LEADING ARTICLE

Sirtuins and Cellular Senescence in Patients with Idiopathic Pulmonary Fibrosis and Systemic Autoimmune Disorders

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Abstract

The sirtuin family is a heterogeneous group of proteins that play a critical role in many cellular activities. Several degenerative diseases have recently been linked to aberrant sirtuin expression and activity because of the involvement of sirtuins in maintaining cell longevity and their putative antiaging function. Idiopathic pulmonary fibrosis and progressive pulmonary fibrosis associated with systemic autoimmune disorders are severe diseases characterized by premature and accelerated exhaustion and failure of alveolar type II cells combined with aberrant activation of fibroblast proliferative pathways leading to dramatic destruction of lung architecture. The mechanisms underlying alveolar type II cell exhaustion in these disorders are not fully understood. In this review, we have focused on the role of sirtuins in the pathogenesis of idiopathic and secondary pulmonary fibrosis and their potential as biomarkers in the diagnosis and management of fibrotic interstitial lung diseases.

1 Introduction

Chronic interstitial lung diseases (ILDs) are a heterogeneous group of disorders. They are a leading cause of morbidity and mortality in respiratory medicine. Idiopathic pulmonary fibrosis (IPF) is the most prevalent idiopathic interstitial lung disease and is more common in the elderly [1]. IPF has a median survival of 2–5 years and though currently available antifibrotic agents slow the decline in lung function [2, 3]. Several researches have shown that other interstitial lung disorders, such as connective tissue disease-related interstitial lung disorders (CTD-ILDs), fibrotic hypersensitivity pneumonitis (F-HP), sarcoidosis, and other less common diseases, can develop a progressive fibrotic phenotype, resulting in gradual functional, clinical, and radiographic decline [4]. Among the various systemic autoimmune diseases, systemic sclerosis (SSc), mixed connective tissue disease (MCTD), and inflammatory idiopathic myopathies are commonly associated with ILD, whereas the prevalence of pulmonary involvement is less common in other CTDs such as rheumatoid arthritis (RA),

Sjögren's syndrome (SS), and systemic lupus erythematosus (SLE) [5]. Despite the differences in prevalence and extent, the presence of ILD is often the leading cause of death in patients with systemic autoimmune disorders [6].

IPF and systemic autoimmune ILDs are now often considered ageing-related conditions similar to cardiovascular disease, cancer, and neurodegenerative diseases, although several differences in histopathology are well established. Common pathophysiological mechanisms have been proposed including epithelial and endothelial cell injury, inadequate epithelial repair, oxidative stress, coagulation abnormalities, immune dysregulation, and excessive transforming growth factor-β (TGF-β) activation, leading to excessive extracellular matrix (ECM) deposition by activated myofibroblasts, the hallmark of fibrosis [7, 8]. Alveolar type II cell (AEC2) senescence is emerging as an early hallmark in the pathogenesis of chronic progressive fibrotic lung disease. Cellular senescence is defined as the permanent arrest of cell growth in which cells exhibit features of the "ageing phenotype" including genomic instability, telomere shortening, epigenetic changes, abnormal proteostasis, mitochondrial dysfunction, and resistance to apoptosis signaling [9]. In IPF, it has been postulated that chronic exposure to risk factors (i.e., smoking, genetic factors, and gastroesophageal reflux disease) leads to alterations in the complex homeostasis of

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AEC2s and fibroblasts, resulting in loss of the reparative response and activation of fibrogenetic pathways. However, the interplay of oxidative stress, genomic instability, telomere attrition, aberrant inflammation, autophagy, and epigenetic alterations appears to promote a self-expanding reservoir of senescent cells, ultimately leading to epithelial–mesenchymal transition (EMT) [10–13].

In this review, we focus on a group of proteins, the sirtuins (SIRTs) and discuss their potential role in the pathogenesis of lung fibrosis. We also explore their potential as biomarkers in the diagnosis and monitoring of fibrotic interstitial lung diseases.

2 Role of SIRTs in Cellular Senescence

The family of proteins known as SIRTs comprises NAD$^+$-dependent deacetylases that are evolutionarily highly conserved across the eukaryotic, archaeal, eubacterial and, in particular, mammalian kingdoms. SIRTs are essential cellular mediators involved in various cellular activities, including cellular energy sensing, DNA repair, mitochondrial structure and metabolism modulation, telomere maintenance, inflammation, redox homeostasis, and cell death [14]. Due to their role in cellular longevity through telomere maintenance and DNA repair, a putative antiageing function has been proposed [14, 15].

