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Review

Role of Sirtuins in the Pathogenesis of Osteoarthritis

Paweł Dec[1], Marek Dzik[1], Paulina Plewa[1] and Andrzej Pawlik[1,*]

[1] Department of Physiology, Pomeranian Medical University, 70-111 Szczecin, Poland

Abstract

Sirtuins (SIRTs) are a family of proteins involved in diverse cellular processes and play important roles in ageing and the development of osteoarthritis (OA). Among them, SIRT1, SIRT3, and SIRT6 have been identified as key regulators of cartilage homeostasis, primarily through their control of oxidative stress and modulation of proinflammatory, anabolic, and catabolic pathways within the extracellular matrix. These protective effects are mediated through the regulation of transcription factors such as nuclear factor kappa B (NF-κB) and p53, as well as through direct inhibition of matrix metalloproteinases. Evidence from current studies suggests that reduced SIRT expression in chondrocytes contributes to apoptosis and autophagy-dependent cartilage degradation. Understanding the mechanisms through which SIRTs function may provide promising opportunities for the treatment of OA. This review aims to summarise current knowledge regarding the role of SIRTs in the pathogenesis of OA.

Keywords: Sirtuins, aging, osteoarthritis, chondrocytes, stress from oxidation, inflammation.

***Address for correspondence**: Andrzej Pawlik, Department of Physiology, Pomeranian Medical University, 70-111 Szczecin, Poland. E-mail: pawand@poczta.onet.pl.

Introduction

Osteoarthritis (OA) is one of the most common diseases leading to the gradual destruction of cartilage in joints. Cartilage is a spongy tissue that cushions the ends of bones within joints, allowing smooth movement. Over time, this breakdown can also affect the bone beneath the cartilage, causing structural and compositional changes. The disease often manifests as inflammation and swelling of the thin, smooth lining inside the joint, known as the synovium. This inflammation can cause severe pain and stiffness, leading to further disability and a reduced quality of life. Symptoms of OA include swelling, tenderness, and limited range of motion in the affected joint. Diseases affecting weight-bearing joints can seriously impair daily activities and overall well-being. A thorough understanding of the disease process in OA is crucial for the development of effective preventive and symptomatic treatment strategies. With the continuing increase in the ageing population, the prevalence of OA is expected to rise, further underscoring the urgent need to understand its pathogenesis [1–4]. A new understanding of OA development in the context of novel preventive and therapeutic interventions may direct research attention towards the sirtuin (SIRT) family of proteins, which are known to regulate cellular and metabolic activity and are associated with longevity. SIRTs play a role in gene silencing and therefore participate in several biological processes associated with OA development, with inflammation and cellular stress responses representing key drivers of the disease [5]. This article provides an overview of the role of SIRTs in OA, focusing on their involvement in the pathogenesis of cartilage destruction and the disruption of homeostasis in cartilage and bone. In the following sections, we provide a detailed discussion of OA pathogenesis, examining the cellular and molecular changes in cartilage and arthritic tissue. This will help us investigate how and to what extent SIRTs can modulate these changes and potentially offer new treatment options.

Pathogenesis of OA

OA is characterised by the progressive breakdown of joint cartilage. Patients typically report pain, swelling, and limited mobility in the affected areas, often worsening with movement. Joint stiffness after periods of inactivity and visible inflammation around the joint are common, significantly affecting quality of life by limiting function.

OA has a multifactorial pathogenesis influenced by mechanical, biological, and genetic factors. Ageing is a major risk factor because the likelihood of developing OA increases with age, while excess body weight exacerbates the condition by increasing pressure on weight-bearing joints such as the hips and knees. Previous sports injuries or joint trauma also increase the risk. Furthermore, genetic predis-

position through inherited traits that influence cartilage nutrition and joint function may make some individuals more susceptible to the disease.

OA can begin with micro-tears in the joint cartilage, which, if left untreated, lead to significant degeneration. Disturbances in cartilage homeostasis are associated with changes in subchondral bone and periarticular inflammation. As the disease progresses, disruption of the balance between cartilage degradation and repair contributes to further disease progression and increased pain severity. The development of OA is also associated with metabolic dysfunction and oxidative stress, both of which exacerbate tissue damage. This association represents a potential therapeutic target because understanding the impact of metabolic imbalances on inflammation and joint health could support the development of improved treatments [3–5].

Degeneration of Cartilage and the Extracellular Matrix (ECM)

Joint cartilage is a specialised connective tissue lacking vascularity and innervation, whose integrity depends on chondrocyte activity and the composition of the ECM [6]. The ECM is primarily composed of type II collagen, which provides mechanical strength and elasticity, and proteoglycans such as aggrecan, which promote water retention and contribute to elasticity [7].

OA is associated with significant structural changes, including loss of proteoglycans, degradation of type II collagen, and a reduced ability of cartilage to retain water [8,9]. This process is driven by increased activity of proteolytic enzymes, such as matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with a thrombospondin (ADAMTS), whose expression is stimulated by proinflammatory cytokines, including interleukin (IL)-1β and tumour necrosis factor-α (TNF-α) [10]. Under physiological conditions, chondrocytes regulate the synthesis and degradation of key ECM components. However, in OA, a distinct imbalance occurs, as excessive activation of catabolic pathways leads to progressive cartilage destruction. This is reflected in the increased activity of MMPs, particularly MMP-1, MMP-3, and MMP-13, which target and degrade collagen and other proteoglycans [11]. Furthermore, overexpression of ADAMTS-4 and ADAMTS-5 further enhances degradation through aggrecan disassembly, while reduced synthesis of ECM components reflects a loss of structural integrity [12]. In addition, chondrocytes in OA often adopt a proinflammatory phenotype, promoting chronic, low-grade inflammation within the joint. This inflammation is driven by elevated levels of cytokines such as IL-1β, TNF-α, and IL-6, which stimulate the production of catabolic enzymes while simultaneously impairing ECM synthesis. The accumulation of reactive oxygen species (ROS) further increases the burden by inducing oxidative stress and causing damage to DNA, lipids, and proteins within cartilage, thereby accelerating its degradation. Activation of the nuclear factor kappa B (NF-κB) signalling pathway perpetuates inflammation and further increases the expression of MMPs and ADAMTS enzymes [13]. Simultaneously, a significant increase in chondrocyte apoptosis and senescence is observed, markedly impairing the regenerative capacity of cartilage. This is associated with increased expression of proapoptotic proteins, such as Bax and caspases, which promote cell death and tissue degradation [14]. Endoplasmic reticulum (ER) stress also plays a key role by mediating chondrocyte apoptosis and disrupting secretory functions, thereby destabilising cartilage homeostasis [15].

Inflammation and the Role of the Synovium

The recognition of chronic inflammation has significantly changed the understanding of OA, which was long considered a purely degenerative disease. Recent findings regarding low-grade inflammation have contributed to a deeper understanding of both the initiation and progression of OA. Early in this process, the immune system becomes activated, and macrophages and lymphocytes migrate into the joint [16]. Among the inflammatory mediators involved, proinflammatory cytokines such as IL-1β, IL-6, and TNF-α are particularly important because they promote cartilage degradation through activation of MMPs [17].

