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Review

Aging hearts, fibrotic fears: The sirtuin connection

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ABSTRACT

Sirtuins are NAD⁺-dependent enzymes involved in metabolic regulation, aging, oxidative stress response, and inflammation, all of which are pivotal in the development of myocardial fibrosis. SIRT1, SIRT3, and SIRT6 are shown to exert protective effects by inhibiting fibroblast activation and reducing oxidative and inflammatory damage, while SIRT4 may promote fibrosis depending on context. This review article explores the multifaceted role of sirtuins (SIRT1–SIRT7) in cardiac fibrosis, a key pathological feature of heart failure characterized by excessive extracellular matrix accumulation. The article sheds light on the regulatory influence of non-coding RNAs and histone modifications on sirtuin expression, and illustrates the complex feedback between sirtuins and mitochondrial homeostasis, AMPK activation, and endothelial-to-mesenchymal transition (EndoMT). This review positions sirtuins as both markers and potential therapeutic targets for cardiac fibrosis, acknowledging their dual roles and context-specific effects. Herein, we highlight the importance of understanding the complex regulatory networks involving sirtuins to inform future anti-fibrotic interventions.

1. Introduction

Sirtuins, a NAD^+ -dependent enzyme with deacetylase, deacylase, and ADP-ribosyl transferase activities, play a crucial role in regulating cellular processes related to metabolic homeostasis, genome stability, stress response, and the control of cellular aging. The sirtuin family comprises seven members (SIRT1–SIRT7), which, despite their differences, share a common structure and consist of: a Zn^{2+} binding module, a helical module, an NAD+ binding module, and a regulatory domain [1]. The structure of sirtuins renders them dependent on NAD+ , one of the most crucial energy carriers and a key player in the pathophysiology of age-related diseases. However, this unique ability to sense changes in the level of NAD+ , a molecule that serves as a key indicator of the cell's metabolic state, enables sirtuins to act as molecular 'sensors' of energy, integrating metabolic signals with the cellular response [2,3].

In recent years, the role of sirtuins in the pathogenesis of cardiovascular disease, including myocardial fibrosis processes, has attracted particular scientific attention [4]. Myocardial fibrosis, defined by an excessive buildup of extracellular matrix (ECM) within cardiac tissue, plays a key role in driving progressive cardiac dysfunction, increased chamber wall stiffness, and ultimately heart failure [5-7]. This process results from a complex interaction between myocardial cells (cardiomyocytes), fibroblasts, immune cells, and ECM components, and its regulation involves multiple signaling pathways and transcription factors [8].

Significant progress has shed light on the molecular basis of fibrosis, yet the role of sirtuins in this context remains only partly understood. Previous studies suggest that sirtuins, particularly SIRT1, SIRT3, and SIRT6, may protect fibroblast activation, reduce oxidative stress (OS), and modulate signaling pathways involved in ECM production and degradation [9]. However, their effect on fibrotic processes appears to depend on the metabolic context, tissue type, and stage of the disease,

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making it difficult to clearly define their role. Furthermore, increasing evidence suggests that sirtuins may interact with key factors, such as TGF-β, NF-κB, or p53, which play a central role in regulating the fibrotic response [8,10,11]. In the context of the heart, sirtuins may also affect mitochondrial function, DNA stability, and autophagy processes, further complicating their involvement in the pathogenesis of fibrosis [9].

This review aims to provide a comprehensive overview of current knowledge on the role of sirtuins in myocardial fibrosis. The basic mechanisms of action of sirtuins are outlined in individual sections, with a particular focus on their dependence on angiotensin (one of the main triggers of aging-related fibrosis and an accelerator of this process). This is followed by an analysis of their involvement in regulating key signaling pathways associated with fibrosis, including the TGF-β/Smad pathway, NF-κB, p53, and reactive oxygen species (ROS)-dependent pathways.

2. Nad+ and sirtuin-mediated regulation of cardiac fibrosis

Nicotinamide adenine dinucleotide (NAD+) plays a crucial role in metabolic processes and signaling regulation, and reduced levels have been associated with the development of cardiac fibrosis and other pathologies [12]. Research indicates that maintaining the intracellular NAD+ pool through the administration of its precursors, such as nicotinamide (NAM) or nicotinamide mononucleotide (NMN), may represent a promising therapeutic strategy [12]. In a model of agonist-induced cardiac hypertrophy, the loss of NAD+ leads to the activation of pro-hypertrophic Akt1-mTOR signaling, whereas exogenous NAD+ activates the LKB1-AMPK pathway *via* SIRT3-dependent deacetylation, inhibiting protein synthesis and hypertrophy [13]. Moreover, research on atrial fibrosis has shown that atrial fibroblasts display heightened sensitivity to TGF-β1 compared with ventricular fibroblasts, which is linked to enhanced reactive oxygen species (ROS) generation via Nox4 [14]. Interestingly, the NAD+ precursor nicotinamide (NAM) improved diastolic dysfunction in HFpEF models, partly by reducing cardiomyocyte stiffness *via* titin deacetylation and improving calcium homeostasis [15]. This mechanism appears to be universal, as in another HFpEF model, NAD^+ deficiency and SIRT3 downregulation resulted in hyperacetylation of mitochondrial proteins and impaired mitochondrial function, both of which were restored by nicotinamide riboside (NR) supplementation [16]. A direct impact on myocardial fibrosis was demonstrated for NMN, which, in an isoproterenol (ISO)-induced fibrosis model, inhibited fibroblast activation, OS, and Smad3 acetylation in an NAD+ /SIRT1-dependent manner [17]. Paradoxically, although NAD+ and its precursors exhibit potent anti-fibrotic effects, their efficacy depends on the pathological context and the dominant signaling pathway. While SIRT3 plays a key role in hypertrophy [13], SIRT1 is essential for inhibiting fibrosis [17]. Why then is elevating NAD+ levels effective in such diverse models? The answer may lie in its fundamental role as a coenzyme for sirtuins, which integrate the cell's metabolic state with the transcriptional response and mitochondrial health [18,19].

3. Angiotensin Ii in cardiac fibrosis

Dysregulation of the renin-angiotensin-aldosterone system (RAAS) is a fundamental initiator of myocardial fibrosis. Angiotensin II (Ang II), acting through its type 1 receptor (AT1R), promotes the expression of TGF-β ligands and activates the canonical Smad2/3 signaling pathway, a key driver of fibroblast transdifferentiation and extracellular matrix (ECM) synthesis [20]. In addition, Ang II stimulates several non-canonical, Smad-independent pathways, including the ERK1/2 (extracellular signal-regulated kinases), JNK (c-Jun N-terminal kinase), and p38 MAPK cascades, all of which converge on the expression of profibrotic genes. Ang II also activates the PI3K/Akt and RhoA/ROCK

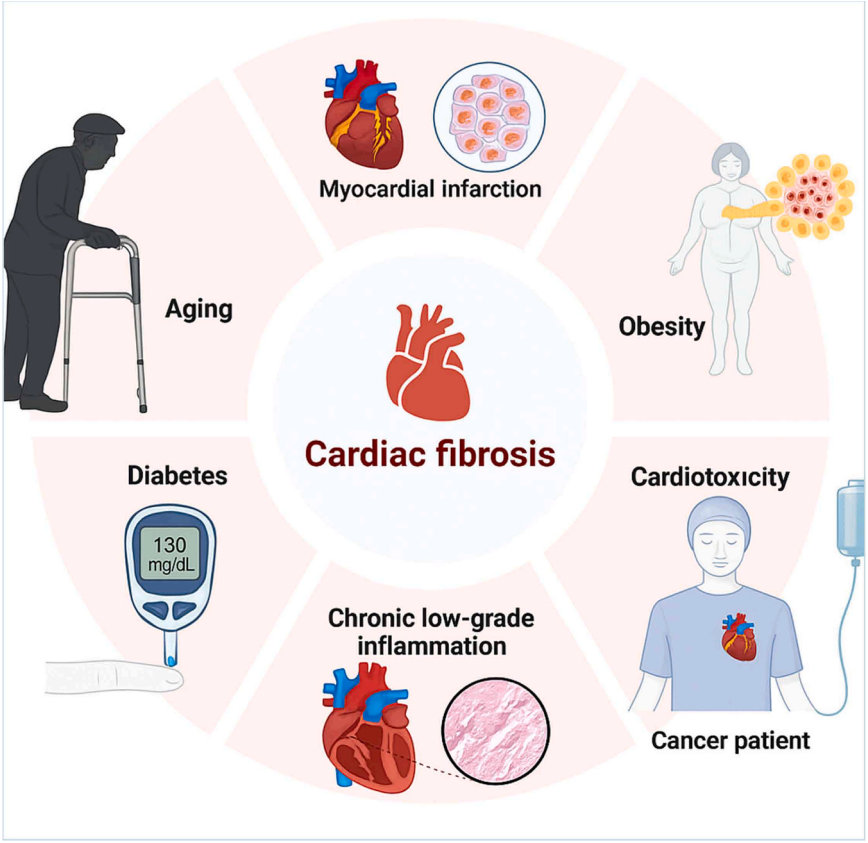

Fig. 1. Risk factors for cardiac fibrosis.

signaling pathways, which enhance myofibroblast transdifferentiation and cytoskeletal remodeling, facilitating the contractile and migratory capacity of fibroblasts [9]. Importantly, Ang II is implicated not only in acute cardiac injury, such as ischemia, but also in chronic remodeling processes by promoting structural and functional alterations of the myocardium. It accelerates cellular aging, particularly in endothelial cells, and strongly correlates with age-related myocardial fibrosis and ventricular stiffening [21]. This is reflected in experimental studies, where angiotensin causes cardiac hypertrophy and hypertension [22, 23]. SIRT1 and SIRT2 exhibit a distinct relationship with angiotensin signaling pathways, not only responding to angiotensin-induced inflammation and OS. They also possess the potential to directly modulate the activity of angiotensin receptors and the early stages of downstream signaling cascades.