A variety of degenerative, inflammatory, or proliferative disorders, including fibrosis and age-related degenerative diseases, obesity, diabetes, cancer, and neurological disorders, have been associated with altered sirtuin activity [16–18]. Based on their enzymatic activity SIRTs have been subdivided into the following classes: class I: SIRT1, SIRT2, and SIRT3 are NAD+-dependent robust deacetylases; class II: the ADP-ribosyltransferase SIRT4: class III: the deacetylase and NAD+-dependent demalonylase and desuccinylase SIRT5; and class IV: the deacetylases SIRT6 and SIRT7 [19, 20]. SIRT1, SIRT6, and SIRT7 are commonly referred to as nuclear sirtuins, SIRT3, SIRT4, and SIRT5 as mitochondrial sirtuins, and SIRT2 as cytosolic sirtuin [21–24] (Fig. 1).

SIRTs have been implicated in fibrosis in several organs. While SIRT1, SIRT3, SIRT6, and SIRT7 are known to play a protective role against the development and progression of pulmonary fibrosis, the modulatory functions of other SIRTs remain to be elucidated. Almost all the major signaling pathways activated during fibrosis are affected by SIRT activity, including the nuclear factor-κB (NF-κB), insulin-like growth

Fig. 1 Sirtuins: cellular location and molecular signaling pathways. *COL* collagen, *EMT* epithelial–mesenchymal transition, *FoxO3* Forkhead box O3, *LKB1* liver kinase B1, *OGG1* 8-oxoguanine glycosylase, *PPAR* peroxisome proliferators-activated receptor, *SASP* senescence-associated secretory phenotype, *α-SMA* α-smooth muscle actin, *SIRT* Sirtuine, *TGF-β1* transforming growth factor-β1

LOCALIZATION

Nucleus
SIRT-1
SIRT-2
SIRT-3
SIRT-6
SIRT-7

Nucleolus
SIRT-7

Mitochondrion
SIRT-3
SIRT-4
SIRT-5

FUNCTION

|	Enzymatic activity	Regulated pathways
SIRT-1	Deacetylase Deacylase	Metabolism, Mitochondrial biogenesis Cellular stress, Chromatin regulation
SIRT-2	Deacetylase Deacylase Demyristoylase ADP-rybosilase	Metabolism, Cell cycle, Cell differentiation
SIRT-3	Deacetylase Deacylase Decrotonylase	Metabolism, Mitochondrial biogenesis, Antioxidant activity
SIRT-4	Deacetylase Deacylase Lypoamidase ADP-rybosilase	Metabolism, Tumor suppression
SIRT-5	Deacetylase Deacylase Desuccinylase Demalonylase Deglutarylase	Metabolism
SIRT-6	Deacetylase Deacylase ADP-rybosilase	DNA repair, Metabolism, Inflammation.
SIRT-7	Deacetylase Deacylase	Ribosome biogenesis, Metabolism.

factor (IGF)/AKT, WNT/β-catenin, transforming growth factor (TGF)-β/Mothers against decapentaplegic homolog 3 (Smad3), Forkhead box O (FOXO), and p53 [25–28]. SIRT1 deacetylates FOXO3 and FOXO4, potentiating the FOXO-induced cell cycle arrest additionally [29, 30] SIRT1 removes acetyl groups from multiple sites on the p53 protein [31], reducing its activity and preventing cells from entering a senescent state triggered by oncogenes or stress. In addition, as histone deacetylases, SIRTs have been postulated to be key mediators of fibrosis pathways, including EMT and fibroblast proliferation and persistence, through epigenetic mechanisms [32].

3 Sirtuins in Idiopathic Pulmonary Fibrosis: Focus on Putative Molecular Mechanisms

The development of pulmonary fibrosis is the result of a complex interplay of genetic and environmental factors. In this scenario, SIRTs may be involved as potential key mediators in the development of fibrosis (Fig. 2).