Another key pathway involves inflammasome activation, particularly that of the NLRP3 inflammasome, which plays a dual role in driving inflammation and facilitating cartilage destruction. Over time, chronic immune-mediated inflammation leads to chondrocyte apoptosis, synovial membrane damage, and increased production of cartilage-degrading enzymes, including MMPs and ADAMTS. Swelling of the tissue lining the joints, known as synovitis, occurs at almost every stage of OA and strongly correlates with pain severity and disease progression [18].

Within this inflammatory environment, synoviocyte proliferation is stimulated, resulting in excessive production of synovial fluid, which further contributes to joint swelling and pain [19]. Fibroblast-like synoviocytes are a major source of enzymes that degrade cartilage and perpetuate the inflammatory cycle [20]. Angiogenesis further supports this process by promoting the growth of new blood vessels in the synovial membrane, thereby sustaining inflammation [21].

The synovium plays a central role in these pathological processes. Synovitis leads to increased production of proinflammatory cytokines [17], while synoviocyte proliferation and overproduction of synovial fluid contribute further to swelling and pain [18]. Additional mechanisms include activation of the NLRP3 inflammasome, impaired cell signalling, and increased angiogenesis within the synovial membrane, all of which promote chronic inflammation. Fragments of degraded cartilage present in the synovial fluid further stimulate the immune response, exacer-

bating disease progression [19,21].

The complement system, including proteins such as C3a and C5a, also plays an important role by recruiting immune cells to the joint and amplifying inflammation. Furthermore, adipokines such as leptin and resistin not only stimulate the production of proinflammatory cytokines but also directly contribute to cartilage degradation [22].

Increased apoptosis and senescence of chondrocytes are also observed in OA. Senescent cells adopt the senescence-associated secretory phenotype (SASP), releasing inflammatory mediators that further contribute to disease progression [23]. OA is additionally characterised by impaired mechanosensation and metabolic dysregulation because chondrocytes rely on mechanical signals to maintain homeostasis. Mechanical overload and metabolic disturbances disrupt chondrocyte function through dysregulation of Wnt/β-catenin signalling, thereby disturbing the balance between ECM synthesis and degradation. In addition, reduced transforming growth factor-β signalling, which is critical for cartilage repair, impairs anabolic responses, while defective autophagy leads to the accumulation of damaged organelles and proteins, further exacerbating chondrocyte dysfunction [24].

Changes in Subchondral Bone

The component of the skeletal system located directly beneath the cartilage, which provides structural support to the joint, is known as subchondral bone. Changes in this structure are consistently associated with the development of OA and are considered among the most important factors contributing to its progression. During the course of the disease, an imbalance between bone resorption and bone formation occurs, leading to alterations in bone microarchitecture [25]. Initially, increased bone resorption is observed, followed by remodelling that leads to sclerosis of the subchondral bone. Osteophytes, or bony outgrowths, also develop at the joint margins. These contribute to joint space narrowing and increased stiffness, ultimately resulting in joint deformation and limited mobility. Increases in the thickness, density, and stiffness of subchondral bone disrupt the distribution of mechanical forces within the joint, thereby secondarily exacerbating cartilage damage [26,27]. As the disease progresses, significant microarchitectural changes occur in the subchondral bone, including initial thinning and loss of trabecular connectivity, followed by increased mineralisation leading to trabecular thickening and fragility [28,29]. Altered angiogenesis also influences this remodelling process because increased vascularisation within the subchondral bone can promote nerve growth, thereby contributing to pain [22]. Furthermore, substantial interactions occur between subchondral bone and cartilage through biochemical signalling pathways. Elevated levels of proinflammatory cytokines, such as IL-1 and TNF-α, together with matrix-degrading enzymes such as MMPs, contribute not only to cartilage breakdown but also to structural changes in the subchondral bone [30,31].

Metabolic Dysfunction and Oxidative Stress

Metabolism plays a key role in supplying energy and nutrients to cartilage, supporting molecular synthesis and generating the energy necessary to maintain the structural matrix. An imbalance between the production and removal of reactive byproducts generated during normal cellular metabolism can lead to oxidative stress. Excess ROS damage lipids, proteins, and DNA through oxidative reactions, thereby exacerbating cartilage degeneration [32]. ROS also enhance the activity of ECM-degrading enzymes, including MMPs, leading to increased cartilage breakdown. Furthermore, oxidative stress initiates inflammatory responses through activation of the NF-κB signalling pathway [33].

Mitochondrial dysfunction contributes significantly to the pathogenesis of OA. It leads to elevated ROS levels, mitochondrial DNA damage, and reduced ATP production. Impaired mitophagy further promotes the accumulation of damaged mitochondria, contributing to cellular ageing and apoptosis [34–37].

Disturbances in energy metabolism in OA lead to a shift from normal anaerobic glycolysis towards increased oxidative phosphorylation. Although this oxidative shift may initially appear beneficial, it actually increases ROS production, thereby intensifying oxidative stress. The resulting reduction in ATP levels impairs the reparative capacity of chondrocytes while simultaneously activating catabolic pathways that promote cartilage breakdown and inflammation. This creates a self-perpetuating cycle that accelerates degeneration of joint tissues [36].

Metabolic dysfunction has been identified as a key factor contributing to oxidative stress and is commonly associated with chronic conditions such as obesity and diabetes. Excess adipose tissue increases levels of proinflammatory cytokines and free fatty acids, both of which exert persistent detrimental effects on joints [38,39]. Insulin resistance reduces tissue sensitivity to insulin, leading to compensatory hyperinsulinaemia, which can trigger inflammatory responses and exacerbate cartilage degradation. Hyperglycaemia, defined as chronically elevated glucose levels, further promotes the formation of advanced glycation end products, which impair cartilage function and increase mechanical stress within joints [17,40–42]. This metabolic imbalance perpetuates chronic inflammation and thereby accelerates joint degradation in OA. The mechanisms through which insulin resistance exacerbates OA are multifaceted. It induces oxidative stress through the overproduction of ROS, causing cellular damage to both chondrocytes and the ECM structures essential for joint integrity. Hyperinsulinaemia also increases the release of proinflammatory cytokines, such as TNF-α and IL-6, which play key roles in cartilage degradation. At the same time, insulin resistance disrupts adipokine homeostasis by increasing levels of proinflammatory mediators such as leptin

and resistin, while simultaneously decreasing levels of the protective adipokine adiponectin [43]. Lipids also play a crucial role in maintaining chondrocyte homeostasis; consequently, lipid imbalances may lead to chondrocyte dysfunction and apoptosis. This condition, referred to as lipotoxicity, occurs when lipid accumulation within cartilage cells causes cellular damage through oxidative stress and inflammation. Saturated fatty acids in particular are associated with increased production of proinflammatory cytokines, which further contribute to the breakdown of the cartilage matrix and loss of structural integrity. Obesity exacerbates this problem not only through additional mechanical loading of joints but also through systemic inflammation associated with dyslipidaemia and adipokine activity. Leptin and resistin, two signalling molecules derived from adipose tissue, enhance inflammatory responses and thereby promote cartilage destruction. Furthermore, disorders of lipid metabolism negatively affect periarticular microcirculation, reducing nutrient delivery to cartilage and accelerating degeneration. These findings highlight the multifaceted impact of lipid dysregulation on joint health and OA progression [44].