3.1. SIRT1 and Angiotensin II

Two decades ago, it was noted that resveratrol (RSV) has potential anti-fibrotic properties, limiting the proliferation and trans-differentiation of cardiac fibroblasts (CF) [24]. The overexpression of SIRT1 induced by RSV may counteract Ang II-induced fibrosis [25]. In mouse aortic samples, RSV modulated AT1R mRNA and protein expression in a dose-dependent manner by enhancing the interaction of SIRT1 with the AT1R promoter through Sp1 [26]. Ang II has been found to target mir-128, whose silencing alleviates apoptosis, fibrosis, and OS-induced damage [27]. The use of EX527 (a SIRT1 inhibitor) reverses the silencing effect of mir-128 [27]. In turn, the downregulation of SIRT1, which occurs during angiotensin II (Ang II) infusion or after transverse aortic constriction (TAC) surgery, can be rescued by circular RNAs (circ-RNAs) [28]. Circ-RNAs are a group of non-coding RNAs characterized by a closed-loop structure and control numerous processes, including cardiac fibrosis [29]. For example, circ_0093887 promotes SIRT1 expression in vessels through interactions with miR-132/212 [30]. circ-SIRT1, through interactions with miR-3681–3p and miR-5195–3p and recruitment of USP22, promotes deubiquitination and increased stabilisation of SIRT1 [28]. In turn, KO-circ-SIRT1 significantly increases fibrosis markers (ANF, BNP) and exacerbates AngII-induced cardiac hypertrophy [28].

3.2. SIRT2 and Angiotensin II

Reduced SIRT2 levels were also found in the hearts of aged rats and those stimulated with AngII [31]. A potential component of Ang II pro-fibrotic pathways that controls SIRT2 levels is CSN6 [22]. In addition, CSN6 is also involved in the development of vascular pathologies, although there is no evidence that this occurs via Ang II signaling [32]. CSN6 has been shown to mediate hypertrophy by downregulating SIRT2, indirectly through upregulation of the SIRT2 transcription suppressor Nkx2.2 [22]. CSN6 is part of the larger group of signalosome (CSN) complex that regulates the ubiquitin-proteasome degradation system, which constitutes other molecules by removing the ubiquitin-like protein RUB1 (Related to Ubiquitin 1). Indeed, significant hypertrophy is associated with higher CSN6 levels, inhibition of Nkx2.2 ubiquitination, and lower SIRT2 levels [22]. Cardiac hypertrophy is naturally accompanied by excessive apoptosis and fibrosis. A crucial question is whether a similar process between CSN6 and SIRT2 also occurs in CF, resulting in their activation. One premise is that the level of ubiquitination of p57, a protein that regulates the cell cycle, depends on CSN6. It has been found that CSN6 negatively regulates p57 stability by increasing the level of p57 ubiquitination in mouse embryonic fibroblasts [33]. Unfortunately, there is a lack of data on SIRT2 regulation in CF.

Histone modifications also regulate the expression of SIRT2. The findings indicate that H3K27me3, through EZH2-dependent repression of genes such as CDKN2a and Timp4, plays a protective role in the pathogenesis of cardiac fibrosis by suppressing replicative senescence in atrial fibroblasts [34]. A reduction in EZH2 levels, observed in atrial fibrosis, leads to a decrease in H3K27me3 modification and derepression of these gene promoters, thereby facilitating the progression of degenerative and fibrotic changes in the heart. PHD finger 19 (PHF19) protein is a protein that controls H3K36me3 and H3K27me3, so it may be involved in Ang II-induced fibrosis [34]. It has been shown that the imbalance between histones H3K36me3 and H3K27me3 in the SIRT2 promoter is induced by PHF19 binding [35]. Knockout of Phf19 reduced the amount of ANP and BNP hypertrophy markers and also inhibited ECM synthesis [35]. Interestingly, it was also discovered that the regulation of H3K27 acetylation also occurs in the galectin-3 promoter and is mediated by SIRT2. H3K27 deacetylation, induced by SIRT2 overexpression, inhibits radiation-induced cardiac fibrosis [36].

The regulation of SIRT2 by mi-RNA in Ang II-induced fibrosis is not yet well understood. As we know, miR-4731 upregulates myocardial hypertrophy and suppresses SIRT2 by targeting the 3′UTR of SIRT2 [37]. Furthermore, a negative regulator of miR-4731 is circ_0018553, whose overexpression supports SIRT2 and inhibits the effect of Ang II [37]. Furthermore, circ_0018553 has the potential to regulate AMP-activated protein kinase (AMPK) and its phosphorylated form [37]. Another non-coding molecule is LcnHrt, whose expression is reduced in dilated cardiomyopathy. It has been indicated that one of the main partners of LcnHrt is SIRT2 [38]. LcnHrt disrupts the interaction between CDK5 and SIRT2, thereby maintaining SIRT2 activity and promoting LKB1-AMPK kinase signalling [38]. SIRT2, similar to SIRT1, has the potential to deacetylate and activate LKB1. SIRT2-dependent translocation of LKB1 to the cytosol is necessary for AMPKα2 phosphorylation and anti-fibrotic effects. This has been confirmed by Sirt2-KO, which resulted in a reduction in p-AMPK [31]. Furthermore, it appears that SIRT2 may be a key molecule for AMPK activity, as Sirt2-KO suppressed metformin-induced AMPK activation [31].

3.3. Clinical perspective: RAAS–sirtuin crosstalk in hypertensive heart disease

From a clinical viewpoint, Ang II remains a central driver of myocardial remodeling in hypertensive and age-related cardiac disease. The intricate interactions between SIRT1/SIRT2 and the angiotensin II signaling pathway suggest promising opportunities to optimize RAAS inhibition strategies. Therapeutic approaches that enhance sirtuin activity—either pharmacologically or via upstream metabolic modulation—could complement conventional drugs, such as ACE inhibitors or ARBs, particularly in patients with hypertensive heart disease or HFpEF, where fibrotic progression is an early and prevalent feature [39].

4. Transforming growth factor-beta in cardiac fibrosis

Transforming growth factor beta (TGF-β) is the central effector of cardiac fibrosis, acting not only as a trigger but also as a long-term amplifier of fibrotic remodeling [9]. Upon receptor activation, it initiates both Smad-dependent and Smad-independent pathways, but its long-lasting profibrotic influence stems from its ability to stabilize the myofibroblast phenotype and remodel gene expression epigenetically. A key interaction in this context involves crosstalk between the TGF-β and Wnt/β-catenin pathways. TGF-β promotes β-catenin stabilization and nuclear translocation, where it cooperates with Smad complexes to induce transcription of pro-fibrotic genes, including Col1a1, Fibronectin, and Postn. Simultaneously, Wnt ligands further potentiate TGF-β signaling, creating a self-reinforcing loop that supports the activation, proliferation, and extracellular matrix deposition of fibroblasts [9]. This synergism also extends to the inhibition of antifibrotic factors and the suppression of fibroblast quiescence. Moreover, TGF-β modulates the expression of sFRPs (secreted frizzled-related proteins), which regulate Wnt activity, and contributes to pathological tissue stiffness through cytoskeletal reorganization via RhoA/ROCK [9]. As such, the TGF-β/Wnt/β-catenin axis serves as a molecular hub integrating

mechanical, biochemical, and epigenetic signals, making it a critical driver of sustained cardiac fibrosis and an attractive therapeutic target [9].

4.1. SIRT1 and TGF-β

Cardiac fibroblasts, as effector cells in the fibrosis process, are regulated by multiple signalling pathways, among which the TGF-β pathway plays a crucial role. There is a strong correlation between TGF-β activity and SIRT1, both systemically and locally, including in the heart [40]. In response to stimulation, SIRT1 can inhibit TGF-β activity in fibroblasts by downregulating the expression of its target genes [41,42]. This has been demonstrated multiple times: RSV inhibits TGF-β-induced collagen synthesis and heart fibroblast transdifferentiation [43,44]. Similarly, the SIRT1 agonist tetrahydrocurcumin reduces the expression of α-SMA, collagen I, and III [45]. ECM remodeling enzymes, such as metalloproteinases (MMPs), are also regulated by SIRT1, and their activity is reduced after treatment with propolis [25] and RSV [46].

Importantly, age-related decline in SIRT1 levels may be both a consequence of increased TGF-β activity and a participant in the regulation of TGFβR expression in CF via miR-22 [47,48]. In many models of cardiovascular disease, reduced SIRT1 levels and an increase in protein acetylation are observed [42,49,50]. SIRT1 controls the acetylation of key transcription factors in the TGF-β pathway, including Smad3, whose interaction site with SIRT1 is located in the Lys-378 residue of the MH2 domain. Acetylation of this site by the p300/CBP complex, whose activity increases in disease, enhances its pro-fibrotic activity [51]. Treatment of isoproterenol (ISO)-induced heart dysfunction with genipostin showed a SIRT1-dependent inhibitory effect, both in vitro and in vivo, on OS, ER stress, Smad3 acetylation, fibroblast transdifferentiation into myofibroblasts, and heart function [52]. Furthermore, SIRT1 has been shown to reduce the acetylation of Smad2 [42], Smad4 [53,54]. Despite intensive research, the full network of relationships between SIRT1 and the Smad axis remains unclear. Mechanistic studies indicate an important role for the Sp1–TGFβ/Smad3–NF-κB axis in the pathogenesis of cardiac fibrosis. Sp1 is involved in the regulation of transdifferentiation, apoptosis and inflammation, and its dysregulation may promote pathological myocardial hypertrophy [55], as well as Ang II-induced fibrosis [56]. The flavonol (–)-epicatechin (EPI) exhibits anti-fibrotic effects through modulation of the Sp1/SIRT1 axis [57]. Increasing attention is also being paid to the role of circRNA in the regulation of fibrosis. In a model of pulmonary hypertension, circ-SIRT1 showed similar dynamics to SIRT1. Its overexpression increased SIRT1 levels while decreasing TGF-β1/Smad3/Smad7 expression, leading to inhibition of cell migration [58]. SIRT1 also limits the level of the phosphorylated Smad2/3 complex [59], disrupting its interaction with Smad4 and reducing the transport of the complex to the cell nucleus [25,60]. As a result, the regulation of these pathways leads to a reduction in the excessive production of ECM elements and the suppression of fibroblast transdifferentiation.