3.1 Potential Mechanisms of Sirtuin-1 in the Pathogenesis of IPF

SIRT1 is involved in several cellular activities, including cell survival, senescence, oxidative homeostasis, DNA repair, inflammation, and autophagy. In addition, SIRT1 is a potent endogenous anti-fibrotic protein. In the nucleus, SIRT1 deacetylates multiple targets, including histone, FoxO3, p53, peroxisome proliferator-activated receptor γ (PPAR γ), PPAR α, and liver kinase B1 (LKB1) [33]. Regarding lung fibrosis, there are reports in literature showing that SIRT1 is reduced in bleomycin-induced lung fibrosis. Recently, Deskata et al. investigated the levels of SIRT1 in plasma, peripheral blood mononuclear cells (PBMCs), and the supernatant from the culture of PBMCs in patients with IPF and healthy controls. They showed that SIRT1 levels were statistically significantly lower in the supernatant of PBMCs from patients with IPF compared with those from controls. Furthermore, the likelihood of being in the IPF group was increased by older age and lower SIRT1 levels [34]. Notably, the activation or overexpression of SIRT1 by resveratrol treatment attenuates the TGF-β1-induced myofibroblast
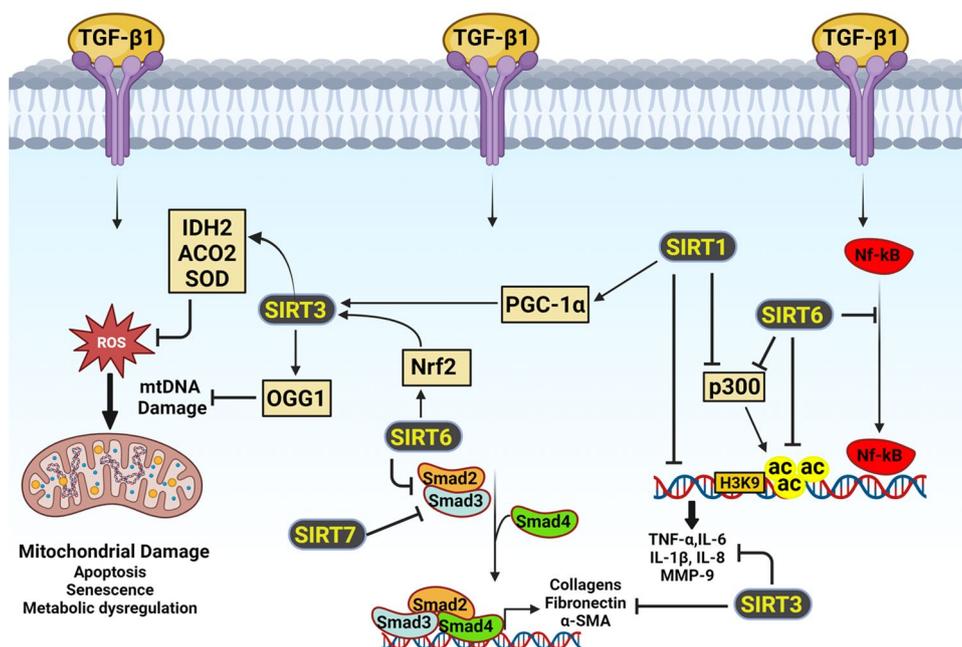
Fig. 2 Fibrogenic signaling and sirtuins. Upon binding to its cell surface receptors, TGF-β1 triggers numerous pathways, with Smad signaling emerging as a prominent driver of transcriptional upregulation of fibrogenic factors. Meanwhile, activation of the NF-κB pathway induces the expression of proinflammatory genes, while inflammation-induced intracellular and mitochondrial reactive oxygen species (ROS) inflict substantial damage to mitochondrial DNA (mtDNA). SIRT1 intervenes by inhibiting NF-κB activation and subsequent transcriptional activity through the inhibition of p300 histone acetyltransferase-mediated chromatin activation for transcription. Additionally, SIRT1 boosts the cellular NAD$^+$/NADH ratio, promoting

SIRT3 transcription via PGC-1α. SIRT6, on the other hand, impedes Smad phosphorylation and Smad signaling, thereby dampening fibrogenic gene expression. It also facilitates SIRT3 transcription via the Nrf2-dependent pathway and inhibits profibrotic gene transcription through the deacetylation of histone 3 lysine 9 (H3K9). SIRT3 shields mtDNA from damage by deacetylating OGG1, thereby stabilizing it. Furthermore, SIRT3 preserves the function of isocitrate dehydrogenase 2 (IDH2), mitochondrial aconitase (ACO2), and manganese super oxide dismutase (MnSOD) to mitigate lung fibrosis. Finally, SIRT7 curtails Smad3 expression and extracellular matrix production

activation by regulating the expression of p300 [35]. In addition, SIRT1 suppresses the expression of senescence-associated secretory phenotype (SASP) factors through histone deacetylation in their promoter regions, resulting in an antifibrotic effect [36]. Lian et al. found decreased levels of the zinc transporter SLC39A8 (ZIP8) in IPF AEC2s, resulting in impaired renewal capacity dependent on the sirtuin SIRT1. Zinc treatment increased both SIRT1 expression and the renewal capacity of AEC2s [37].