Characterization of Sirtuins

SIRTs are a diverse group of proteins whose structural variability supports their enzymatic roles in numerous cellular processes. They catalyse reactions involving protein acetyl groups through a highly conserved catalytic core domain and are dependent on nicotinamide adenine dinucleotide (NAD^+). This domain contains the Rossmann fold, a structural motif commonly found in nucleotide-binding proteins, which is essential for proper NAD^+ binding [5,45,46]. This cofactor, nicotinamide adenine dinucleotide, is critical not only for deacetylation but also for cellular energy regulation because it is cleaved during the reaction into nicotinamide and O-acetyl-ADP-ribose, thereby influencing numerous metabolic pathways [47]. SIRTs deacetylate both histone and non-histone proteins, including p53, forkhead box O (FOXO) transcription factors, PGC-1α, and NF-κB, thereby regulating metabolism, apoptosis, and cellular stress responses [48]. The diversity of mammalian SIRTs, ranging from SIRT1 to SIRT7, highlights both their compartmental and functional diversity. SIRT1, SIRT6, and SIRT7 are primarily localised in the nucleus, whereas SIRT2 is mainly found in the cytoplasm, and SIRT3, SIRT4, and SIRT5 are localised to mitochondria (Table 1). In addition to the catalytic domain, the structural modularity of SIRTs often includes additional regulatory regions that modulate enzymatic activity and facilitate interactions with other proteins. This structural complexity highlights the adaptability and broad functional scope of the SIRT family within the cellular environment [49].

Role of Individual Sirtuins in OA

SIRT 1

SIRT1, a key enzyme of the class III histone deacetylase family, has been proposed as an important regulator of OA because of its ability to modulate cartilage homeostasis by influencing inflammatory processes, oxidative stress, and ECM catabolism. It is essential for the differentiation of mesenchymal stem cells into chondrocytes [50]. SIRT1 deacetylates target proteins such as p53, NF-κB, and FOXO, all of which are crucial for chondrocyte survival and regeneration. In OA, SIRT1 expression is reduced, leading to increased activation of the NF-κB pathway, enhanced production of SASP factors including IL-6, IL-8, IL-1β, and TNF-α, and accelerated ECM degradation driven by MMPs and aggrecanases such as ADAMTS-4 and ADAMTS-5 [51,52]. SIRT1 inhibits chondrocyte apoptosis through several mechanisms, including inhibition of tyrosine phosphatase 1B and regulation of mitochondrial pathways [53]. Cartilage-specific SIRT1 deficiency causes hyperactivation of mTORC1 signalling, leading to reduced chondrocyte proliferation and hypertrophy, as well as increased apoptosis [54]. SIRT1 also promotes chondrocyte survival by scavenging ROS through the FOXO3 pathway, thereby helping to prevent cartilage damage [55]. Furthermore, it deacetylates FOXO4 and SRYbox transcription factor 9 (SOX9), directly enhancing SOX9 activity and supporting the expression of cartilage-specific genes, thus preserving ECM homeostasis (Fig. 1) [56]. It also regulates mitochondrial apoptotic pathways involving Bcl-2 and Bax [53]. Modulation of inflammatory mediators by SIRT1 highlights its potential protective role in cartilage metabolism and its possible utility as a biomarker for monitoring OA progression [57–59]. In addition, SIRT1 enhances BMP2-induced differentiation of cartilage stem cells and promotes cartilage formation while reducing apoptosis under conditions of oxidative stress. Its activity helps maintain a less oxidative intracellular environment, thereby creating more favourable conditions for mesenchymal stem cell chondrogenesis [60]. Furthermore, the ability of SIRT1 to promote autophagy facilitates the removal of damaged cellular components, helping to maintain cellular homeostasis and protect the synovium from further degeneration [61]. Because of the heterogeneous role of mitophagy in OA, SIRT1 may bidirectionally regulate this process and thereby mediate cartilage protection. First, by acting through PGC-1α, SIRT1 reduces BNIP3 expression. This results in reduced mitophagy through inhibition of mitochondrial depolarisation and preservation of oxidative respiration capacity. In addition, SIRT1 regulates mitophagy through downstream AMPK-dependent signalling, promoting restoration of mitochondrial function [62].

Studies have shown that SIRT1 expression levels increase in the early stages of OA but decrease in the later stages. In the early stages of OA, the increase in SIRT1 levels has a protective effect by inhibiting inflammatory

Table 1. Biological functions and localisations of SIRTs.

SIRT	Localisation	Biological function	References
SIRT1	Nucleus, cytoplasm	Regulates ageing, metabolism, DNA repair, inflammation, and stress resistance	[49,51,52,55,61]
SIRT2	Nucleus, cytoplasm	Controls cell cycle, mitosis, and oxidative stress responses	[49,50]
SIRT3	Mitochondria	Regulates mitochondrial metabolism, oxidative stress, and energy homeostasis	[49,71,74,75]
SIRT4	Mitochondria	Controls insulin secretion, lipid metabolism, and glutamine metabolism	[49,71,82,83]
SIRT5	Mitochondria	Involved in ammonia detoxification, fatty acid oxidation, and cellular respiration	[49,85,87]
SIRT6	Nucleus	Regulates DNA repair, genome stability, inflammation, and glucose metabolism	[49,90–92,95]
SIRT7	Nucleus	Controls ribosome biogenesis, stress responses, and cellular homeostasis	[49,98]

