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REVIEW

Sirtuins and Cartilage Preservation: From Cellular Function to Therapeutic Innovation

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ABSTRACT

The bones are cushioned by a thin layer of hyaline cartilage that permits physical activity to be performed without experiencing any discomfort. However, these tissues are susceptible to several diseases involving osteoarthritis and rheumatoid arthritis resulting in cartilage degradation. Sirtuins (SRTs) and SRT-activating molecules have been shown in previous studies to affect cartilage and chondrocytes positively. This review aims to explore the potential protective effects of SRTs on cartilage and chondrocytes. It also highlighting various SRT-activating substances and their potential therapeutic applications in managing cartilage-related diseases. Google Scholar, Cochrane Library, and PubMed were used to search about related studies. The impacts of SRTs on cartilage and chondrocytes are beneficial. Additionally, numerous SRT-activating substances may enhance chondrocyte viability and cartilage anabolism which provide a potential therapeutic option in the management of cartilage-related diseases. However, additional studies are essential to clarify the effectiveness of such candidates in the treatment of these diseases.

Keywords: Cartilage, Chondrocyte, Sirtuins, Osteoarthritis, Rheumatoid arthritis

1. Introduction

A thin layer of hyaline cartilage serves as a cushion for the bones. This cartilage is devoid of nerves, blood vessels, and lymphatic components. It provides protection and lubrication, enabling participation in a physical activity without any discomfort. In addition, cartilage prevents the degeneration of bones and the deformity or atrophy of skeletal components. However, this highly specialized connective tissue is extremely susceptible to damage and degeneration, making it one of the most sensitive tissues (Groen et al., 2017).

Adult cartilage is actively synthesized during growth and development by chondrocytes, which make up about 1–3 percent of the tissue. Chondrocytes are metabolically active cells responsible for synthesizing and recycling substantial quantities of extracellular matrix (ECM) components, such as collagen, glycoproteins, proteoglycans, and hyaluronan. The interactions of chondrocytes with the ECM govern numerous biological activities essential for maintaining homeostasis and repair of the cartilage. These activities involved cell attachment, proliferation, differentiation, and viability (Gao et al., 2014). The metabolic functions of chondrocytes are affected by numerous factors in their chemical and mechanical environment. Furthermore, their ability to heal damaged tissues declines with age, in a process known as cellular senescence or chondrosenescence. As a result, the tissue is susceptible to several diseases such as osteoarthritis (OA) and rheumatoid arthritis (RA) (Mobasheri et al., 2015; Xie et al., 2021).

OA is a collection of diseases that are attributed to a compromised integrity of cartilage and alterations in the underlying bone. These diseases damage cartilage

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by reducing the ability of chondrocytes to maintain ECM homeostasis and increasing proteolytic enzyme production, ultimately leading to cartilage loss. The risk of OA is increased with the presence of mechanical factors that involve trauma, obesity, and joint instability. Age is also considered a risk factor for the increased progression of OA. When a predisposing factor, like a prior trauma, is present, OA is typically categorized as secondary; otherwise, it is categorized as primary (Beasley, 2012). Furthermore, RA is a systemic, inflammatory, autoimmune disease primarily triggered by pro-inflammatory cytokines, including interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α). This disease causes hyperplasia of the synovial membrane and the formation of proliferative synovial tissue, which then invades the cartilage and contributes to the destruction of both the cartilage and underlying bone (Peck et al., 2018). However, despite the presence of various therapeutic options, many patients still experience cartilage degeneration due to poor drug response or intolerance, leading to low adherence and uncontrolled disease (Peng et al., 2025).

Historically, the discovery of sirtuins (SRTs) started with the finding of yeast SRT2 more than ten years ago, opening the door to a fresh understanding of their physiological significance in mammals. The original investigation demonstrated that SRT2 could prolong the lifespan of yeast by suppressing the instability of the genome (Dvir-Ginzberg, Mobasheri, and Kumar, 2016). In mammals, there are seven types of SRT enzymes (SRT1 – SRT7) that are present in the nucleus and cytoplasm and are involved in a wide range of processes. These processes include energy metabolism, stress tolerance, deoxyribonucleic acid (DNA) repair, and inflammation, which have essential roles in preserving the homeostasis of cartilage and chondrocytes (McBurney et al., 2013; Liu et al., 2023).