3.2 Potential Mechanisms of Sirtuin-3 in the Pathogenesis of IPF

SIRTs, particularly SIRT3, are also associated with mitochondrial dysfunction, altered NAD$^+$/NADPH ratio, and increased reactive oxygen species (ROS) [38]. Increased expression of NADPH oxidase 4 (NOX4) has been reported in the lungs of patients with IPF, which may be key to modulating profibrotic signaling [39]. The NOX4 enzyme promotes the death of AEC2s and impairs mitochondrial function, increasing the production of mitochondrial ROS. This stimulates fibroblast-myofibroblast differentiation. NOX4 stimulates myofibroblast migration and differentiation through a signaling pathway upstream of TGF-β1 via ALK5/Smad3 [40].

Conversely, SIRT3 expression may play a role in counterbalancing the effects of NOX4, but SIRT3 is deficient AEC from patients with IPF [41]. It has been reported that the reduction in SIRT3 observed in ageing leads to increased mitochondrial ROS levels and mitochondrial DNA (mtDNA) damage [42, 43]. SIRT3 expression was found to be significantly downregulated in isolated fibroblasts from lung explants of IPF human subjects as compared with control fibroblasts [44]. Furthermore, mice that are deficient in SIRT3 are more susceptible to asbestos- and bleomycin-induced lung fibrosis [43]. SIRT3 deficiency would lead to inactivation of manganese superoxide dismutase (MnSOD) at lysine residue K68, a target of SIRT3 deacetylase that contributes to mitochondrial integrity. Therefore, reduced levels of SIRT3 would significantly contribute to the development of IPF by promoting acetylation of MnSOD and 8-oxoguanine DNA glycosylase-1 (OGG1) in AEC2, resulting in mtDNA damage and apoptosis in AEC2 [42] and induction of TGF-β1 expression. TGF-β1 is a potent inducer of fibrosis and plays a central role in promoting the transformation of fibroblasts into myofibroblasts. In addition, SIRT3 deficiency results in hyperacetylation of glycogen synthase kinase 3β (GSK3β) at residue K15 [45]. This hyperacetylation negatively regulates GSK3β activity. Reduced GSK3β activity leads to decreased phosphorylation of its substrates, such as Smad3 and β-catenin.

Conversely, studies have demonstrated that increased expression of SIRT3 mitigates pulmonary fibrosis by diminishing mitochondrial DNA (mtDNA) damage and enhancing the recruitment of fibrotic monocytes into the lungs [41]. In aged mice with bleomycin lung injury, restoration of SIRT3 via a cDNA overexpression plasmid significantly reduced lung fibrosis by attenuating myofibroblast differentiation [44]. It has been suggested that SIRT3 modulates mtDNA damage by modulating acetylation of OGG1 [46]. Additionally, SIRT3 regulates the transition of fibroblasts into myofibroblasts by inhibiting the profibrotic TGF-β1 signaling pathway through deacetylation-dependent activation of GSK3β [45]. Elevated levels of SIRT3 lead to a reduction in Smad3 levels, thereby dampening the effects of TGF-β1 [47].

3.3 Potential Mechanisms of Sirtuin-6 in the Pathogenesis of IPF

SIRT6 is another key modulator of fibrosis, blocking IGF/AKT, NF-κB, Wnt/β-catenin, and TGFβ/Smad3 signaling [27, 48, 49]. Overexpression of SIRT6 was found to prevent the TGF-β1-induced epithelial-to-mesenchymal transition-like phenotype [28]. Another study on the role of SIRT6 in human bronchial epithelial cells found that TGF-β-induced senescence was associated with increased p21 expression and IL-1β secretion, which in turn triggered cellular transdifferentiation to myofibroblasts; however, SIRT6 overexpression prevented the development of profibrotic senescence via proteasomal degradation of p21 and depletion of IL-1β [50]. In addition, SIRT6 indirectly regulates the expression of the mitochondrial sirtuin (SIRT3) by controlling Nrf2 activity [51].

3.4 Potential Mechanisms of Sirtuin-7 in the Pathogenesis of IPF

Finally, another mechanism in the progression of IPF involves Smad3 signaling [52]. The antifibrotic effect of SIRT7 is partly due to a decrease in Smad3 levels. Overexpression of SIRT7 in lung fibroblasts reduces COL1A1, COL1A2, and COL3A1 levels, thereby exerting an antifibrotic effect. Furthermore, SIRT7 overexpression attenuates the TGF-β-induced increase in collagen and α-smooth muscle actin mRNA and protein levels. These observations suggest that SIRT7 protects against fibrosis in adult human lung fibroblasts and supports the antifibrotic effects of SIRT1 and SIRT3. A significant reduction in SIRT7 expression was observed in the nucleus of lung fibroblasts from patients with IPF compared with healthy controls [53].

In conclusion, while some studies have shown an important role for SIRT1, SIRT3, SIRT6, and SIRT7 in the development and progression of lung fibrosis, the role of SIRT2, SIRT4, and SIRT5 needs to be further investigated [54].