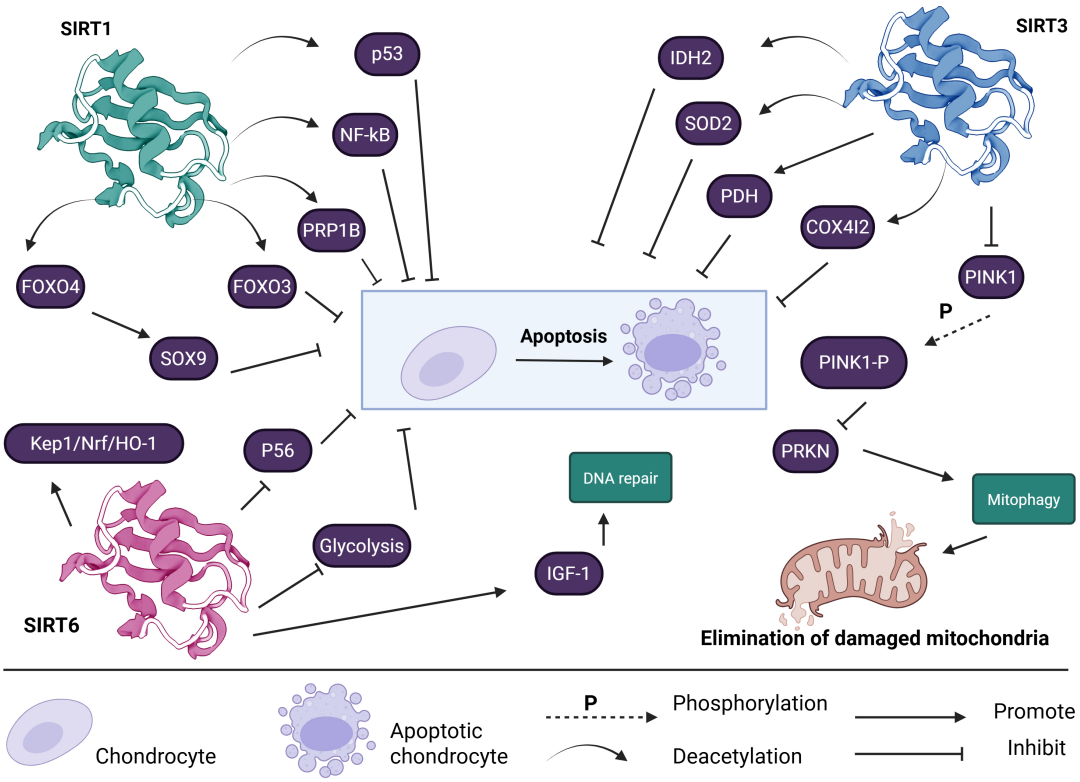

Fig. 1. The role of sirtuins SIRT1, SIRT3, and SIRT6 in regulating chondrocyte apoptosis. These proteins participate in various signalling pathways, modulating processes related to cell survival, stress response, and homeostasis, which influence the course of cartilage degeneration. Created in BioRender. Plewa, P. (2026) https://BioRender.com/uj48oh9

processes and pathways associated with NF-κB activation, which in turn inhibits the production of MMPs and reduces chondrocyte apoptosis. In the later stages of OA, enzymes such as MMPs and caspases are activated, leading to degradation of the SIRT1 protein. Furthermore, as the disease progresses, chondrocytes lose their ability to biosynthesise SIRT1. In advanced disease, mitochondrial dysfunction and increased oxidative stress lead to a decrease in cellular levels of NAD^+, which serves as a cofactor for SIRT1. This results in reduced SIRT1 activity [63–67].

SIRT 2

SIRT2 plays a key role in maintaining chondrocyte homeostasis by regulating the cell cycle, oxidative stress, and inflammation. In OA, decreased SIRT2 expression leads to excessive activation of NF-κB and increased production of proinflammatory cytokines, particularly IL-1β and TNF-α [5]. Reduced SIRT2 activity also results in increased ROS accumulation and enhanced ECM degradation through upregulation of MMP expression (Fig. 2). SIRT2 additionally contributes to microtubule stability and centrosome function, thereby influencing chondrocyte proliferation and regenerative capacity. The importance of SIRT2 becomes even more evident in the context of cellular ageing. With age, cells commonly experience increased oxidative stress and mitochondrial dysfunction. SIRT2 helps counteract these age-related changes by promoting mitochondrial health and supporting efficient cellular respiration. In this way, it may slow age-related functional decline and potentially contribute to improved health during ageing [68]. Studies have shown that SIRT2 can exert multifaceted effects on chondrocytes and bone cells. On the one

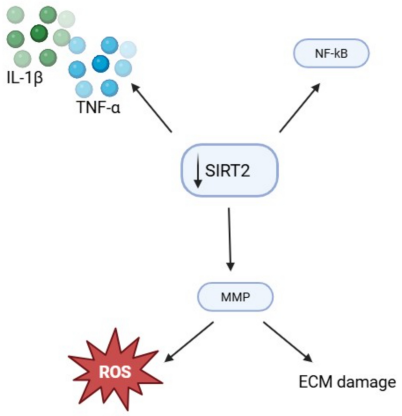

Fig. 2. The effect of reduced SIRT2 expression on OA. Created in BioRender. Plewa, P. (2026) https://BioRender.com/f8p9gbd

hand, it may have a protective effect by inhibiting the NLR family pyrin domain containing 3/NF-κB (NLRP3/NF-κB) pathway. SIRT2 deacetylates the p65 subunit of the NF-κB complex, thereby inhibiting the synthesis of pro-inflammatory cytokines, including interleukin-1β and tumour necrosis factor-α, as well as the NLRP3 inflammasome. By deacetylating FOXO1, SIRT2 enhances mitophagy, enabling the removal of damaged mitochondria from the cell [69]. SIRT2 also reduces inflammation and the expression of MMPs (MMP-3 and MMP-13), protecting type II collagen and aggrecan from degradation [70]. On the other hand, SIRT2 can inhibit microtubule acetylation, which plays a crucial role in the transport of amorphous calcium phosphate (ACP) vesicles that mediate the osteogenic differentiation of bone marrow mesenchymal stem cells [69].

SIRT 3

SIRT3 is a mitochondrial NAD^+-dependent deacetylase that plays a key role in regulating energy metabolism and cellular stress responses in OA. In OA, decreased SIRT3 expression in chondrocytes contributes to mitochondrial dysfunction, increased ROS production, and enhanced catabolic activity within cartilage [71,72]. SIRT3 deacetylates and activates antioxidant enzymes such as superoxide dismutase 2 (SOD2) and isocitrate dehydrogenase 2, thereby reducing oxidative stress and directly inhibiting chondrocyte apoptosis through neutralisation of excess ROS [73,74]. Enhancement of the SIRT3/SOD2 signalling pathway provides additional protection against oxidative damage in cartilage. Furthermore, SIRT3 regulates the pyruvate dehydrogenase complex, thereby influencing cellular energy metabolism and attenuating cartilage degradation. Its role in maintaining redox balance and increasing chondrocyte resistance to oxidative stress is crucial for cartilage preservation [74]. SIRT3 inhibits OA progression by targeting and deacetylating cytochrome c oxidase subunit 4 isoform 2 (COX4I2) [75], thereby helping to maintain mitochondrial protein homeostasis. Loss of SIRT3 function promotes upregulation of MMPs and ADAMTS, while subsequent activation of COX4I2 accelerates cartilage degeneration, ECM degradation, and OA progression. SIRT3 regulates the acetylation status of more than 100 mitochondrial proteins. This enhances antioxidant capacity and contributes to reduced production of mitochondrial ROS. In addition, it positively influences maintenance of mitochondrial redox balance, thereby protecting chondrocytes from oxidative stress [76]. Inhibition of SIRT3 expression in chondrocytes leads to significant disruption of mitochondrial function and further accelerates OA development (Fig. 1) [77]. SIRT3 also plays a key role in preventing mitochondrial dysfunction by promoting Pink1/Parkin-mediated mitophagy, a mechanism that helps attenuate chondrocyte ageing, limit cartilage degradation, and reduce ROS-induced damage. Furthermore, it improves the survival of human chondrocytes [78,79]. SIRT3 additionally inhibits glycolysis while enhancing mitochondrial respiration and fatty acid metabolism, an effect that may exacerbate OA progression in the context of a high-fat diet. These metabolic changes contrast with the beneficial role of SIRT3 in chondrogenesis [80]. It was shown that reduced SIRT3 levels in the cartilage of mice fed a high-fat diet protected against the development of cartilage degeneration and synovial hyperplasia. This effect was associated with increased levels of cartilage glycolytic proteins and decreased levels of fatty acid metabolism proteins in mitochondria. These findings suggest that SIRT3 may induce diet-related changes in the metabolism of mature chondro-

cytes that promote the development of OA [80]. Therefore, the use of SIRT3 modulators in the treatment of OA may be challenging because the effects of this SIRT appear to depend on the metabolic state of the cartilage.