Additionally, numerous investigations have demonstrated that certain SRT-activating molecules positively influence chondrocyte survival and result in good preliminary outcomes for OA and RA improvement (Chen et al., 2018; Wątroba et al., 2017). However, the evidence supporting the beneficial impacts of SRTs on cartilage and chondrocytes is still limited by insufficient data assessing the effectiveness and the specificity of these substances. This review aimed to provide a comprehensive summary of the fundamental data regarding SRTs, their molecular pathway, and their potential benefits for chondrocyte lifespan and cartilage preservation, thereby establishing a theoretical foundation for medicinal targets in this field.

2. Methods

In this narrative review, the effects of SRTs on chondrocytes and cartilage are mainly discussed, and their potential as alternative treatments for cartilage-related diseases. Between 1st January 2025 and 1st April 2025, the literature search was conducted using keywords relevant to the primary topic of the study. Google Scholar, Cochrane Library, and PubMed were used for collecting the data. Cartilage, chondrocyte, sirtuins, osteoarthritis, and rheumatoid arthritis were used both individually or in combination to identify articles that were relevant to the primary matter till the time of preparing this review. Articles that investigated the impacts of SRTs on the homeostasis of chondrocytes and cartilage were included in the inclusion criteria, as well as those that examined the clinical implications of SRT-activating molecules in the management of cartilage-related diseases.

3. Sirtuins classification, locations, and functions

SRTs are classified as nicotinamide adenine dinucleotide (NAD^+)-dependent class III histone deacetylases. However, although the early identification of SRTs with histone deacetylases, accumulating evidence supports the concept that SRTs have non-histone deacetylase activity (Haigis and Sinclair, 2010).

Of the seven SRTs, SRT1 is the most well-studied and is found in the cytoplasm and nucleus. Under calorie restriction, SRT1 improves mitochondrial function and fatty acid metabolism. Deacetylating of proliferator-activated receptor gamma coactivator 1-α (PGC-1α) contributes to this impact thereby inducing gluconeogenesis, aerobic respiration, and mitochondrial biogenesis (Austin and St-Pierre, 2012). Additionally, SRT1 induces the expression of gluconeogenic genes via deacetylating and stimulating the nuclear translocation of forkhead box protein O1(FOXO1). SRT1 also targets another route that depends on 5- adenosine monophosphate-activated protein kinase (AMPK). Being an ATP energy sensor, low energy levels boost AMPK activity, which raises NAD^+ levels in the cell and indirectly activates SRT1 as NAD^+ is the primary substrate for SRT1 (Morris, 2013).

(Low energy levels → AMPK activation → Increased NAD^+ levels → SRT1 activation)

SRT2 is located in the cytoplasm but can also transfer during the transition from the G2 to the M phases of mitosis to the nucleus. In the nucleus and during

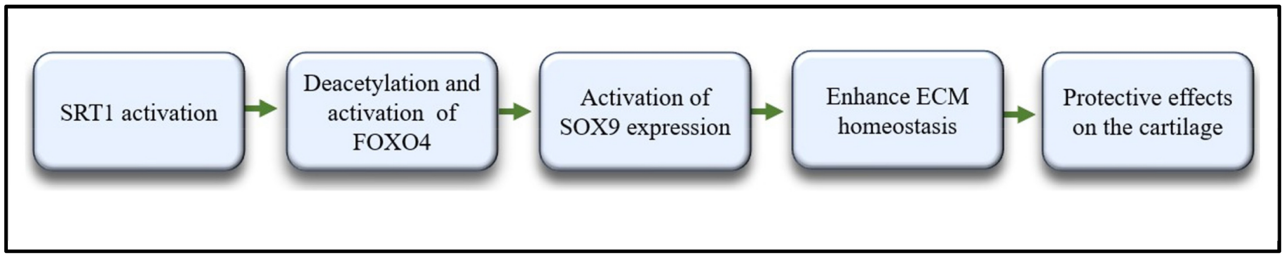

Fig. 1. SRT1-FOXO4-SOX9 pathway in cartilage homeostasis.
SRT1: Sirtuin 1; FOXO4: forkhead box protein O4; SOX9: SRY-Box transcription factor 9; ECM: extracellular matrix. SRT1 deacetylates and activates the FOXO4 protein, which binds to the promoter of SOX9 to transcriptionally activate its expression, resulting in maintaining the ECM stability of cartilage (Ma et al., 2021).

mitosis, SRT2 promotes chromatin condensation by deacetylating histone 4 and histone 3. While microtubule remodeling occurs as a result of cytoplasmic SRT2 deacetylating α-tubulin proteins (Wu et al., 2022).

SRT3 attains its deacetylase activity by the cleavage of its N-terminal 142 amino acids with matrix metalloproteinases. The cleaved which is the active form of SRT3 is located in the mitochondria. SRT3 safeguards the chondrocyte and the mitochondria against the harmful effects of oxidative stress by promoting the stimulation of FOXO3A and superoxide dismutase 2, which reduce reactive oxygen species (Scher, Vaquero, and Reinberg, 2007).