4 Preclinical and Clinical Studies of SIRTs Pathways in Connective Tissue Disorders

Connective tissue diseases (CTDs) are a heterogeneous group of disorders characterized by a high mortality and morbidity burden and a huge impact on healthcare systems worldwide. With their pleiotropic functions, SIRTs have recently attracted increasing interest due to their significant role in the pathogenesis of CTDs and their potential involvement in future therapeutic perspectives (Table 1) [55].

4.1 Systemic Sclerosis

Systemic sclerosis (SSc) is a severe immune-mediated disease characterized by premature activation of the molecular mechanisms of ageing. This leads to fibrosis of the skin and internal organs and vasculopathy. While the accumulation of extracellular matrix components within the affected organs is considered the pathological hallmark, the alteration of both innate and adaptive immune responses to microvascular endothelial injury is a critical event for the development of systemic sclerosis [56–58]. In addition to their central role in ageing and cellular senescence, SIRTs may also play an important role in several pathways involved in fibrosis. In a cohort of ten patients with diffuse cutaneous SSc (dcSSc), significantly lower SIRT1 levels were found in SSc skin biopsies compared with five healthy controls [59]. To explore the underlying mechanisms, Wei et al. incubated explanted normal dermal fibroblasts with TGF-β or platelet-derived growth factor (PDGF) for 24–96 h. They found a 33% reduction in SIRT1 mRNA ($P < 0.05$) [59]. A similar result was obtained when fibroblasts were exposed to prolonged hypoxia (1.5% O_2 for 24 h) or H_2O_2, resulting in a significant downregulation of SIRT1 protein ($P < 0.005$).

The relevant role of SIRT1 in fibrotic changes is supported by the ability of resveratrol to significantly inhibit the effects induced by TGF-β. Interestingly, in SIRT$^{-/-}$ mice, embryonic fibroblasts showed resistance to the effect of resveratrol when incubated with TGF-β [60]. In this regard, the authors proposed epigenetic changes involving the p300 acetyltransferase and the Smad pathway as exploitable pathways [59]. It has been reported that the levels of SIRT3, similar to SIRT1, are reduced in the fibrotic area within the dermis of patients with SSc. In contrast, ectopic expression of SIRT3 in normal lung fibroblasts was sufficient to suppress the TGF-β-induced stimulation of collagen synthesis [61].

SSc is also associated with major systemic complications, although it is divided into three subgroups according to cutaneous involvement (diffuse cutaneous, limited cutaneous and sine scleroderma). Tissues potentially affected include the lungs, heart, and kidneys. Interstitial lung abnormalities are present in more than 80% of patients with SSc, with 25% of these showing a progressive pattern [62]. Significantly lower levels of mRNA transcript for SIRT1 in PBMCs have been observed in patients with SSc with pulmonary involvement compared with patients with SSc without pulmonary involvement ($P < 0.0006$) [60]. Conversely, in a mouse model of bleomycin-induced pulmonary fibrosis, activation of SIRT1 by pretreatment with resveratrol significantly improved profibrotic changes such as collagen accumulation and disruption of alveolar units [60].

According to Manetti et al., patients with SSc had significantly lower serum levels of SIRT1 and SIRT3 than controls [63]. In particular, the reduction in circulating SIRT1 and SIRT3 in patients with SSc was associated with a greater extent of cutaneous fibrosis, the presence of lung fibrosis on high-resolution computed tomography of the chest, and worse lung function. Wyman et al. also found a significant decrease in SIRT7 expression in lung fibroblasts from patients with SSc–ILD [53].

Pulmonary arterial hypertension (PAH) is a severe complication in patients with SSc and is more common in patients with limited cutaneous systemic sclerosis. Interestingly, reduced expression of SIRTs may play a role, although in a yet unidentified way. SIRT3 mRNA levels have been shown to be reduced in human pulmonary arterial smooth muscle cells from patients with idiopathic PAH. This decrease inhibits mitochondrial-dependent apoptosis and activates proliferative transcription factors that promote vascular remodeling and PAH development. There is an urgent need to elucidate the role of SIRTs in CTD-related pulmonary hypertension is urgently needed.

4.2 Other Connective Tissue Disorders

Rheumatoid arthritis (RA) is a common chronic autoimmune disease with a global prevalence of 0.4–1.3% [64]. It is characterized by an inflammatory infiltration of the synovial membrane with subsequent hyperplasia and destruction of cartilage and bone. Although the presence of rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPA) is the first step in the development of RA, dysfunction of innate and adaptive immune cells is required for the transition from asymptomatic autoimmunity to tissue inflammation [65].