SIRT 4

SIRT4, a mitochondrial SIRT with ADP-ribosyltransferase and deacylase activity, plays an important role in cellular metabolism, regulation of oxidative stress, and inflammatory processes in OA. Studies indicate that SIRT4 expression is reduced in OA-affected chondrocytes, contributing to metabolic disturbances and increased catabolic activity. SIRT4 inhibits the activity of glutamate dehydrogenase, an enzyme involved in excessive glutamine utilisation during energy metabolism. This inhibition helps prevent mitochondrial overload and the associated cellular stress. Furthermore, reduced SIRT4 expression contributes to accelerated chondrocyte ageing, which in turn promotes cartilage degradation. SIRT4 deficiency also disrupts PINK1-dependent mitophagy, resulting in accumulation of dysfunctional mitochondria and increased ROS production, ultimately contributing to the development of SASP [71,81,82]. In addition, SIRT4 modulates inflammation through effects on the NF-κB pathway, thereby reducing production of proinflammatory cytokines such as IL-1β and TNF-α. Reduced SIRT4 activity leads to ROS accumulation and activation of MMPs and ADAMTS, further accelerating cartilage degradation [82,83]. Enhanced SIRT4 function protects chondrocytes from apoptosis through regulation of antioxidant enzymes, including SOD1 and peroxiredoxins. Moreover, increased SIRT4 activity may contribute to cartilage protection by inhibiting inflammation and reducing ROS accumulation, accompanied by increased expression of antioxidant enzymes such as SOD1, SOD2, and catalase [70]. The use of SIRT4 in the treatment of OA requires further investigation because current evidence regarding its effects on cartilage tissue comes mainly from animal studies, which are often difficult to translate into clinical settings. Furthermore, SIRT4 may inhibit glutamate dehydrogenase, thereby limiting amino acid metabolism. Because chondrocytes alter their metabolic profile under inflammatory conditions, inhibition or activation of SIRT4 may trigger unforeseen systemic effects [84].

SIRT 5

SIRT5 regulates oxidative stress, energy metabolism, and chondrocyte homeostasis in OA. Studies have shown that SIRT5 expression is decreased in affected chondrocytes, leading to impaired removal of post-translational modifications from mitochondrial proteins. This results in respiratory chain dysfunction, increased ROS production, and reduced metabolic adaptation. SIRT5 has a significant influence on mitochondrial function, which is particularly important in the context of OA. Mitochondria are responsible for supplying energy to cells, and mitochondrial dysfunction impairs this process, leading to increased oxidative stress and inflammation. In OA, this dysfunction contributes to cartilage degradation and the development of joint pain. SIRT5 helps maintain mitochondrial health by regulating metabolic processes and promoting the removal of damaged proteins. This protective effect on mitochondria reduces cellular stress and thereby contributes to the suppression of inflammation [85]. Inflammation represents another key process influenced by SIRT5. It has been shown to regulate inflammatory signalling pathways, helping to control the excessive inflammatory response commonly observed in OA. By modulating the activity of cytokines and inflammatory proteins, SIRT5 supports a more balanced immune response, potentially slowing cartilage degradation and preserving joint function. Through maintenance of mitochondrial integrity and regulation of inflammation, SIRT5 creates favourable conditions for cartilage maintenance and repair. Reduced SIRT5 expression increases mitophagy, suggesting that SIRT5 regulates this process through its involvement in glutamine metabolism [86]. In addition, SIRT5 deficiency leads to increased levels of post-translational modifications in numerous cartilage metabolic proteins, which may contribute to the early onset of OA [87]. Liu *et al*. [88] showed that SIRT5 expression decreases in cartilage during ageing. SIRT5 deficiency in chondrocytes was also associated with decreased expression of extracellular matrix proteins and increased expression of pro-inflammatory proteins. These authors also identified a human SIRT5 F101L mutation in a family with hereditary OA. This rare mutation may inhibit SIRT5 and contribute to OA pathogenesis by altering chondrocyte metabolism. The use of SIRT5 as a therapeutic target in OA remains highly uncertain because the pathways through which this SIRT influences cartilage metabolism are not yet fully understood, and selective modulators of its activity are not currently available [88].

SIRT 6

SIRT6 regulates chondrocyte homeostasis by modulating inflammation, energy metabolism, and DNA repair in OA. Overexpression of SIRT6 has been shown to attenuate catabolic signalling pathways, including oxidative stress-dependent accumulation of phosphorylated p65 within the nucleus [89–91]. By activating the Keap1/Nrf2/HO-1 signalling pathway, SIRT6 attenuates chondrocyte ageing, enhances DNA damage repair mechanisms, and consequently inhibits OA progression. Reduced SIRT6 expression in OA chondrocytes leads to increased NF-κB activation, which promotes production of proinflammatory cytokines such as IL-1β, TNF-α, and IL-6. SIRT6 inhibits the expression of MMPs and ADAMTS, thereby protecting the cartilage ECM from degradation. It also regulates glucose metabolism by inhibiting glycolysis and promoting oxidative phosphorylation, which reduces metabolic stress and

chondrocyte apoptosis. Furthermore, SIRT6 participates in DNA damage repair through its deacetylase activity and counteracts telomere dysfunction, helping to prevent cellular ageing and cartilage degeneration [92–94]. This process is further influenced by interactions between SIRT6, insulin-like growth factor-1, and insulin-like growth factor-binding proteins (Fig. 2) [95,96]. SIRT6 deficiency leads to telomere dysfunction and accumulation of DNA damage, ultimately promoting cellular ageing [92]. It has been shown that SIRT6 deficiency accelerates OA progression. SIRT6 regulates the insulin-like growth factor 1/AKT signalling pathway, which contributes to the protection of articular cartilage and slows OA progression. The therapeutic modulation of SIRT6 appears difficult to predict because cellular NAD^+ levels, which act as a cofactor for SIRT6, decline with age. Because SIRT6 is strictly dependent on NAD^+, simply increasing SIRT6 protein levels may prove ineffective [97].