SRT4 is primarily functions through adenosine diphosphate (ADP)-ribosyltransferase activity and has limited deacetylase activity, and it is located in mitochondria. By suppressing glutamate dehydrogenase through ADP-ribosylation, SRT4 regulates the mitochondrial metabolism of lipids and glutamine (Haigis et al., 2006).

SRT5 functions as a lysine deacetylase, desuccinylase, and demalonylase in the mitochondria. Because it controls the nitrogen balance in mitochondrial metabolism, SRT5 is involved in the urea cycle. Among other functions, SRT5 increases the liver's ability to eliminate ammonia by activating carbamoyl phosphate synthetase-1, the first enzyme in the urea cycle (Nakagawa et al., 2009).

SRT6 is a nuclear enzyme that exhibits modest ADP-ribosyltransferase activity and deacetylase activity. SRT6 regulates the secretion rate of TNF-α and exhibits comparable effects on health and lifespan to those that have been previously identified for SRT1 (Kanfi et al., 2012).

SRT7 is situated in the nucleus also found in the nucleolus and has a deacetylase activity. Ribonucleic acid (RNA) polymerase I, ribosomal DNA transcription, and chromatin remodeling complexes are all regulated by SRT7. Although the precise impact of SRT7 on its binding partners remains unknown, SRT7 null in rodents exhibit hypertrophic inflammatory cardiomyopathy, accelerated apoptosis, fatty liver disease, and a reduction in their lifespan (Grob et al., 2009). In summary, SRTs are essential for regulating metabolic genes and mitochondrial metabolism, in addition to preserving genome stability and enhancing cell viability in stressful environments, which give SRTs the potential to get an essential role in preserving cartilage and chondrocytes (Núñez, Arenas-Gómez, and Carbonell Medina, 2024).

4. Mechanisms of cartilage preservation via sirtuins

SRT1 is crucial for the preservation of cartilage integrity by facilitating the homeostasis of the ECM. Additionally, the inhibition of SRT1 can lead to a reduction in hyaluronan synthase 2 production, which results in decreased expression of hyaluronic acid and promotes the development of diseases, such as OA (Han, Wang, and Li, 2021). Moreover, SRT1 can deacetylate FOXO4 and subsequently activate SRY-Box transcription factor 9 (SOX9) expression. This transcription factor can regulate the synthesis of cartilage-specific genes, thereby enabling cartilage to preserve its ECM homeostasis, as shown in Fig. 1 (Ma et al., 2021). Additionally, activation of SRT1/AMPK signaling exerts anti-inflammatory effects by regulating the polarization of M1 and M2 macrophage phenotypes, thereby reducing inflammatory responses in RA (Poniewierska-Baran et al., 2023). Furthermore, SRT1 has been shown to inhibit the onset of chondrocyte senescence by downregulating the production of factors that are associated with senescence, such as IL-6, IL-8, and IL-1β Fig. 2 (Coryell, Diekman, and Loeser, 2021).

Likewise, it has been proposed that SRT5 regulates chondrocyte metabolism through the tricarboxylic