The role of SIRTs in RA remains controversial. While some studies have shown that SIRTs are downregulated in RA, others failed to show this [66, 67]. However, recent evidence has highlighted the potential role of SIRTs in the pathogenesis of RA. As shown by Park et al., resveratrol (0–50 μM), which, as noted, is a pharmacological activator of SIRT1, significantly reduced the adhesion of RA synovial fluid monocytes (RAMCs) incubated with phorbol 12-myristate 13-acetate (PMA), a monocyte activator, in a concentration-dependent manner. Similarly, pretreatment

Table 1 SIRTs in systemic autoimmune disorders: main clinical and preclinical studies

Authors (years) [Reference]	Population	Study aims	Marker	Main results
Wei et al. (2015) [59]	SSc $n = 10$	Expression of SIRTs in SSc	SIRTs	↓ SIRT-1 mRNA in skin biopsy samples
		SIRT-1 effects on fibrotic responses in vitro and in vivo		No significant difference mRNA levels for SIRT2 through SIRT6
				↑ SIRT-7 level
				Expression of SIRT-1 mRNA negatively correlated with MRSS
				Resveratrol markedly attenuated TGFβ induced alteration through SIRT-1
				Resveratrol mitigated the activated phenotype of SSc fibroblasts
Akamata et al. (2016) [61]	SSc $n = 29$ Murine models	Expression and activity of SIRT-3 in skin and lung biopsies	SIRT-3	SIRT-3 expression and function are decreased in SSc and in fibrotic tissues in the mouse
				SIRT3 negatively regulates fibrotic responses
				Hexafluoro ameliorates experimentally-induced organ fibrosis in mouse through SIRT3 activation
Chu et al. (2018) [60]	SSc–PF $n = 145$ Murine models	SIRT1 function and its links to proinflammatory and profibrotic pathways in SSc-related lung fibrosis in clinical samples, in vitro and in vivo, and in a model of bleomycin-induced pulmonary fibrosis	SIRT-1	SIRT-1 mRNA decreased in PBMCs of patients with SSc with PF
				SIRT-1 activation attenuates pulmonary fibrosis in bleomycin-treated mice
				SIRT-1 activation attenuates pulmonary inflammation in bleomycin-treated mice
				SIRT-1 represses TNF-α and NF-κB induced inflammation
Li et al. (2021) [66]	RA $n = 141$	Clinical value of SIRT-1 in diagnosis of RA	SIRT1	↑ Serum SIRT-1 compared with controls
				Cutoff value 49 ng/mLAUC 0.87Specificity 97%Sensitivity 70.9%
				Combined SIRT-1 and anti-CCP measurement have superior Youden index
Li et al. (2018) [67]	RA $n = 12$	Role of SIRT-1 in RA-FLS	SIRT1	↓ SIRT-1 in synovial tissue and RA-FLS
				↓ RA-FLS proliferation
				↓ proinflammatory cytokine secretion
				↓ NF-κB family proteins
				↑ RA-FLS apoptosis
Park et al. (2016) [68]	RA $n = 9$	SIRT-1 effect on differentiation of monocytes into macrophages	SIRT-1	↓ monocyte to macrophage differentiation
				↓ PU.1 phosphorylation
				↓ NF-κB during monocyte differentiation
Hussain et al. (2021) [72]	RA $n = 306$	Expression and epigenetic variations of mitochondrial SIRTs	mSIRTs	↓ SIRT-3; SIRT-4; SIRT-5
				↓ histone deacetylation compared with controls
Hisada et al. (2022) [77]	SLE $n = 6$ Murine models	SIRT-2 role in the pathogenesis of SLE	SIRT-2	↓ IL-2 production by CD4$^+$ T cells via deacetylation of c-Jun and the Il-2 promoter
				Induction of Th17-cell differentiation
				Deacetylation of p70S6K and regulation of the mTORC1/HIF-1α/ RORγt pathway in Th17 cells
Olivares et al. (2018) [78]	SLE–LN	SIRT-1 as biomarker of disease activity in LN	SIRT-1	↑ SIRT-1 mRNA in pts with active LN
				↑ SIRT-1 expression in proliferative forms of LN
Yang et al. (2022) [79]	SLE $n = 89$	SIRT-1 levels in SLE pts	SIRT-1	↑ SIRT-1 levels compared with controls
				SIRT-1 plasma concentration significantly associated with disease activity (cutoff value 4.323 ng/ml, AUC 0.985, specificity 61.43%, sensitivity 95.51%)

FLS fibroblast-like synoviocytes, *LN* lupus nephritis, *MRSS* modified Rodnan skin score, *PBMCs* peripheral blood mononuclear cells, *PF* pulmonary fibrosis, *RA* rheumatoid arthritis, *SSc* systemic sclerosis, *TGFβ* transforming growth factor beta

with resveratrol significantly reduced NF-κB acetylation (0.83 ± 0.08-fold, $P < 0.01$) as well as NF-κB binding activity (1.57 ± 0.16-fold, $P < 0.01$) in RAMCs exposed to PMA. Furthermore, PMA-induced elevated levels of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 were significantly reduced by pretreatment with resveratrol (50 μM). Interestingly, pretreatment with sirtinol, a SIRT1 inhibitor (20 μM), antagonized these suppressive effects of resveratrol [68].