SIRT 7

SIRT7 has emerged as an important factor in the pathophysiology of OA because of its effects on inflammation and cartilage integrity. SIRT7 contributes to maintenance of chondrocyte homeostasis through regulation of transcription, DNA repair, and cellular stress responses in OA. Reduced SIRT7 expression in OA chondrocytes increases NF-κB activation, resulting in elevated levels of proinflammatory cytokines and enhanced cartilage catabolism. SIRT7 appears to play a protective role against cartilage degradation. In healthy cartilage, SIRT7 supports balanced cellular function by promoting cell survival and reducing apoptosis. However, this protective role is diminished in OA, contributing to accelerated cartilage breakdown. The association between SIRT7 expression and cartilage integrity suggests that targeting this protein may help alleviate inflammatory responses and slow cartilage degeneration. Furthermore, SIRT7 maintains ribosomal stability and regulates rRNA biogenesis, thereby influencing chondrocyte regeneration and ECM protein synthesis. It also appears to inhibit the transcriptional activity of SOX9, which paradoxically results in increased mRNA levels of ECM components, including type II collagen and aggrecan, in chondrocytes. SIRT7 deficiency contributes to oxidative stress and reduces the activity of DNA repair enzymes, thereby accelerating cellular ageing and cartilage degeneration [98]. There are also studies suggesting that SIRT7 plays a detrimental role in OA. Mice with a knocked-out Sirt7 gene have been shown to be resistant to the development of OA. Sirt7 knockout increased the formation of a glycosaminoglycan-rich extracellular matrix. It has also been shown that SIRT7 inhibits the activity of the SOX9 in chondrocytes. Therefore, SIRT7 cannot be considered a straightforward therapeutic target in OA, as its activation may interfere with the body's natural cartilage repair processes through inhibition of SOX9 [98].

Sirtuin-Mediated Regulation of Mitochondria-Associated Endoplasmic Reticulum Membranes (MAM) and Mitophagy

Mitochondria-associated ER membranes are junctions between the ER and the outer mitochondrial membrane [99]. They participate in the regulation of numerous cellular processes, including apoptosis, lipid metabolism, calcium ion transport, and mitophagy. Mitophagy eliminates damaged cellular organelles or proteins from cells to ensure their proper functioning [100]. Disruption of this process can lead to many age-related diseases, including OA. OA is a degenerative disease that progresses with age and is characterised by damage to cartilage tissue. This process involves disturbances in apoptosis, mitochondrial dysfunction, and often impaired function of mitochondria-associated ER membranes and mitophagy [101].

Mitochondria, as the site of many energy-generating processes in cells, are susceptible to oxidative damage. Mitophagy, which eliminates damaged mitochondria, plays an important role in regulating mitochondrial function [102]. SIRTs are key regulators of mitophagy. SIRT1, SIRT3, and SIRT6 enhance mitophagy, whereas SIRT2, SIRT4, SIRT5, and SIRT7 often inhibit it [103]. SIRT-mediated regulation of mitophagy is crucial for maintaining proper cellular function, including that of chondrocytes, and is associated with the development of OA. Recent studies have shown that impaired mitochondrial function and cartilage metabolism may be caused by the loss of mitofusin-2 (MFN2) expression in chondrocytes. SIRT3 has been shown to regulate mitochondrial function and MFN2 expression, thereby protecting mitochondria and improving their function in chondrocytes. SIRT3 influences the deacetylation and deubiquitination of MFN2, inhibiting its degradation. MFN2-dependent mitochondria–ER junctions regulate chondrocyte function by reducing ER oxidative stress and maintaining mitochondrial calcium balance. They also regulate mitophagy, thereby slowing chondrocyte ageing [104]. SIRT1 has been shown to enhance mitophagy by deacetylating and activating transcription factor EB. Furthermore, SIRT1 reduces ER stress, protects against mitochondrial membrane damage, improves calcium homeostasis between the ER and mitochondria, and prevents the accumulation of reactive oxygen species [105,106]. SIRT2 has the opposite effect, inhibiting mitophagy and promoting microtubule destabilisation through the deacetylation of tubulin and autophagy-related protein 5, which is essential for autophagosome elongation [107,108]. SIRT3 enhances mitophagy by increasing the deacetylation of mitochondrial transcription factor A (TFAM), FOXO3, and ATPase inhibitory factor 1 [107]. Furthermore, SIRT3 inhibits mitochondrial apoptosis by regulating the BCL-2/BAX axis [108]. It has also been shown that SIRT3 reduces the formation of abnormal ER membranes associated with mitochondria [109]. SIRT4, in turn, prevents mitochondrial fis-

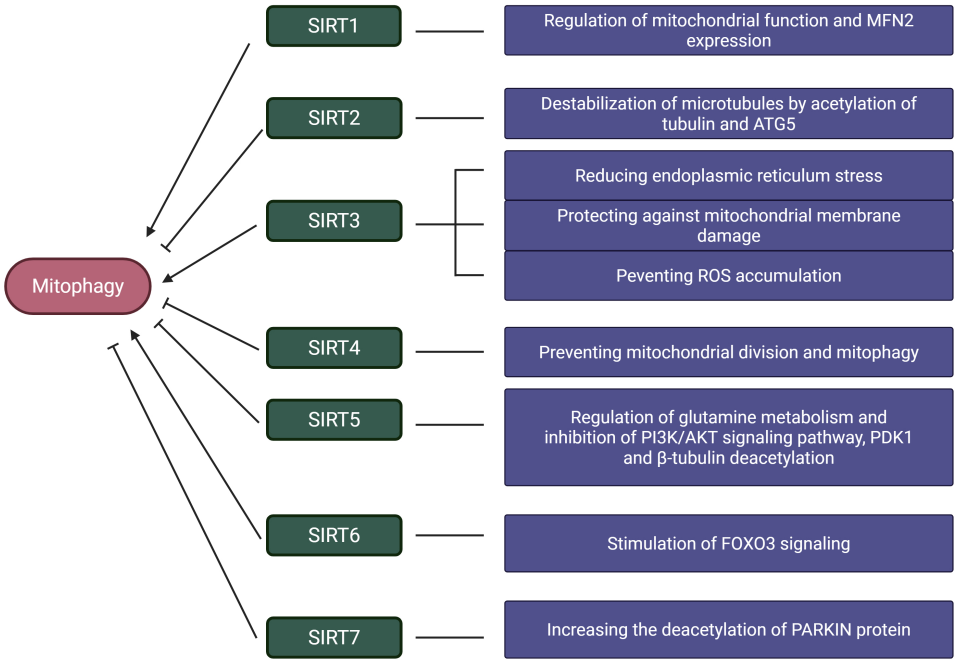

Fig. 3. The role of sirtuins in the regulation of mitophagy and mitochondrial homeostasis. SIRT1, SIRT3, and SIRT6 promote mitophagy and mitochondrial protection by limiting cellular stress and activating autophagy-related signalling pathways. SIRT2, SIRT4, SIRT5, and SIRT7, on the other hand, primarily inhibit mitophagy, affecting mitochondrial dynamics, the cytoskeleton, and the activity of proteins involved in this process. Created in BioRender. Plewa, P. (2026) https://BioRender.com/lr5rjqr

sion and mitophagy [110]. SIRT5 regulates mitophagy by affecting glutamine metabolism and inhibiting the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signalling pathway, as well as pyruvate dehydrogenase kinase 1 (PDK 1) and β-tubulin deacetylation [111]. SIRT6 enhances mitophagy by stimulating FOXO3 signalling, which increases the expression of proteins involved in this process [112–115]. SIRT7 inhibits mitophagy by increasing the deacetylation of Parkin, a protein involved in mitochondrial quality control, thereby inhibiting its activation and suppressing mitophagy (Fig. 3) [116].