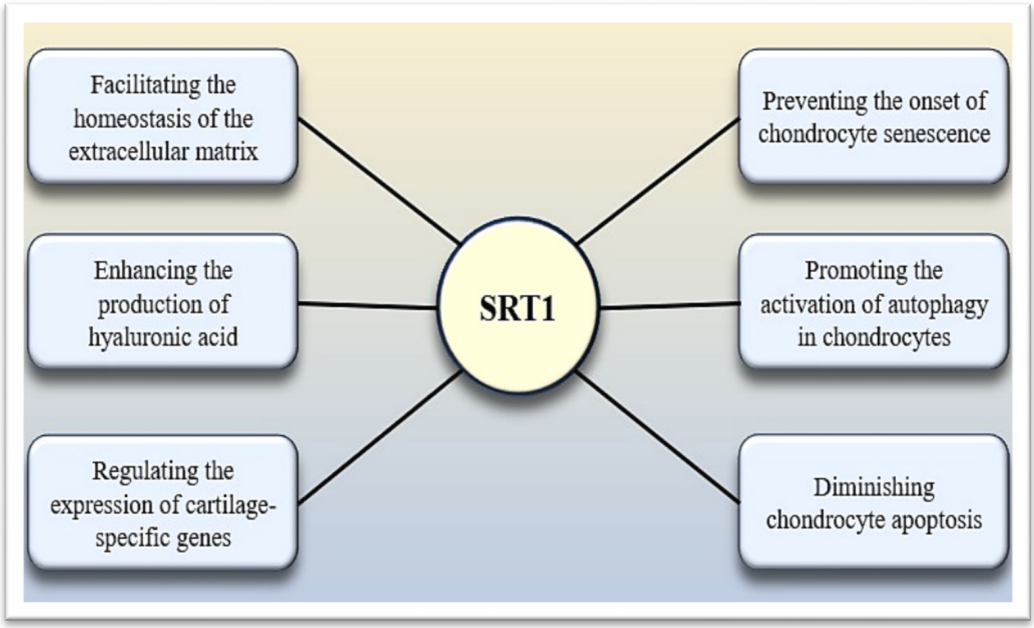

Fig. 2. The roles of sirtuin 1 (SRT1) in maintaining cartilage and chondrocyte homeostasis (Han, Wang, and Li, 2021; Coryell, Diekman, and Loeser, 2021; Xu et al., 2020).

acid cycle, amino acid metabolism, and glycolysis. (Zhu et al., 2021). In addition, there is strong evidence that improving chondrocyte autophagy has positive impacts on chondrocytes and cartilage. By controlling the binding of transcription factors, SRT1, an autophagy initiator mainly located in the nucleus, can enhance the expression of the autophagy gene (Xu et al., 2020). Also, SRT2 can deacetylate FOXO1 and activate autophagy through its direct interactions with autophagy-related proteins (Yue et al., 2022).

Moreover, endoplasmic reticulum (ER) stress, one of the processes that regulates apoptosis in chondrocytes, has a major impact on chondrocyte secretory activity, resulting in dysfunctional cartilage homeostasis (Rellmann, Eidhof, and Dreier, 2021). The reduction of chondrocyte mortality is one of the primary targets of activating SRTs, which involves targeting excess ER stress. It has been proposed that the activation of the SRT1/AMPK signaling pathway can diminish chondrocyte apoptosis by preventing ER stress (Liu, Li, and Huang, 2020). Furthermore, the activation of SRT3/AMPK pathway enhances mitophagy and mitochondrial membrane potential, preventing mitochondria-mediated apoptosis (Xu et al., 2021).

In addition, oxidative stress could be the driving force of the signaling imbalance of catabolic and anabolic pathways of cartilage, which could result in progressive cartilage damage. Studies have shown that overexpression of both SRT4 and SRT6 decreases the inflammation and reduces oxidative stress in the chondrocyte (Dai et al., 2020; Collins et al., 2021). Conversely, SRT7 suppresses SOX9 activity, resulting in damaging effects on cartilage, while its inhibition increases the expression of aggrecan and collagen II in chondrocytes (Korogi et al., 2018). Table 1 summarizes the roles of SRTs in maintaining cartilage and chondrocyte homeostasis.

5. Potential therapeutic applications of sirtuins-activating molecules in cartilage regeneration and the management of cartilage-related diseases

Regenerating cartilage is one of the most complicated procedures in the management of damaged cartilage. Chondrocytes are isolated from cartilage, expanded in cell culture, and then reimplanted to repair damaged cartilage. However, as chondrocytes undergo dedifferentiation, their ability to regenerate cartilage after re-implantation progressively decreases. Heywood HK et al. showed that activating SRT1 by SRT1720, which is a synthetic activator, in cultured chondrocytes, enhances cartilage regeneration by increasing cell numbers and ECM production (Heywood et al., 2022). Furthermore, Choi et al. revealed that treated mesenchymal cells (MSCs) with resveratrol, an SRT1 activator, resulting in increased ability of these cells to regenerate cartilage in vivo compared to untreated cells (Choi et al., 2018).

Table 1. The role of sirtuins in maintaining cartilage and chondrocyte homeostasis.

Name	Functions	References
SRT1	Has multiple effects on cartilage and chondrocyte homeostasis, involving facilitating the homeostasis of the ECM, enhancing the production of hyaluronic acid, regulating the expression of cartilage-specific genes, preventing the onset of chondrocyte senescence, promoting the activation of autophagy in chondrocytes, and diminishing chondrocyte apoptosis by preventing ER stress	(Han, Wang, and Li, 2021; Ma et al., 2021; Coryell, Diekman, and Loeser, 2021; Xu et al., 2020; Liu, Li, and Huang, 2020)
SRT2	Promotes the activation of chondrocyte autophagy.	(Yue et al., 2022)
SRT3	Promotes mitochondrial mitophagy and prevents mitochondria-mediated apoptosis in chondrocytes.	(Xu et al., 2021)
SRT4	Reduces inflammation and oxidative stress.	(Dai et al., 2020)
SRT5	Controls chondrocyte metabolism through modulating glycolysis, tricarboxylic acid cycle, and amino acid metabolism	(Zhu et al., 2021)
SRT6	Reduces inflammation and oxidative stress.	(Collins et al., 2021)
SRT7	Has a negative impact on chondrocytes by suppressing the transcriptional activity of SOX9. Chondrocytes exhibit an increase in the mRNA expression of ECM components, such as aggrecan and collagen II, when SRT7 is inhibited.	(Korogi et al., 2018)