Another intersection between SIRT1 and TGF-β is AMPK. AMPK is a key metabolic kinase that plays an important role in the regulation of the TGF-β pathway and other important pathways such as mTOR. Its activation occurs through the interaction of the LKB1 kinase with the α subunit of the AMPK complex. SIRT1 is responsible for the deacetylation and activation of LKB1, enabling its translocation from the cell nucleus to the cytoplasm, where it activates AMPKα. Importantly, LKB1 deletion leads to the development of pathological hypertrophy and fibrosis of the heart muscle [61]. The fibroblast growth factor FGF21 promotes the formation of a complex between SIRT1, LKB1 and the transcription factor FoxO1, which further enhances AMPK activation [62]. In a rat model of diabetic cardiomyopathy, it was observed that a decrease in phosphorylated AMPK (p-AMPK) in rat myoblasts correlates with a decrease in SIRT1 expression, indicating an important role of the SIRT1/LKB1 axis in counteracting fibrosis [63]. It is also worth noting that in ageing vascular endothelium exposed to Ang II, the reduction in levels of ROS, p21 protein, and plasminogen activator inhibitor-1 (PAI-1) was regulated by the AMPK/SIRT1 pathway [64]. Furthermore, ageing itself has been indicated as an independent risk factor for the development of myocardial fibrosis. In ageing rat hearts, progressive myocardial fibroblast activation, enhanced extracellular matrix deposition were observed, which correlated with impaired AMPK/SIRT1 signaling, particularly during the transition from 15 to 24 months of age [65].

The presence of α-SMA (a marker of myofibroblasts) indicates fibroblast transdifferentiation, including through endoendothelial-mesenchymal transition (EndoMT), in which cells lose markers such as VE-cadherin [66]. EndoMT, as a new source of myofibroblasts, plays an increasingly important role in the pathogenesis of cardiac fibrosis. In pathological conditions such as diabetes, high levels of OS lead to vascular damage and induction of EndoMT, accompanied by a decrease in SIRT1 protein expression in CF, a reduction in Akt phosphorylation, and more intense CF transdifferentiation into myofibroblasts [67]. RSV improves nitric oxide metabolism and activates eNOS, counteracting these changes [68]. Similar phenomena occur in diabetic cardiomyopathy – reduced SIRT1 expression is associated with increased EndoMT, while its restoration inactivates the Notch1 pathway, helping to reverse this process [69]. Interestingly, the BHYF herbal mixture used in Chinese medicine has antioxidant properties and counteracts EndoMT precisely by activating the SIRT1/Notch1 pathway [70]. In an isoproterenol-induced fibrosis model, EndoMT is characterized by an increase in the expression of α-SMA, vimentin, and FSP1, and a decrease in VE-cadherin levels [60]. Both in vitro and in vivo, SIRT1 limits EndoMT, as evidenced by an increase in the expression of endothelial markers (VE-cadherin, CD31) and a decrease in mesenchymal markers (α-SMA, vimentin, FSP1) in cells treated with RSV [60]. Furthermore, SIRT1 counteracts EndoMT in diabetic cardiomyopathy by suppressing NF-κB activity [71]. Consistent with this, ZEB1-AS1 was recently shown to alleviate diabetic myocardial fibrosis by sponging miR-181c-5p and preserving SIRT1 activity, which in turn promotes YAP deacetylation [72]. In high-glucose-treated CF, this mechanism suppressed proliferation, migration, and myofibroblast transformation, whereas in diabetic mice, ZEB1-AS1 overexpression reduced ECM protein accumulation. These findings indicate that SIRT1 protects the heart not only by limiting EndoMT but also by restraining fibroblast activation under diabetic conditions [72].

The Wnt/β-catenin axis also plays a key role in DCM. The study evaluated the effect of systemic administration of RSV, alone and in combination with MSCs (with or without RSV pre-incubation), on the activity of this pathway in a streptozotocin-induced DCM model. All RSV-treated groups demonstrated improved heart function, with the best results achieved in the MSC group that was pre-incubated with RSV. Histological analysis confirmed a reduction in hypertrophy, fibrosis, and microcirculatory damage, as well as decreased expression of sFRP2 and activity in the Wnt/β-catenin pathway [73].

4.2. SIRT3 and TGF-β

Studies have shown that mice lacking SIRT3 (Sirt3-KO) spontaneously develop fibrosis in many organs, including the heart, with age, in contrast to mice overexpressing SIRT3 [74]. Mechanistically, the absence of SIRT3 leads to hyperacetylation of GSK3 kinase on the K15 residue, which inhibits its phosphorylation activity of Smad3 and β-catenin [75,76]. SIRT3, by deacetylating GSK3, restores its activity and blocks TGF-β1 signal transduction through the degradation of β-catenin [76]. In the context of estrogen deficiency-induced cardiac remodelling, activation of SIRT3 by theacrine led to a reduction in fibrosis and improved cardiac function through modulation of the β-catenin/PPARγ pathway [76]. Additionally, in an Ang II-induced cardiac fibrosis model, Sirt3-KO mice exhibited increased pericyte-to-myofibroblast transition and enhanced OS and TGF-β1

expression, confirming the role of SIRT3 in regulating the ROS–TGF-β1 pathway [77]. Further evidence indicates that SIRT3 counteracts fibrosis by inhibiting the transdifferentiation of CF into myofibroblasts through deacetylation and inhibition of STAT3 activity, which in turn reduces the expression of its effector, NFATc2 [78]. Furthermore, SIRT3 activators, such as 2-APQC, attenuate fibrosis by inhibiting the mTOR-p70S6K, JNK, and TGF-β/Smad3 pathways, as well as by improving mitochondrial homeostasis, confirming the dependence of the protective effect on the presence of SIRT3 [79]. Similarly, SIRT3 activation by RSV and quercetin attenuates CFs transdifferentiation by inhibiting the TGF-β/Smad3 pathway, but this effect is absent in Sirt3-KO mice, confirming the necessity of SIRT3 in this mechanism [80,81]. In atrial fibrosis, decreased SIRT3 expression promotes the activation of fibroblasts and atrial remodeling. In contrast, SIRT3 activation or sulfhydration limits fibroblast proliferation and migration, reduces fibrosis, and decreases the risk of atrial fibrillation, highlighting its potential as a therapeutic target for fibrotic heart conditions [82].

4.3. SIRT4 and TGF-β

SIRT4 plays an active role in regulating the expression of genes that remodel the heart muscle, especially in response to angiotensin II (Ang II) stimulation. Overexpression of SIRT4 increases the expression of genes typically activated in hypertrophic cardiomyopathy and fibrosis, such as ANP, BNP, and β-MHC [83]. In vitro, in Ang II-treated cardiomyocytes, SIRT4 expression was higher than in control conditions, which coincides with an increase in cell surface area and expression of hypertrophy markers [83,84]. This function is co-regulated by the miR-93–5p/SIRT4 axis, where miR-93–5p acts as a translational inhibitor of SIRT4, suppressing its prohypertrophic action. Inhibition of miR-93–5p results in increased SIRT4 expression, enhanced expression of ANP, BNP, β-MHC, and cell hypertrophy [83]. It has also been confirmed that lncRNA MALAT1 acts as a molecular sponge for miR-93–5p, stabilizing SIRT4 and enhancing remodeling signaling [83]. In rheumatoid arthritis, SIRT4/miR-93–5p/Smad7 mechanistically reduces the inhibitory effect on Smad2/Smad3, promoting profibrotic processes [85]. This indicates that SIRT4 is involved in complex molecular regulation involving non-coding RNA and profibrotic genes.

4.4. SIRT5 and TGF-β

Overexpression of SIRT5 in the hearts of mice subjected to TAC resulted in significant inhibition of the transcription of genes associated with fibrosis and the TGF-β pathway. RNA-seq analysis revealed suppression of Tgfβ1, Gdf15, Icam1, Col1a1, Col4a2, Fbn1 and ECM remodeling enzymes (Plod3, Adamts4, Timp1) compared to the WT group [86]. Sirt5-KO mice infused with AngII/PE showed increased CF proliferation and type I and III collagen synthesis, with concomitant increases in Col1a1 and Col3a1 expression [87]. SIRT5OE mice also showed reduced expression of fibroblast activation genes (Postn) and fibrosis-stimulating cytokines (Spp1, Thbs1) [86]. [87]. In in vitro models, treatment of fibroblasts with TGF-β1 strongly activated them metabolically, which was abolished by SIRT5 overexpression [87]. Mechanistically, SIRT5 protects fibroblasts from the metabolic transition from oxidative phosphorylation to glycolysis through desuccinylation and activation of phosphoenolpyruvate carboxykinase 2 (Pck2). Loss of SIRT5 resulted in the hypersuccinylation of Pck2, a decrease in its enzymatic activity, and increased activation of fibroblasts [88]. Inhibition of glycolysis attenuated this effect, confirming the dependence of fibroblast activation on SIRT5-regulated metabolism. Collagen staining showed significantly less ECM accumulation in SIRT5OE myocardium after TAC, which correlated with preserved contractile function and inhibited cardiac remodeling [86]. SIRT5, therefore, acts both by suppressing transcriptional pathways (TGF-β) and by maintaining energy balance, supporting fatty acid oxidation and mitochondrial function [86,89].