Type B synoviocytes, called fibroblast-like synoviocytes (FLS), are a particular type of mesenchymal cells lining the synovium. FLS are critical for synovial homeostasis through the production of lubricin, whose function is to lubricate the synovium. Some unique surface markers expressed by FLS include CD55, vascular cell adhesion molecule 1 (VCAM-1), integrins and their receptors [69]. Interestingly, FLS also plays a prominent role in the pathogenesis of RA [69]. This includes cytokine production, synovial hyperplasia, chondrocyte activation, and cartilage and bone destruction. Inhibiting the proliferation of FLS by promoting their apoptosis may be a mechanism for slowing the progression of RA. In this context, SIRT1 has been shown to induce the apoptosis of FLS via the caspase-3 and PI3K/Akt pathways and has emerged as a promising therapeutic target in RA. Conversely, it reduces inflammation and osteoblast apoptosis by downregulating NF-kB signaling and deacetylating p53 [70].

As mentioned above, in the SIRT family, SIRT3, SIRT4, and SIRT5 possess an N-terminal sequence that directs their translocation to the mitochondria. A significant downregulation of all mitochondrial SIRTs has been reported in RA patients [71, 72]. A negative correlation between oxidative stress and the expression levels of mitochondrial SIRTs has also been reported [72]. In a mouse model, when animals with RA were treated with methotrexate and a high dose of adenovirus-SIRT5, there was significant suppression of the proinflammatory cytokines monocyte chemoattractant protein-1, TNF-α, IL-1β, and IL-6, as well as a reduction in erythrocyte sedimentation rate and serum C-reactive protein levels, highlighting the potential anti-inflammatory role of SIRTs in the treatment of RA [68]. The lung compartment is the most common extra-articular site involved in RA with various potential clinical manifestations, including ILD, pleural effusion, cricoarytenoiditis, bronchiectasis, and pulmonary hypertension [73]. Despite the growing interest in SIRTs in the pathogenesis, diagnosis and treatment of RA, a comprehensive understanding of the role of SIRTs in the pulmonary involvement of RA patients is still lacking. Studies in this area are urgently needed.

Systemic lupus erythematosus (SLE) is an extremely heterogeneous autoimmune disease characterized by a complex interplay of genetic predisposition, environmental triggers, and an impairment of the innate and adaptive immune systems resulting in a widespread tissue inflammation [74]. Recently, there has been increasing interest in epigenetic modifications, such as DNA hypomethylation, DNA methylation, histone modification, and noncoding RNA modification, in the maintenance of immune dysfunction in SLE pathogenesis.

Histone deacetylases (HDACs) regulate protein function and stability by deacetylating or promoting histone modifications or DNA methylation [75]. As class III HDACs, SIRTs are central to several complex molecular mechanisms, such as the development and differentiation of the innate and adaptive immune systems [76].

The role of SIRTs in SLE is controversial. Hisada et al. reported that SIRT2 primarily drives Th17 differentiation rather than the other Th1, Th2, or T-reg cells. Levels of Th17 cells are elevated in patients with SLE, leading to a significant increase in inflammatory cytokines that can recruit inflammatory cells and promote tissue damage. In this context, SIRT2 inhibitors have been shown to suppress IL-17A while promoting IL-2 production, thereby facilitating lupus-like disease [77]. Similarly, SIRT1 levels, both mRNA and protein expression, correlated significantly with anti-dsDNA levels ($r = 0.599$, $P = 0.01$ and $r = 0.483$, $P = 0.04$, respectively) in a cohort of 40 patients with SLE [78]. In addition, urinary levels of SIRT1 mRNA have been shown to significantly discriminate not only between patients with SLE with and without lupus nephritis [area under the curve (AUC) 0.845, $P < 0.0001$] but also the severity (active or remission) of lupus nephritis [AUC 0.732 (0.66–0.88, $P = 0.007$) [78].