Role of SIRTs in OA

Natural and synthetic activators constitute a diverse group of compounds with the potential to modulate key molecular pathways associated with cellular ageing, oxidative stress, inflammation, and ECM degradation. Their effects are primarily mediated through the regulation of processes such as autophagy, apoptosis, ER stress, and mitochondrial function, all of which play significant roles in the pathogenesis of degenerative diseases, including OA. Of particular importance is modulation of signalling pathways involving SIRTs (especially SIRT1 and SIRT3), AMPK, NF-κB, and p53, which integrate cellular responses to stress and metabolic factors. In this context, natural and synthetic activators may represent promising therapeutic tools aimed at providing multilevel protection of cartilage cells and slowing degenerative processes (Fig. 4).

Within this field, natural activators of different SIRTs represent a particularly numerous and diverse group. Among compounds affecting SIRT1, resveratrol is one of the best characterised [117]. In vitro studies have demonstrated that stimulation of OA chondrocytes induces degenerative changes that can be reversed by resveratrol. Resveratrol increased SIRT1 expression and phosphorylation of the transcription factor FOXO1. Furthermore, it enhanced chondrocyte autophagy and increased expression of SOX9 and aggrecan. Resveratrol also inhibited apoptosis and ECM degradation, thereby protecting cells from IL-1β-induced damage. The use of SIRT1 or FOXO1 inhibitors significantly attenuated these effects, indicating that the action of resveratrol is largely dependent on the SIRT1/FOXO1 pathway and its effects on ECM metabolism, autophagy, and chondrocyte survival [118]. Numerous studies have also been performed, which have demonstrated the positive effects of resveratrol in alleviating OA symptoms and inhibiting disease progression. Correlation analyses demonstrated significant associations between changes in SIRT1 concentrations and improvements in functional parameters [119].

The greatest challenge to the clinical use of resveratrol appears to be its low bioavailability. Following oral administration, approximately 75% is absorbed, primarily through diffusion across the intestinal epithelium. However, the compound undergoes extensive metabolism in the intestine and liver. Consequently, its systemic bioavailabil-

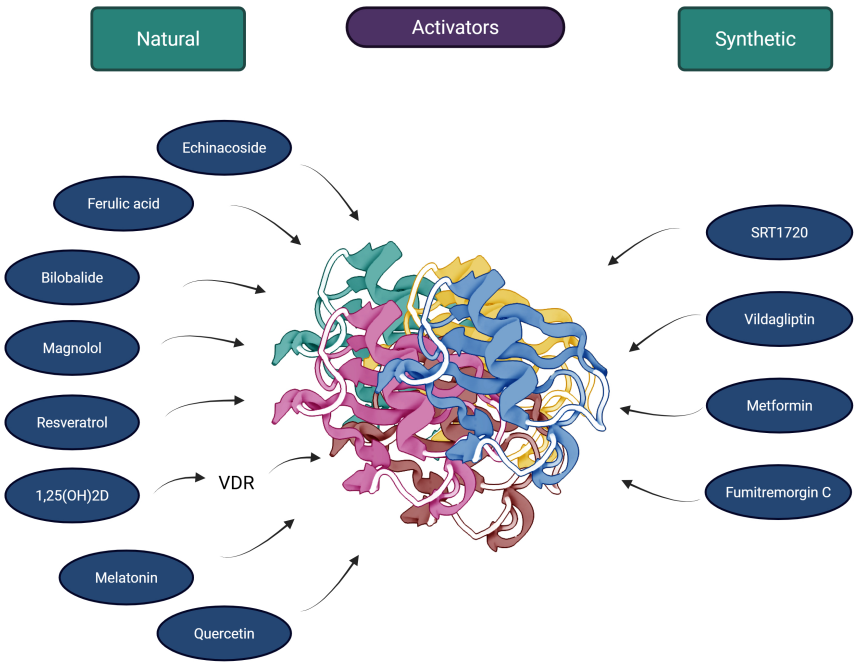

Fig. 4. Natural and synthetic activators are divided into two main groups of compounds with the potential to modulate cellular processes. Both classes affect key molecular pathways related to cellular homeostasis and stress response, which translates into their potential use in therapeutic strategies aimed at protecting and slowing down degenerative processes. Created in BioRender. Plewa, P. (2026) https://BioRender.com/hfzcb3c

ity is less than 1% and does not improve substantially with higher doses or repeated administration. An additional limitation is its rapid elimination, as plasma concentrations of resveratrol decline markedly within 30–60 minutes after administration, limiting its utility in systemic therapy [120]. In addition, articular cartilage is an avascular tissue, and its dense extracellular matrix, composed of collagen and proteoglycans, acts as a physical barrier that hinders the free passage of molecules [121]. To improve the bioavailability of resveratrol, liposomal systems and nanoemulsions have been developed, allowing significantly better penetration through cell membranes and increased target concentrations in joint tissues. Micronised formulations are also used, facilitating absorption through reduced particle size. In clinical trials, resveratrol has been administered directly into the joint cavity, often in the form of sustained-release nanoparticles such as poly(lactic-co-glycolic acid), allowing the compound to act directly on cartilage [122].

$1,25(OH)_2D$ (active vitamin D) is also considered to play a significant role in alleviating degenerative changes in knee joints. Vitamin D supplementation may exert beneficial effects primarily by reducing pain and improving functional outcomes in patients with OA. The active form of vitamin D, $1,25(OH)_2D$, may inhibit the progression of OA by preventing the degradation of the extracellular matrix and the aging of chondrocytes, acting at least in part through the SIRT1 pathway [123].

Melatonin also belongs to this group of natural activators. In studies conducted in rats with knee OA, melatonin suppresses excessive NF-κB activation through SIRT1 activation in IL-1β-stimulated chondrocytes, thereby reducing expression of proinflammatory markers and downstream signalling components [124]. In another study, melatonin additionally counteracted activation of the Nrf2/HO-1 pathway, although it was unable to reverse the effects of EX527. This finding suggests that inhibition of SIRT1 abolishes the protective effects of melatonin on this pathway, indicating that melatonin-mediated modulation of Nrf2/HO-1 signalling depends on SIRT1 activity [125]. Another study demonstrated for the first time that melatonin inhibits the IRE1α–XBP1s–CHOP signalling pathway by increasing SIRT1 expression in LPS-treated human chondrocytes and also slows OA progression [126]. In addition, melatonin reduces inflammatory bone loss by inhibiting mitophagy and lactate production [127]. Melatonin dissolves in both water and fats. This allows it to freely pass through cell membranes and reach the deep layers of cartilage directly. Recent studies have demonstrated the high efficacy of melatonin administered in the form of drug-loaded nanoparticles with a natural polymer hydrogel consisting of oxidized chondroitin sulfate (OCS) and carboxymethylchitosan (CMC) [128,129].