4.5. SIRT6 and TGF-β

SIRT6 acts as a crucial regulator of this pathway, where its deficiency leads to hyperactivation of TGF-β signaling, thereby accelerating fibrosis associated with aging and disease [90]. Mechanistically, SIRT6 directly binds to SMAD3 and deacetylates it, dampening its transcriptional activity. It also targets histones at the promoters of TGF-β-responsive genes, repressing their expression through epigenetic silencing. In aged mice, even partial loss of SIRT6 (haploinsufficiency) is sufficient to trigger the transdifferentiation of fibroblasts, resulting in multiorgan fibrosis—including cardiac fibrosis [90]. Restoration of SIRT6 expression reverses these pathological changes, underscoring its therapeutic potential.

Interestingly, in certain contexts, SIRT6 suppresses TGF-β signaling independently of its deacetylase activity, hinting at additional non-enzymatic functions [91]. Beyond TGF-β, SIRT6 also interferes with the STAT3 signaling cascade. In cardiomyocytes, SIRT6 overexpression reduces STAT3 phosphorylation and nuclear translocation, thereby lowering the expression of BNP [92]. Another protective mechanism involves the regulation of NFATc4: SIRT6 enhances its phosphorylation, thereby preventing its accumulation in the nucleus and the activation of pro-fibrotic genes [93]. At the post-translational level, the stability of SIRT6 is maintained by USP10-mediated deubiquitination. This interaction is reinforced by natural compounds such as limonin, which protect SIRT6 from proteasomal degradation and preserve its anti-fibrotic function [94]. In pressure overload-induced cardiac remodeling, SIRT6 activation via epigallocatechin gallate (EGCG) inhibits hypertrophy through modulation of the PSMB5/Nmnat2/SIRT6 axis [95]. Furthermore, SIRT6 plays a crucial role in maintaining genomic stability during stress by promoting telomere integrity through the upregulation of telomerase reverse transcriptase (TERT) and telomere repeat-binding factor 1 (TRF-1) [96].

Diabetes significantly worsens cardiac fibrosis through chronic inflammation and metabolic dysregulation. In diabetic hearts, SIRT6 expression is markedly reduced, contributing to the EndoMT [97]. SIRT6 deficiency upregulates the long non-coding RNA MALAT1, which in turn promotes EndoMT by increasing the expression of Snail, a master regulator of fibrotic reprogramming [98].

In the context of type 2 diabetes, diminished SIRT6 levels suppress AMPK signaling while activating the TGFβ1/Smad2/3 axis, thus promoting progressive myocardial fibrosis [99]. SIRT6 overexpression restores AMPK activity, inhibits TGFβ1 signaling and its downstream mediators, ultimately reducing fibrosis and improving cardiac performance [99].

SIRT6 also modulates the Notch1 signaling pathway in diabetic cardiomyopathy. Knockdown of SIRT6 in cardiac microvascular endothelial cells (CMECs) exacerbates inflammation and fibrosis induced by high glucose and palmitic acid, largely through Notch1 hyperactivation [97]. Pharmacological activation of SIRT6, for instance with the selective activator MDL-800, mitigates these effects, improving diastolic function and reducing cardiac lipid accumulation [100].

4.6. SIRT7 and TGF-β

The role of SIRT7 in modulating TGF-β/Smad2/3 signaling has been extensively studied, particularly in the context of liver fibrosis. Previous studies indicate that SIRT7 expression may be increased in hepatocellular carcinoma, while a decrease is observed under conditions of chronic liver stress [101]. In this context, it has been shown that SIRT7 deacetylates Smad2/3, thereby inhibiting their phosphorylation, which leads to the suppression of hepatic stellate cell activity [101]. In breast cancer, SIRT7 deacetylates and inactivates Smad4, and its level is reduced by TGF-β, which correlates with increased activation of this signaling pathway [102].

Interestingly, in the heart, the interactions between SIRT7 and TGF-β appear to differ from those observed in other organs. In pressure

overload models, increased SIRT7 expression is accompanied by elevated levels of remodeling markers, such as ANP and BNP [103]. Similar results were obtained in mice with SIRT7 gene deletion [104]. The transcription of ANP and BNP, regulated by GATA4, a key regulator of natriuretic peptides, occurs primarily in cardiomyocytes [105]. Importantly, CF do not synthesize these peptides but express their receptors; thus, stress-induced upregulation of ANP/BNP in cardiomyocytes may directly influence fibroblast activity through receptor-mediated signaling. The degree of GATA4 acetylation determines its transcriptional activity; SIRT7, in combination with the p300 acetyltransferase, participates in the regulation of this modification. In the SIRT7 KO model, increased GATA4 acetylation and enhanced cardiac remodeling processes were observed [104].

However, discrepancies in studies on the effect of SIRT7 on TGF-β signaling are surprising. Although SIRT7 deficiency has been shown to affect Smad2 translocation to the CF nucleus [106], other studies do not confirm the effect of KO-SIRT7 on Smad2 phosphorylation and translocation [107]. As researchers indicate, Sirt7 primarily supports repair processes via TGF-β in CF [108], and KO-Sirt7, or its deficiency, weakens TGF-β signaling in CF [106,108]. This mechanism is based on the interaction of SIRT7 with the adaptor protein PICK1, which is responsible for the stability of the TβRI complex. The absence of SIRT7 leads to lysosomal degradation of the receptor [108].

The role of the negative regulator of this pathway, Smad7, has been confirmed in a model of Ang II-induced cardiac fibrosis. Deletion of Smad7 (KO-Smad7) resulted in increased fibrosis, increased deposition of type I collagen and expression of α-SMA, as well as exacerbation of the inflammatory response – increased production of IL-1β, TNF-α, and infiltration of CD3 + T cells and F4/80 + macrophages [109]. These data confirm the importance of precise control of TGF-β signaling in the protection against pathological cardiac remodeling.

Evidence for the regenerative role of SIRT7 is provided by its increased expression (2.5-fold) in the myocardial infarction zone in mice [107], which is consistent with findings indicating a larger area of fibrosis in animals deficient in this protein [104]. In another study, Sirt7 deletion led to severe myocardial fibrosis, increased expression of α-SMA and type IV collagen, as well as accelerated ageing processes and accumulation of lipofuscin (a product of abnormal lipid oxidation resulting from excess ROS) [110]. Surprising data come from a KO-SIRT7 mouse model of heart attack, where, despite previous results, a reduction of α-SMA expression and decreased collagen I expression were observed [107]. At the same time, enhanced TGF-β1 signaling and increased expression of PAI-1 and α-SMA were found in cells overexpressing SIRT7 [107].

It is worth noting that SIRT7 also regulates the YAP signaling pathway in primary cardiac fibroblasts, which is strongly activated in fibrosis processes and interacts with TGF-β [111,112]. TGF-β/YAP signaling leads to the phosphorylation of Akt and ERK1/2 kinases, promoting fibroblast proliferation. Overexpression of SIRT7 in an angiotensin II treatment model reduced YAP levels, and knockdown of SIRT7 blocked TGF-β1-induced ERK activation [107,111]. The potential of sirtuins (particularly SIRT1, SIRT3, and SIRT6) to interfere with Smad signaling or EndoMT suggests that sirtuin modulation could be used to delay progression in patients with myocardial fibrosis (Fig. 2). This may be particularly clinically relevant in early-stage non-ischemic cardiomyopathy, where fibrosis precedes symptomatic dysfunction [113].

5. Inflammation and cardiac fibrosis

Inflammation plays a crucial role in the pathogenesis of myocardial fibrosis, and its main mediator is the nuclear factor NF-κB. Activation of NF-κB leads to increased expression of proinflammatory genes, including cytokines such as IL-1β, IL-6 and TNF-α, which promote fibroblast transdifferentiation and excessive synthesis of ECM [114]. In response to cardiomyocyte damage, for example, in the course of ischaemic heart disease or doxorubicin-induced cardiotoxicity (a drug that causes DNA damage and aging of both healthy and cancer cells - In this way, it exacerbates SASP and chronic inflammation), NLRP3

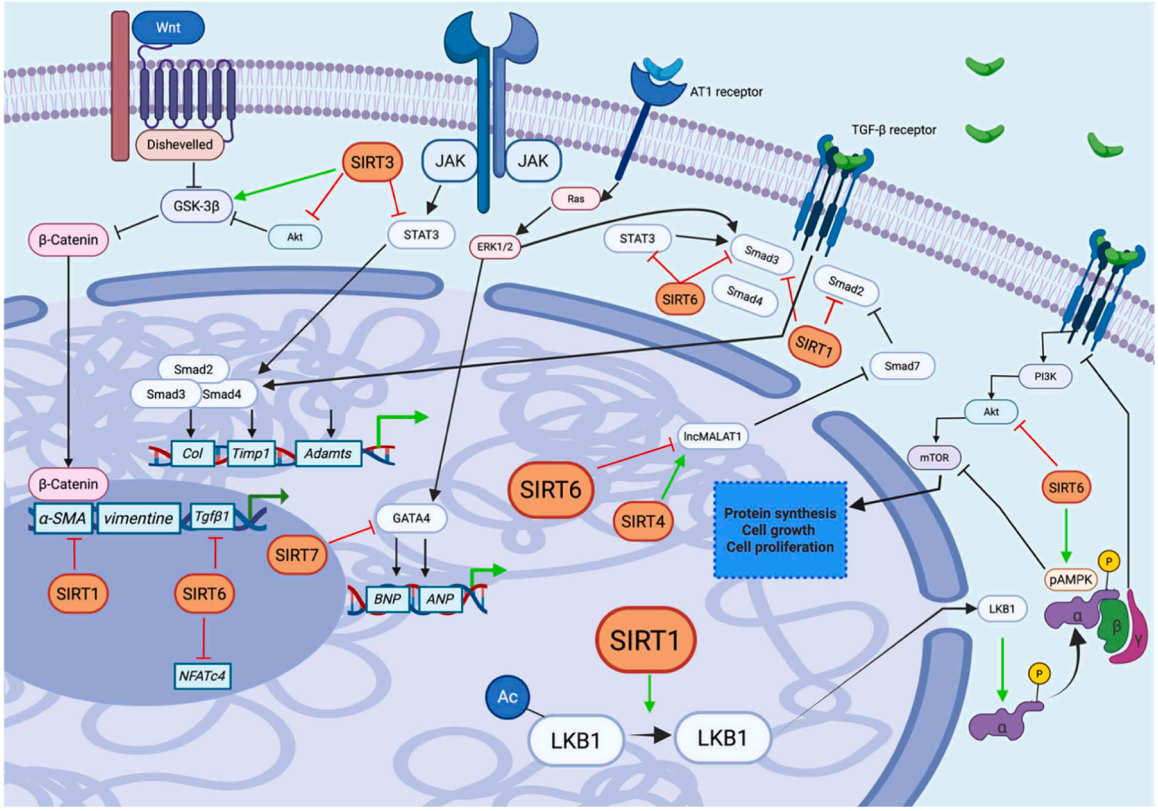

Fig. 2. Regulation of fibrosis pathways by SIRT family proteins: interactions with TGF-β/Smad, Wnt/β-Catenin and JAK/STAT.

inflammasome activation also occurs, which further exacerbates the inflammatory response by increased release of IL-1β and IL-18 [115]. Chronic inflammation, which is common in older people, is particularly important in the development of HFpEF [116]. HFpEF is a strongly age-related phenotype of heart failure in which low-grade inflammation plays a key role in myocardial remodeling and disease progression [116]. In addition the NLRP3 inflammasome has been associated with pericarditis, an inflammation of the sac surrounding the heart [117]. This association has been used to develop potent anti-inflammatory therapy in the form of colchicine or monoclonal antibodies directly targeting key factors in the inflammatory cascade such as IL-1-antagonists.

