Patients Treated With Senolytic Therapy: Potential Predictor of Clinical Response? *Arthritis Rheumatol.* **2019**, *71*, 1766–1767. doi:10.1002/art.40934.

56. Smer-Barreto V, Quintanilla A, Elliott RJR, Dawson JC, Sun J, Campa VM, et al. Discovery of senolytics using machine learning. *Nat. Commun.* **2023**, *14*, 3445. doi:10.1038/s41467-023-39120-1.

57. Yamamoto T, Nishioka K. Increased expression of p53 and p21 (Waf1/Cip1) in the lesional skin of bleomycin-induced scleroderma. *Arch. Dermatol. Res.* **2005**, *296*, 509–513. doi:10.1007/s00403-005-0550-3.

58. Ahmad O, Haris M. Inhibiting IL11: a novel approach to turning back the clock. *Imm. Ag.* **2024**, *21*, 71. doi:10.1186/s12979-024-00477-6.

59. Frangogiannis NG. Cardiac fibrosis: Cell biological mechanisms, molecular pathways and therapeutic opportunities. *Mol. Aspects Med.* **2019**, *65*, 70–99. doi:10.1016/j.mam.2018.07.001.

60. Zhou J, Chen H, Wang Q, Chen S, Wang R, Wang Z, et al. Sirt1 overexpression improves senescence-associated pulmonary fibrosis induced by vitamin D deficiency through downregulating IL-11 transcription. *Aging Cell* **2022**, *21*, e13680. doi:10.1111/acel.13680.