Consistent with these data, Yang et al. showed that SIRT1 plasma levels were significantly elevated in patients with SLE compared with healthy controls [6.28 (5.89–6.68) versus 2.42 (2.10–2.74) ng/mL, $P < 0.001$). Furthermore, SIRT1 plasma levels can help clinicians differentiate SLE from patients without SLE with a sensitivity and specificity of 95.51% and 61.43%, respectively, at an optimal cut-off of 4.323 ng/mL [79]. Interestingly, SIRT1-null mice develop an autoimmune disease similar to SLE, with an accumulation of immune complexes in the liver and kidneys [80]. Gan et al. demonstrated that B cell downregulation of SIRT1 can promote class-switched and hypermutated T-dependent and T-independent antibody responses and autoantibody generation [81].

Interestingly, resveratrol was protective against pristane-induced lupus in mice, reducing proteinuria, renal immunoglobulin deposition, and serum IgG1 and IgG2 [82]. Studies are needed to elucidate the potential effects of resveratrol in human SLE.

5 Therapeutic Perspective for Sirtuins Modulation in Pulmonary Fibrosis

HDACs represent novel therapeutic targets for controlling or reversing the major dysfunctional events leading to IPF [83]. Efforts to develop modulators have focused particularly on SIRT1 and SIRT2. Early compounds showed limited potency and poor selectivity for SIRT1 [84]. For example, resveratrol was the first activator identified and can simultaneously stimulate a number of SIRTs other than SIRT1 [32, 85]. Using rats with bleomycin-induced pulmonary fibrosis, Qian et al. showed that astragaloside IV (AS-IV), a compound extracted from astragalus root, attenuated pulmonary fibrosis by inhibiting TGF-β1-dependent EMT. In another study using A549 cells, a human adenocarcinoma cell line with type II alveolar epithelial characteristics, Andrographolide (Andro), a diterpenoid derived from *Andrographis panicola* (Chinese alfalfa), activates the antioxidant stress pathway SIRT1/FOXO3, resulting in increased expression of superoxide dismutase 2 (SOD2) and inhibits EMT by decreasing phosphorylation of extracellular protein signal-regulated kinase (ERK) 1/2 [86].

Other molecules that have been proposed to target SIRT1 include YK-3-237, a combretastatin analogue that deacetylates both mutant p53 and wild-type p53 and SRT1720, a potent synthetic SIRT1 stimulator that is structurally independent of resveratrol [87, 88]. Similar to resveratrol treatment and SIRT1 overexpression, SRT1720 induces mitochondrial biogenesis when used for prolonged periods. Carbazole compounds also seem promising. In fact, carbazole-3-carbohydrazide activates Sirt3 and reduces intracellular ROS levels [89].

Furthermore, certain compounds serve to activate SIRT3. Metformin is able to increase the expression of SIRT3 [90]. Melatonin is another interesting compound that acts as an agonist of SIRT3. Mechanistically, melatonin enhances SIRT3 expression by activating the PI3K/Akt-PGC-1α signaling pathway and inhibition of the melatonin receptor (MT)-1 blocks melatonin-induced SIRT3 expression [91]. Additionally, melatonin promotes SIRT3 expression by inhibiting mammalian sterile 20-like kinase 1 phosphorylation [92]. Activated 5′AMP-activated protein kinase has also been shown to be involved in the SIRT3 activity activated by melatonin [93]. Moreover, 7-hydroxy-3-(4′-methoxyphenyl) coumarin (C12) has been identified as a new type of SIRT3 agonist. C12 forms a complex with SIRT3 and MnSOD acetylated at Lys68, leading to SIRT3 activation and subsequent deacetylation and activation of the downstream molecule MnSOD [94]. Notably, C12 exhibits high specificity and affinity for SIRT3, making it the closest known positive regulator of SIRT3 to date.

As these compounds have potential in the field of pulmonary fibrosis, their integration with currently available treatments for pulmonary fibrosis would provide a broad range of strategies to limit the underlying fibrogenetic mechanism.

6 Conclusions

SIRTs are currently being considered with increasing interest as a potential tool for the treatment of fibrotic interstitial lung diseases, as they are key cellular mediators of ageing and fibrosis. Preclinical and clinical data have begun to suggest a role for the SIRT family in the pathogenesis of pulmonary fibrosis and CTD with or without ILD. However, more extensive studies are needed to better understand the potential role of SIRTs in the therapeutic scenario of these diseases.

Declarations

Conflicts of interest The authors declare no conflict of interest.

Availability of data and materials Not applicable.

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Author contributions V.D.'A., A.B., and F.P.: conceptualization, supervision, writing—original draft, and writing—review and editing. D.F.M., R.P., M.S.F., A.S., F.S., and G.S.: systematic clinical review of the literature and writing—review and editing. M.G.M. and M.C.: validation and writing—review and editing.

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