5.1. SIRT1 and inflammation

SIRT1 is an antagonist of NF-κB, and its overexpression leads to deacetylation of p65 NF-κB [118,119]. NF-κB plays a crucial role in promoting cardiac fibrosis by activating the EndoMT process, as evidenced by increased p65 expression and its nuclear translocation in endothelial cells following doxorubicin treatment [71]. This pathway activation facilitates the reduction of endothelial markers, acquisition of fibroblast-like features, and enhanced collagen deposition, thereby driving the progression of fibrotic remodeling in the heart [71]. In ischemic disease model, reduced SIRT1 expression in cardiomyocytes was associated with increased expression of NF-κB and its target gene mir-155 [120]. Regulation via SIRT1/NF-κB inhibits cell proliferation and inflammation of cardiomyocytes [121]. The cardiotoxicity of doxorubicin is antagonized by acacetin, which stimulates stronger SIRT1 signaling, leading to reduced Nrf2 acetylation and decreased ROS levels through increased transcription of cardiomyoblast antioxidant defense genes [122]. Finally, SIRT1 emerges as a central regulator linking resveratrol to the control of senescence and inflammatory activation in CF [123]. Activation of Sirt1 by resveratrol suppresses p53 acetylation, thereby attenuating cellular senescence and apoptosis. In parallel, Sirt1 signaling downregulates inflammasome components such as NLRP3 and caspase-1 p20 and limits NF-κB nuclear translocation, resulting in reduced secretion of pro-inflammatory cytokines [123]. Through this dual action, Sirt1 mediates the protective effects of resveratrol by simultaneously curbing fibroblast senescence and dampening inflammatory responses, mechanisms that are critical for mitigating fibrosis and the progression of ischemia-induced heart failure. Another SIRT1 agonist, astaxanthin, which has anti-inflammatory properties, protects the heart and reduces inflammatory cell infiltration and excessive collagen deposition [124]. It has been indicated that the responsible pathway is the activation of SIRT1, which deacetylates p65 NF-κB and Nrf2 [124].

The anti-inflammatory properties of SIRT1 are partly due to the regulation of the inflammasome (NLRP3) [125]. SIRT1 regulates the inflammatory response via NLRP3, among others in the vascular endothelium [125]. In a mouse model of ischaemia-induced cardiac ageing, RSV inhibited ageing and CF apoptosis by inhibiting inflammasome activation [123]. In turn, in Ang II-induced fibrosis, it was shown that the attenuation of hypertrophy and fibrosis occurs through the inhibition of the inflammasome in cardiomyocytes [126]. Excessive NLRP3 activation is one of the main drivers of inflammation in doxorubicin-induced cardiomyopathy. Sulfiredoxin 1 (Srxn1) counteracts doxorubicin treatment by inhibiting NLRP3 inflammasome, mediated by SIRT1 [127]. Furthermore, Srxn1 influences the synthesis of antioxidant genes and the secretion of pro-inflammatory cytokines through Nrf2 and the Akt/GSK-3β signaling pathway, which represents another intersection between Srxn1 and SIRT1 [128]. Similarly, (-)-epicatechin (EPI) protects against cardiac fibrosis by modulating cardiac fibroblast activation through SUMOylation-dependent activation of SIRT1, which inhibits Ang II-induced myofibroblast transformation via the Akt/GSK-3β pathway [129]. This underscores the convergence of Srxn1 and SIRT1 signaling in controlling fibroblast-driven OS and fibrotic remodeling, highlighting their potential as therapeutic targets in cardiac fibrosis [129]. A few studies on primary myocardial fibroblasts show that isoprenaline-induced cardiac fibrosis causes a decrease in SIRT1 activation. Inhibition of the mir-217/SIRT1 pathway reverses cardiac fibrosis and reduces NLRP3 activity and caspase-1 and IL-1β levels [130].

SIRT1 also inhibits the production of the pro-inflammatory cytokine monocyte chemoattractant protein-1 [118]. The negative regulation of monocyte chemoattractant protein-1 is mediated by peroxisome proliferator-activated receptor-α (PPARα), whose silencing inhibited the positive effect of SIRT1 [118]. PPARα is an important mediator in the SIRT1/NF-κB interaction [118]. The formation of the SIRT1-PPARα complex supports NF-κB deacetylation and the induction of an antioxidant response [118]. In another study examining three PPAR isomers, α, δ and γ, only PPARδ increased SIRT1 promoter activity and protein expression, inhibiting premature endothelial ageing [131]. In turn, other data indicate that PPARα/SIRT1 signaling is promoting the progression of heart failure via mitochondrial dysfunction [132]. However, the intensity of SIRT1 stimulation effects depends on the dose of the activator, and in the case of excessive overexpression in the heart (approximately 10-fold), adverse effects are induced [42,133]. Therefore, data on the positive effect of Sirt1 haploinsufficiency on cardiac hypertrophy are puzzling [132].

5.2. SIRT2 and inflammation

SIRT2 exhibits similar anti-inflammatory properties, although its mechanisms of action are slightly different. TLR4 (Toll-like receptor 4) is activated in inflammation of the heart induced by LPS administration. Fibrosis was accompanied by increased p53 acetylation, secretion of pro-inflammatory cytokines (IL-6, TNF-a), and reduced SIRT2 levels in cardiomyocytes [134]. The receptor for LPS signaling is TLR4, which means that it is an important mediator of inflammatory fibrosis, mediated by the weakening of SIRT2 activity [134].

NFAT in the heart acts as a key transcription factor that activates pathological gene programs, leading to cardiac hypertrophy and failure [135]. NFAT is controlled by calcineurin, a $Ca2+$-dependent phosphatase [136]. It has been noted that increased acetylation of NFATc2 is associated with lower levels of SIRT2 in CF and cardiomyocytes, and overexpression of SIRT2 is required to suppress NFAT and inhibit pathological cardiac hypertrophy [137]. GSK3β phosphorylates NFAT and inhibits its transcriptional activity. SIRT2 can deacetylate GSK3β at Lys183, increasing its activity and may positively affect heart failure [138]. Interestingly, a reduction in GSK3β led to a reduction in the positive effects of SIRT2, indicating that this process is superior to deacetylation of NFAT by SIRT2, in cardioprotection [138]. In addition, SIRT2 regulates NF-κB activity in fibroblasts by deacetylating the p65 subunit, which limits its translocation into the cell nucleus [139]. Also important in modeling NF-κB activity is the deacetylation of poly (ADP-ribose) polymerase 1 (PARP1), which promotes inhibition of NF-KB [140]. In diabetic cardiomyopathy, SIRT2 also inhibits the activation of the NLRP3 inflammasome, presumably through tubulin deacetylation and stabilization of microtubules, which play a role in the transport of this complex [141,142]. Interestingly, colchicine, which is used to treat doxorubicin-induced cardiomyopathy, works in part by restoring SIRT2 activity and reducing NLRP3 activity [141].

5.3. SIRT3 and inflammation

Studies have shown that SIRT3 acts as a mitochondrial deacetylase that protects against oxidative damage, inhibits the activation of inflammatory factors such as NF-κB and AP-1, and regulates pathways responsible for fibrosis, including by controlling the expression of inflammatory cytokines and ECM (e.g., collagen I and III) [143-145]. In heart disease models such as TAC and diabetic cardiomyopathy, reduced SIRT3 levels correlate with increased inflammation and fibrosis, leading

to cardiac remodeling and impaired function [145-147]. In addition, SIRT3 suppresses NLRP3 inflammasome activity and promotes autophagy, which contributes to the protection of cardiomyocytes from damage caused by factors such as doxorubicin or ischaemia-reperfusion [148,149]. The findings of Palomer et al. (2020) demonstrate that the loss of SIRT3 leads to spontaneous development of cardiac inflammation and fibrosis, associated with enhanced AP-1 activity and overexpression of its subunit FOS [144]. SIRT3 knockout mice exhibited increased expression of pro-inflammatory cytokines (IL-6, MCP-1, ICAM-1) and OS markers, along with greater collagen deposition in the heart. Importantly, no significant hypertrophy or marked deterioration of systolic function was observed, suggesting that the key mechanism involves interstitial cardiac remodeling toward fibrosis rather than cardiomyocyte hypertrophy [144].