Magnolol counteracts mitochondrial dysfunction and oxidative stress, whereas ginsenoside Rg3 activates SIRT3 and inhibits cellular apoptosis [130]. Other natural activators include bilobalide, which promotes autophagy and

exerts anti-inflammatory effects [131], and ferulic acid, which inhibits oxidative stress and supports ECM integrity [132]. Dioscin supports cell survival by reversing growth arrest and limiting apoptosis [133], while quercetin inhibits both oxidative stress and ER stress [134]. Echinacoside suppresses ER stress and ECM degeneration [135], saffron inhibits ER stress, and curcumin inhibits apoptosis [136]. Furthermore, honokiol activates SIRT3 and reverses cartilage degeneration while maintaining ECM metabolic balance. These findings highlight the importance of mitochondrial deacetylation in maintaining cellular homeostasis. Studies conducted in both patients and mouse models demonstrated a strong association between SIRT3-dependent mitochondrial deacetylation and OA development. Deletion of SIRT3 leads to dysfunction of the mitochondrial respiratory chain, including defects related to COX4I2, resulting in accelerated cartilage ECM degradation and exacerbated OA progression. Administration of honokiol activates SIRT3, thereby reversing processes associated with cartilage destruction and restoring ECM metabolic balance. In addition, intra-articular injection of honokiol significantly inhibits cartilage destruction and reduces abnormal osteophyte formation and synovitis. At the molecular level, honokiol activates SIRT3, which promotes COX4I2 deacetylation and proper mitochondrial respiratory chain function. Moreover, SIRT3-dependent activation of SOD2 further enhances mitochondrial antioxidant mechanisms, thereby improving mitochondrial function and reducing oxidative stress [137]. Despite promising results in animal models, the main therapeutic challenge remains the low oral bioavailability of these compounds and their poor penetration into avascular articular cartilage. Clinical trials of targeted synthetic sirtuin activators (STACs) in rheumatology still require the refinement of tissue-targeted drug delivery systems (e.g., via intra-articular nanocarriers) [138]. In addition to natural compounds, an important group of SIRT activators comprises synthetic SIRT activators. One such compound is metformin. In a mouse model of knee OA induced by destabilisation of the medial meniscus, as well as in IL-1β-stimulated chondrocytes, metformin increased not only SIRT1 expression but also AMPKα phosphorylation, thereby promoting autophagy while simultaneously limiting catabolic processes and apoptosis. Inhibition of either AMPKα or SIRT1 suppressed metformin-induced autophagy. Silencing of AMPKα2, but not AMPKα1, reduced SIRT1 levels and consequently decreased autophagy. These findings indicate a key role for the AMPKα2/SIRT1 axis in this mechanism [127]. In another experiment using human OA chondrocytes and rat chondrocytes treated with IL-1β, activation of the AMPK/SIRT1 pathway by metformin was shown to regulate cholesterol metabolism by increasing expression of LXRα, ABCA1, and ApoA1. Furthermore, this pathway promoted cholesterol efflux, which may be important for the maintenance of cartilage cellular homeostasis [139]. In a study involving human OA chondrocytes, metformin inhibited the expression of microRNA-34a while simultaneously increasing SIRT1 levels. In addition, inhibition of cellular senescence was observed, reflected by decreased SA-β-gal activity together with enhanced proliferation and increased clonogenic capacity [140]. In studies using chondrocyte cultures, fumitremorgine C was shown to reduce inflammation induced by advanced glycation end products. Furthermore, it reduced degradation of type II collagen and aggrecan. These effects were mediated through the SIRT1/NF-κB/MAPK pathway, suggesting a protective role for fumitremorgine C in OA through suppression of inflammatory responses and preservation of cartilage ECM integrity [141]. Although the results are promising, metformin still requires larger, long-term randomized trials before it can become the standard of care for treating OA in people without metabolic disorders. Vildagliptin influences p53 deacetylation, thereby limiting processes associated with cellular ageing [142], whereas SRT1720 prevents apoptosis through regulation of the p53/Bax and NF-κB/PGC-1α pathways [143].

Conclusions and Future Research Directions

Research to date indicates that sirtuins play a multifaceted role in the pathogenesis of OA by regulating inflammatory processes, oxidative stress, energy metabolism, extracellular matrix homeostasis, and chondrocyte survival. The role of SIRT1 is particularly well documented, whereas the functions of the other isoforms (SIRT2–SIRT7) remain incompletely understood. Available evidence suggests that modulation of sirtuin activity may not only slow cartilage degradation but also attenuate subchondral bone remodeling, reduce synovial inflammation, and improve mitochondrial function and cellular metabolism within the joint. Despite these promising experimental findings, most of the available evidence has been derived from in vitro studies and animal models. Well-designed clinical trials are still needed to establish the efficacy and safety of SIRT activators or inhibitors in patients with OA. Another major challenge is the development of selective modulators targeting individual sirtuin isoforms to maximize therapeutic efficacy while minimizing adverse effects resulting from the broad involvement of sirtuins in the regulation of cellular processes.

Future research should focus on elucidating the molecular mechanisms underlying the actions of individual sirtuins, identifying their interactions with key signaling pathways, including NF-κB, mTOR, AMPK, and FOXO, and determining their roles at different stages of OA progression. Particular attention should also be given to evaluating the potential of sirtuins as biomarkers for early diagnosis, disease progression, and treatment response. The development of combination therapies, combining modulation of SIRT activity with anti-inflammatory treatments, cell therapies, tissue engineering, or modern drug delivery systems

such as nanocarriers, is also a promising research direction. There is also growing interest in the influence of lifestyle factors, including physical activity, caloric restriction, and bioactive compounds of natural origin, such as resveratrol, melatonin, and curcumin, on sirtuin activity and the course of OA.

List of Abbreviations

ACP, amorphous calcium phosphate; ADAMTS A, disintegrin and metalloproteinase with a; CMC, carboxymethylchitosan; COX, cytochrome c oxidase; ECM, extracellular matrix; ER, endoplasmic reticulum; IL, interleukin; MAM, mitochondria-associated endoplasmic reticulum membrane; MFN2, mitofusin-2; MMP, matrix metalloproteinases; OA, osteoarthritis; OCS, oxidized chondroitin sulfate; PDK, pyruvate dehydrogenase kinase; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; SIRT, sirtuin; SOD2, superoxide dismutase 2; STAC, synthetic sirtuin activator; TFAM, mitochondrial transcription factor A; TNF-α, tumour necrosis factor-α; 1,25$(OH)_2$D, active vitamin D; NF-κB, nuclear factor kappa B; NAD^+, nicotinamide adenine dinucleotide; FOXO, forkhead box O; SOX9, SRYbox transcription factor 9.

Availability of Data and Materials

Not applicable.

Author Contributions

Conceptualization, AP; writing—original draft preparation, PD, MD, PP and AP; writing—review and editing, PD, MD, PP and AP; supervision, AP. All authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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