5.4. SIRT5 and inflammation

In hyperglycaemic (HG) models, SIRT5 deletion led to increased production of inflammatory cytokines (IL-6, TNF-α), enhanced activation of NLRP3 inflammasome, caspase-1 and GSDMD-N, and secretion of IL-1β and IL-18 in cardiomyocytes [150]. An increase in the number of apoptotic cells, DNA damage (TUNEL+) and enhanced cell ageing were also observed [150,151]. Conditioned medium from damaged cardiomyocytes with SIRT5 knockout strongly activated CF, leading to increased synthesis of collagen I and III and their proliferation [151]. Overexpression of SIRT5 mitigated these effects by reducing inflammation, and its action was mediated by the regulation of the expression and stability of GSTP1, an enzyme responsible for controlling OS and pyroptosis [151].

5.5. SIRT 7 and inflammation

In mice with induced SIRT7 deficiency, cardiomyopathy developed in adulthood, mediated by increased inflammation [110]. There is growing evidence that not only is the fibrotic conversion of heart tissue following a heart attack controlled by macrophages and other inflammatory cells, but that this also occurs in senile fibrosis. Mice with SIRT7 deficiency exhibited not only increased numbers of granulocytes and T lymphocytes in the blood, but also increased infiltration of inflammatory cells into the heart muscle [110]. Infarct-induced fibrosis and the accompanying increased secretion of IL-1β, IL-6 and TNF-α were reduced by therapy with exosomes derived from bone marrow mesenchymal stem cells (BMSCs) carrying miR-125b [152]. Inhibition of SIRT7 by miR-125b reduced the regulation of Bax and caspase-3 and increased the regulation of Bcl-2 [152]. In coronary vessels, miR-125b targets SIRT7 and exacerbates calcification induced by high glucose levels [153].

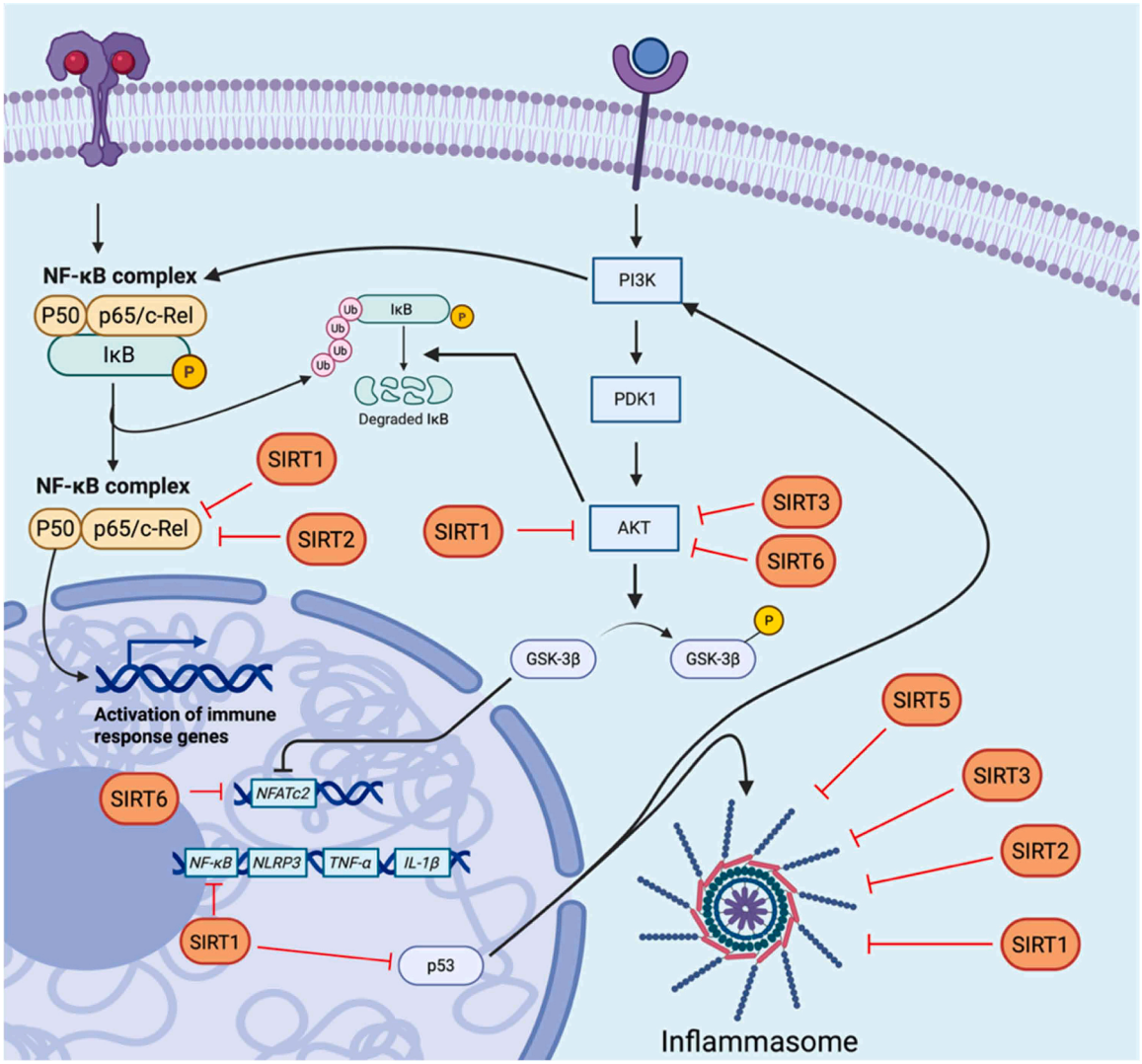

Fig. 3. Modulation of inflammatory response by SIRTs: regulation of NF-κB, NLRP3, and cytokine pathways.

5.6. Sirtuin-based anti-inflammatory strategies in fibrotic heart disease

From a clinical perspective, the ability of SIRT1, SIRT2, and SIRT3 to negatively regulate key inflammatory mediators such as NF-κB, NLRP3, IL-6, TNF-α, and IL-1β offers promising therapeutic potential. Sirtuin activation has been shown to intersect with cardioprotective pathways, including PPARα, AMPK, and autophagy, while also stabilizing mitochondrial and microtubular function. These properties align with the mechanisms of action of emerging anti-inflammatory therapies, including IL-1 antagonists [138] and colchicine [154]. As such, targeted modulation of sirtuin signaling may augment standard anti-inflammatory approaches and provide a synergistic strategy in patients with systemic or cardiotoxic inflammation driving fibrotic remodeling.

6. Oxidative stress and cardiac fibrosis

OS, defined as an imbalance between the production of ROS and the antioxidant defense system, plays a pivotal role in the initiation and progression of cardiac fibrosis [155]. Excess ROS directly damages cardiomyocytes and activates CF, leading to enhanced synthesis and deposition of ECM, such as collagen type I and fibronectin. Furthermore, OS facilitates the transdifferentiation of fibroblasts into myofibroblasts and reinforces pro-fibrotic signaling pathways, particularly those involving TGF-β and Wnt/β-catenin [156]. Mitochondrial dysfunction, which generates significant ROS in the aging heart, worsens the process by impairing energy metabolism and driving cellular senescence [157]. Notably, OS also contributes to the persistence of fibrosis by altering redox-sensitive transcription factors and epigenetic regulators, which stabilize the activated fibroblast phenotype [157]. In aging-related cardiac remodeling, cumulative oxidative damage is a key mechanism linking metabolic dysfunction with structural deterioration of the myocardium [158]. Therefore, targeting OS—either by enhancing mitochondrial resilience or boosting endogenous antioxidant systems—emerges as a promising strategy to prevent or attenuate fibrotic remodeling, particularly in age-associated forms of heart failure.

6.1. SIRT1 and oxidative stress

SIRT1 has a well-established position among factors regulating ageing and resistance to OS [133]. SIRT1, the best-known member of the sirtuin family, plays a key role in delaying cellular ageing and increasing resistance to OS. It activates the SIRT1/PGC-1α pathway is essential for mitochondrial biogenesis and the maintenance of mitochondrial membrane integrity. Under physiological conditions, SIRT1 deacetylates PGC-1α, increasing its transcriptional activity and promoting the expression of genes encoding proteins involved in oxidative phosphorylation (OXPHOS) and β-oxidation of fatty acids [159,160]. In diabetic cardiomyopathy, a progressive decrease in SIRT1 and PGC-1α expression is observed, which correlates with a decrease in mitochondrial membrane potential (ΔΨm) and an increase in mtROS production. Importantly, SIRT1 deletion in animal models leads to a phenotype resembling dilated cardiomyopathy (DCM), which can be reversed by administration of RSV, a natural activator of SIRT1. RSV not only restores mitochondrial DNA (mtDNA) copy number and membrane potential, but also increases the expression of the nuclear respiratory factor (NRF) and reduces the level of malondialdehyde (MDA), a marker of lipid peroxidation [161,162]. In turn, malondialdehyde (MDA) levels decrease and PGC-1α deacetylation increases [162]. Increased PGC-1α deacetylation through interactions with SIRT1 likely improves fatty acid oxidation [118]. On the other hand, efficiently functioning mitochondria protect SIRT1 from degradation due to increased ROS concentrations [163]. Stimulation of Grim-19, a crucial component of mitochondrial complex I, reduces ROS levels and affects SIRT1-regulated pathways [163]. Among the pathways relevant to cardiac fibrosis, a link between Grim-19 levels and the SIRT1/Stat3 pathway has been demonstrated in diabetic cardiomyopathy [163]. Stat3 signaling, whose activation is crucial in neoplastic processes, was attenuated, contributing to a reduction in fibroblast proliferation and migration and a decrease in cardiac fibrosis [163].

RSV treatment protects heart cells from functional loss during ageing in mice [164]. It has been noted that oral administration of RSV caused a simultaneous increase in Mn-SOD levels in cardiomyocytes, a reduction in cardiac fibrosis, an increase in cell survival and a reduction in ROS levels [159]. In turn, SIRT1 knockout abolished the effect of RSV on ROS levels [159]. Regulation of the FOXO family of transcription factors (mainly FOXO1 and FOXO3a), which control the expression of antioxidant enzymes, including manganese superoxide dismutase (Mn-SOD) and catalase, is dependent on SIRT1. Deacetylation of FOXO1 by SIRT1 in response to fibroblast growth factor 21 (FGF21) leads to increased transcription of antioxidant genes, while deacetylation of FOXO3a inhibits proapoptotic pathways (e.g. Bim, Bax) and reduces ROS accumulation in ageing cardiomyocytes [165-167]. In isoproterenol-induced fibrosis models, SIRT1/FOXO3a controls ROS reduction and Mn-SOD induction, thereby limiting cell damage [166]. However, excessive activation of FOXO3a may also enhance apoptosis signaling and contribute to diastolic dysfunction, highlighting the complexity of this regulation [168]. In studies, OS in the heart increases with the use of sirtuin inhibitors, such as nicotinamide or sirtinol [162,166]. In contrast, the use of SIRT1 activators may be beneficial in the ageing heart by weakening the FOXO1-Bim signaling axis [169]. FOXO1-Bim is responsible for maintaining proapoptotic signals in the heart [170], and the use of RSV reduces FOXO1 acetylation and decreases the levels of BAX and p53 (elements of proapoptotic processes), while maintaining the ejection fraction and shortening fraction in mice [169]. A reduction in FOXO1 activity, against the background of SIRT1 activation, was associated with a reduction in COL1A1 deposition in heart tissue [169], and also resulted in a reduction in ischaemic-reperfusion injury and an increase in Mn-SOD expression in cardiomyocytes [171].

Inhibition of pro-inflammatory and pro-apoptotic pathways through deacetylation of p53 protein (in particular lysine residues K373/K382) and suppression of the NF-κB axis. In cardiomyocytes exposed to angiotensin II (Ang II), SIRT1 counteracts cellular ageing by deacetylating p53 and increasing the availability of glutathione (GSH) and superoxide dismutase (SOD) activity [172]. SOD is a target gene of SIRT1, but GSH activation is a further effect of Nrf2 deacetylation by SIRT1 and GCLC and GCLM synthesis [122]. Furthermore, in vascular endothelium, SIRT1 inhibits ageing by regulating the SIRT1/p53 pathway, while in diabetic cardiomyopathy, excessive p53 acetylation is observed, which correlates with increased apoptosis [168,173]. In cardiac fibroblasts, viral myocarditis-induced sST2 promotes fibrosis by inhibiting senescence by the SIRT1/p53/p21 pathway, thereby sustaining fibroblast activation and collagen deposition [174]. These findings suggest that SIRT1–p53 signaling is not only central to cardiomyocyte survival but also crucial for the regulation of fibroblast-driven remodeling during cardiac injury [174].

6.2. SIRT2 and oxidative stress

The role of SIRT2 in the heart is strongly dependent on the pathological context. On the one hand, in diabetic cardiomyopathy, SIRT2 has a protective effect by deacetylating FOXO3a and Nrf2, which leads to increased transcription of antioxidant genes (HO-1, SOD, GSH) and counteracts the negative effects of miR-140–5p, a microRNA that inhibits the expression of SIRT2 and Nrf2 [175-177]. On the other hand, in models of ischaemia/reperfusion (I/R) or pressure overload (TAC), SIRT2 deletion improves heart function by increasing NRF2 nuclear translocation and improving mitochondrial function [178] [179]. This apparent contradiction may result from differences in signaling dependent on the type of myocardial damage. Additionally, in coronary artery disease, the SIRT2/Nrf2/FOXO3 pathway is inhibited by miR-339, and SIRT2 inhibition abolishes its beneficial effects by reducing SOD and

GSH expression [180]. The role of SIRT2 in the regulation of fibrosis is questionable – while in the liver its knockout increases FOXO1 acetylation and endoplasmic reticulum stress [181], in the heart its effect on fibroblast transdifferentiation remains unclear.

6.3. SIRT3 and oxidative stress

SIRT3, as the main mitochondrial deacetylase, plays an important role in protecting cardiomyocytes from OS and apoptosis [182]. It occurs in two isoforms (44 kDa and 28 kDa), the shorter of which is located exclusively in mitochondria, where it deacetylates proteins essential for their function, e.g. Ku70, inhibiting the translocation of proapoptotic Bax and stabilizing the membrane potential (ΔΨm) [182]. Furthermore, SIRT3 indirectly supports mitochondrial biogenesis and energy functions of heart cells by regulating PGC-1α levels and improving mitochondrial enzyme activity [183]. In Ang II-induced models, it has been shown that its action leads to a decrease in SIRT3 levels, resulting in increased production of ROS, decreased SOD2 activity, and increased OS and mitochondrial damage [143,184]. The loss of SIRT3 in cardiomyocytes also promotes the activation of inflammatory pathways, including NF-κB, and increases the expression of cytokines such as TNF-α and IL-6, which exacerbates the inflammatory process and myocardial remodeling [143,145]. SIRT3 plays a key role in regulating the proliferation and survival of CF under hypoxic conditions by modulating mitochondrial function and reducing OS [185]. Its activity inhibits necroptosis and decreases the expression of fibrosis markers, suggesting a potential role for SIRT3 in limiting cardiac remodeling in ischemic heart disease [185]. SIRT3 overexpression mitigates the effects of Ang II by limiting the expression of cardiac hypertrophy markers (ANP, BNP) and inhibiting the activation of mTOR/p70S6K, JNK and p38MAPK pathways [79]. Under OS, SIRT3 expression increases in both mitochondria and cell nuclei, where the protein deacetylates Ku70, inhibiting the translocation of proapoptotic Bax to mitochondria and thus preventing apoptosis [182]. The protective mechanisms of SIRT3 also include the regulation of the NF-κB pathway – SIRT3 activator RSV protects cardiomyocytes from H2O2-induced apoptosis by inhibiting NF-κB activation and regulating the expression of its target genes, including SOD2, Bcl-2 and Bax [143]. Sesamin exerts a SIRT3-dependent effect on cardiac remodeling, as indicated by the finding that its antioxidant properties mediate the suppression of AngII-induced TGF-β1 secretion in neonatal rat CF [146]. In diabetic cardiomyopathy, SIRT3 plays a key role in cardiac fibroblasts by mediating the epigenetic regulation of BCAA metabolism through deacetylation of H3K27ac on the promoters of BCAT2 and PP2Cm, thereby limiting OS, CF proliferation, and periostin-induced cardiomyocyte injury [186]. Moreover, RSV activates SIRT3 in DCM, reducing the acetylation of the mitochondrial transcription factor TFAM and improving mitochondrial function, further highlighting SIRT3 as a central regulator of CF and mitochondrial homeostasis and a potential therapeutic target in diabetic cardiomyopathy [187].

In a model of pressure overload-induced heart failure, the drug LCZ696 exhibits protective effects by activating the SIRT3/MnSOD pathway, reducing ROS accumulation and cardiomyocyte apoptosis [188]. In 2015 sacubitril in combination with valsartan has become a pillar of heart failure therapy, based on the findings of multiple randonized contrelled trials [189,190]. SIRT3 appears to be a central mediator in the cardioprotective effects of colchicine under pressure overload, particularly by modulating cardiac fibroblast (CF) function, as its activation reduces CF-driven OS and fibrosis [191]. Similarly, hydrogen sulphide (H_2S) protects against Ang II- or TAC-induced myocardial fibrosis by increasing SIRT3 expression and promoter activity in CFs, an effect abolished upon SIRT3 silencing [192]. These results highlight SIRT3 as a key regulator of fibroblast activation and extracellular matrix remodeling, and a potential therapeutic target to prevent cardiac fibrosis in models of pressure overload and Ang II-induced injury.

Tetrahydrocurcumin (THC) protects against heart dysfunction after myocardial infarction by activating the Nrf2-SIRT3 pathway, which leads to a reduction in OS and mitochondrial damage [193]. The small molecule SIRT3 activator 2-APQC alleviates isoproterenol-induced cardiac hypertrophy and myocardial fibrosis by regulating mitochondrial homeostasis and inhibiting the mTOR-p70S6K, JNK and TGF-β/Smad3 pathways [79]. In a model of T-2 toxin-induced cardiotoxicity, the Sirt3/FoxO3α/MnSOD pathway is inhibited and OS is increased, leading to fibrotic myocardial damage [194].

6.4. SIRT4 and oxidative stress

Unlike other sirtuins, which are involved in suppression or change their activity under the influence of OS SIRT4 mediates the generation of OS. Mechanistically, SIRT4 inhibits the interaction of MnSOD with SIRT3, leading to an increase in MnSOD acetylation, which reduces its ability to neutralise ROS [195]. Excess ROS activates pro-inflammatory pathways and increases the production of pro-fibrotic factors such as TGF-β, IL-6 and TNF-α, although these were not directly measured in this study. Concurrently, in a doxorubicin-induced cardiotoxicity model, SIRT4 expression was reduced, suggesting that its role may be context-dependent. In this case, SIRT4 overexpression had a protective effect, reducing levels of myocardial damage markers and limiting apoptosis [196]. This indicates that under conditions of acute mitochondrial stress, SIRT4 may also have a protective function, depending on the balance between autophagy and apoptosis.

6.5. SIRT5 and oxidative stress

SIRT5 plays a key role in maintaining redox homeostasis by regulating the activity of mitochondrial enzymes through desuccinylation of SDHA, IDH2, G6PD, SOD1, and Pck2 [88,197-199]. The absence of SIRT5 leads to hypersuccinylation of these enzymes, decreased respiratory chain activity (OXPHOS), increased NADH and mtROS levels, and reduced ATP production [198-200]. In models of ischaemia-reperfusion (I/R) injury, Sirt5-/- hearts showed increased ROS production and enhanced necrosis, which could be mitigated by the SDH inhibitor (dimethylmalonate), confirming the complex II-based pathomechanism [197]. SIRT5 also supports FOXO3A activation and the pentose phosphate pathway (PPP), increasing NADPH generation and alleviating OS [201]. SIRT5 deficiency led to mitochondrial dysfunction and loss of control over ROS production, which was associated with increased fibrosis and cardiac hypertrophy in both TAC and DCM models [88,150,151].

6.6. SIRT6 and oxidative stress

Under stressful conditions (e.g., under the influence of angiotensin II or pressure overload), a decrease in NAD+ impairs SIRT6 activity. To compensate for this, SIRT6 increases the expression of Nmnat2, an enzyme essential for NAD+ biosynthesis, restoring its own deacetylase function [202]. Additionally, SIRT6 inhibits the activation of NADPH oxidases (NOX2 and NOX4), which are the major sources of ROS in the heart. Pharmacological inhibition of poly(ADP-ribose) polymerase 1 (PARP-1) using compounds such as AG-690/11026014 (6014) prevents NAD+ depletion, restores SIRT6 activity, and alleviates Ang II-induced OS and hypertrophy [203]. SIRT6 emerges as a crucial mediator of the antifibrotic action of SGLT2 inhibitors, as its upregulation prevents OS and fibroblast-to-myofibroblast transition [204]. These findings position SIRT6 as a central node linking metabolic modulation with the suppression of myocardial fibrosis. SIRT6 increases the expression of antioxidant genes by histone deacetylation in their promoters and interaction with transcription factors such as FOXO3, which regulates autophagy and OS response pathways [205]. In diabetic cardiomyopathy, SIRT6 deficiency exacerbates ROS production and lipid peroxidation, while its overexpression or activation by small molecules (e.g.,

MDL-800) improves mitochondrial function and reduces OS [100]. Furthermore, the ability of SIRT6 to inhibit NF-κB and TGF-β signaling in CF, indirectly reduces inflammation-induced OS, creating a protective feedback loop against fibrotic remodeling [90,206]. In CF stimulated with angiotensin II, SIRT6 depletion increases NF-κB DNA binding activity, leading to increased expression of α-SMA, a marker of fibroblast transdifferentiation. Overexpression of SIRT6 reverses this effect, restoring normal fibroblast function [206]. This mechanism involves histone deacetylation in NF-κB target gene promoters via SIRT6, which reduces their transcriptional activity. Pharmacological inhibition of NF-κB with pyrrolidine dithiocarbamate (PDTC) mimics the anti-fibrotic action of SIRT6, further confirming the importance of this pathway [206]. Additionally, SIRT6 interacts with Nrf2, increasing the expression of antioxidant genes and supporting the autophagy process [202, 203]. The discovery that SIRT6 can function as a transcriptional coactivator for GATA4 independently of its deacetylase activity [207] suggests alternative pathways for counteracting OS. This is particularly relevant in doxorubicin-induced cardiotoxicity, where SIRT6 preserves heart function by activating GATA4-dependent anti-apoptotic genes, even when its deacetylase activity may be impaired by NAD+ deficiency [207].

6.7. SIRT7 and oxidative stress

SIRT7 is responsible for maintaining the homeostasis of proteins essential for mitochondrial function, and SIRT7 deficiency induces systemic mitochondrial dysfunction [208]. Lower SIRT7 levels promote mitochondrial ageing and cardiac fibrosis [209]. SIRT7 regulates the formation of the GABPα/GABPβ complex (a regulator of adaptive processes in mitochondria) through the deacetylation of GABPβ1, which is responsible for the activation of cytochrome oxidase expression [208]. Furthermore, Sirt7 deacetylates p53, thereby protecting cardiomyocytes from apoptosis [110]. Interestingly, in ischaemic heart disease, activation of the miR-148b-3p/SIRT7/p53 axis and its potential to modulate p53 acetylation have been demonstrated [210]. Aortic valve stenosis is one of the pathologies that induce cardiac hypertrophy and fibrosis. Senile calcification of the aortic valve leaflets leads to restricted opening of the valve and OS is a strong component in the pathophysiology of this disease. The development of aortic stenosis in mice was limited by the Sirt7-Nrf2-ARE axis, which influenced the oxidative potential of aortic valve interstitial cells by stabilizing the mitochondrial membrane potential and supporting antioxidant levels in valve leaflet cells [211].

6.8. Clinical implications of oxidative stress and mitochondrial dysfunction in cardiac fibrosis

The interplay between mitochondrial dysfunction and OS not only underpins molecular pathways in cardiac fibrosis but also holds translational relevance in cardiology practice. The evidence on SIRT3, SIRT5, and SIRT6 highlights their crucial role in maintaining mitochondrial integrity and mitigating oxidative stress. These insights align with emerging diagnostic strategies using non-invasive imaging modalities, such as cardiac magnetic resonance imaging (cMRI), which enable the early detection of fibrotic changes and OS-related myocardial remodeling [212]. In clinical settings, patients with age-related HFpEF, diabetic cardiomyopathy, or chemotherapy-induced cardiotoxicity may potentially benefit from therapies that activate mitochondrial sirtuins to enhance antioxidant defense and mitochondrial resilience.

7. Conclusion

In summary, sirtuins represent a complex and dynamic family of proteins that intricately modulate key pathways involved in cardiac fibrosis, acting as both guardians and potential contributors depending on cellular context, disease stage, and metabolic environment. Their ability to regulate fibrosis-related signaling cascades such as TGF-β, NF-κB, and ROS production, along with their interactions with non-coding RNAs and epigenetic factors, underscores their central role in the

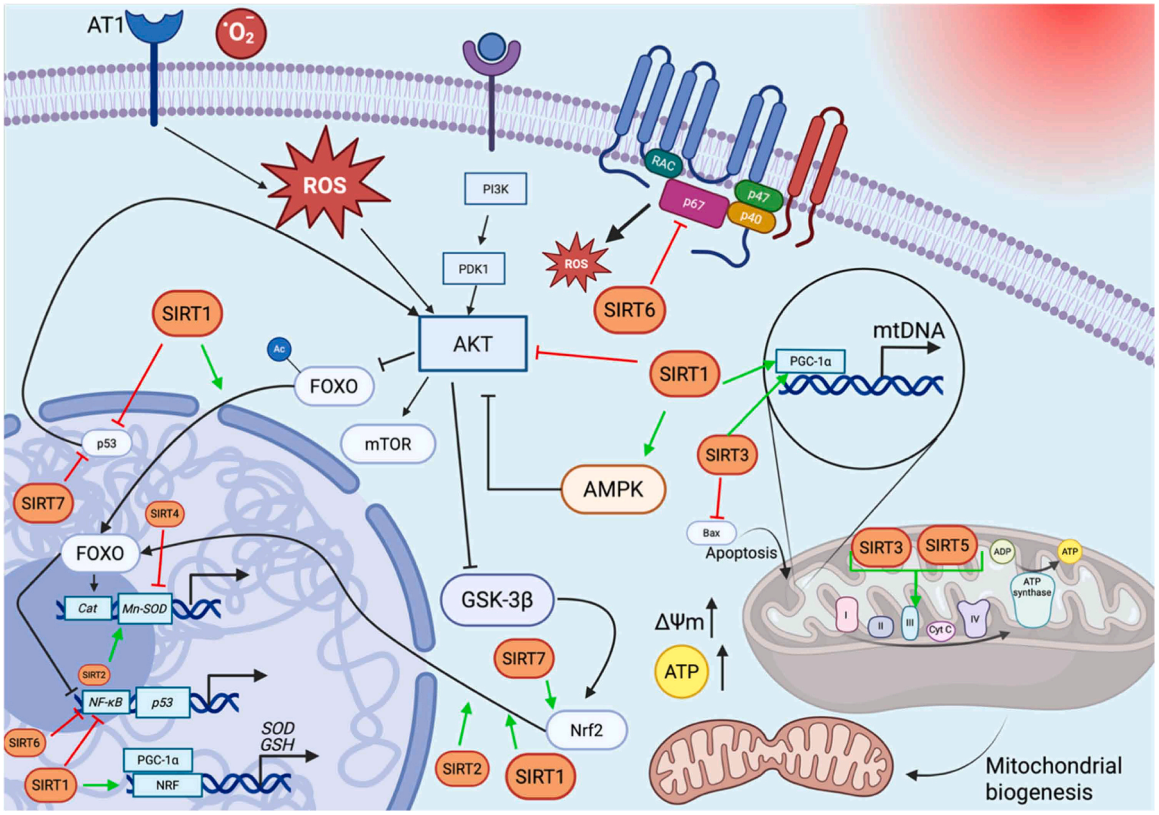

Fig. 4. The role of SIRT1–SIRT7 in combating OS: from ROS detoxification to mitochondrial protection.

pathogenesis and progression of myocardial remodeling. The therapeutic modulation of sirtuins, particularly SIRT1, SIRT3, and SIRT6, holds considerable promise in reversing fibrotic processes and preserving cardiac function. However, the dual nature of some sirtuins, like SIRT4 and SIRT7, necessitates a nuanced understanding of their tissue- and condition-specific actions. As research advances, a more refined targeting of individual sirtuins or their upstream regulators could offer precise and effective strategies against cardiac fibrosis. Ultimately, unraveling the complex molecular crosstalk surrounding sirtuins may unlock novel interventions capable of altering the trajectory of heart failure and age-associated cardiac deterioration.

CRediT authorship contribution statement

Xutong Gong: Writing – review & editing. **Szymon Graczyk:** Writing – original draft. **Sebastian Spethmann:** Writing – review & editing. **Jan Gröschel:** Writing – review & editing. **KORDOWITZKI Pawel:** Writing – review & editing, Visualization, Supervision, Conceptualization. **Arkadiusz Grzeczka:** Writing – original draft, Visualization, Conceptualization.

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Declaration of Competing Interest

All authors declare that they have no conflicts of interest.
Besides, all authors declare the following:

- The work described has not been published previously except in the form of a preprint, an abstract, a published lecture, an academic thesis, or a registered report. See our policy on multiple, redundant or concurrent publication.
- the article is not under consideration for publication elsewhere.
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Data Availability

No data was used for the research described in the article.

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