SRT: Sertuin; ER: Endoplasmic reticulum; SOX9: SRY-Box transcription factor 9; ECM: extracellular matrix.

Additionally, Chae DS et al. showed that overexpression of SRT1 in MSCs resulted in the production of chondrocytes with protective and therapeutic effects (Chae et al., 2021).

In the management of OA, resveratrol has shown a protective effect on chondrocytes and can reduce the progression of OA by upregulating the expression of the SRT1 gene. Resveratrol increased SRT1 levels in a manner that was dependent on the dose in both normal and osteoarthritic chondrocytes (Kim, Braun, and Dragoo, 2014). In RA, the activation of SRT1/AMPK signaling pathway by resveratrol reduces pro-inflammatory cytokines (TNF-α, IL-1β) and promotes M2 macrophage polarization, resulting in synovial and cartilage protection (Park et al., 2017).

STRs are influenced by natural compounds involving curcumin, quercetin, fisetin, honokiol, and safflower yellow. It has been proposed that curcumin and quercetin can decrease chondrocyte apoptosis and articular cartilage degradation by lowering the ER stress response via SRT1 activation (Feng et al., 2019; Qiu, Luo, and Chen, 2018). Fisetin, a natural flavonoid, has shown activity on SRT6 and lowering effects on oxidative stress and DNA damage response in chondrocytes (Wang et al., 2024). Xie S. et al. have revealed that honokiol (SRT3 activator), a bioactive polyphenol, improved the characteristics of aged chondrocytes and enhanced the recovery of degenerative cartilage (Xie et al., 2023). Furthermore, safflower yellow can protect chondrocytes and reduce inflammation via stimulating the SRT1/AMPK signaling pathway, which in turn mitigates ER stress (Wang et al., 2020).

In addition, by targeting the mitochondrial function through SRT3, several compounds may show a potential promising effect in targeting joint diseases. Supportive evidence demonstrates that both cyanidin and dihydromyricetin activate SRT3 in order to modulate the activity of numerous proteins in the mitochondria of chondrocytes, thereby maintaining mitochondrial homeostasis (Jiang et al., 2019; Wang et al., 2018). Wang FS. et al. showed that irisin promoted SRT3 signaling, which in turn retained mitochondrial biogenesis in chondrocytes (Wang et al., 2020). Moreover, Wang C. et al. proposed that metformin could promote SRT3-mediated mitophagy, which would result in the suppression of inflammation in chondrocytes (Wang et al., 2018).

Under circumstances of oxidative stress, hydroxytyrosol has shown beneficial effects on chondrocytes by modulating the level of micro-RNA-9 (a small non-coding RNA molecule that has a regulatory effect on gene expression) through SRT1 activation D'Adamo et al., 2017. Wu WT et al. found that silymarin (SRT3 activator) has protective impacts on chondrocytes by enhancing ECM homeostasis (Wu et al., 2021). Table 2 provides a summary of substances that positively affect cartilage and chondrocytes by activating SRTs.

6. Future recommendations

Although SRTs have proven activity on the cartilage, more studies are required for a better understanding of the molecular mechanisms of SRTs in the preservation of cartilage and chondrocyte homeostasis. Furthermore, the development of targeted SRT-activating molecules is essential for selectivity and specificity in the management of cartilage-related diseases. Also, preclinical and clinical analyses are required to assess the efficacy of SRTs-activating substances with their safety profile throughout the long term of these substances. Moreover, explores the potential ability of these

Table 2. Substances that positively affect cartilage and chondrocytes by activating sirtuins.

Substance	SRT activations	Effects on cartilage and chondrocytes	References
Resveratrol	SRT1	Protective and repairing effects on chondrocytes and can reduce the progression of OA and RA.	(Chae et al., 2021; Kim, Braun, and Dragoo, 2014; Park et al., 2017)
Quercetin	SRT1	Decreases the ER stress response to slow down the deterioration of articular cartilage and prevents chondrocyte apoptosis.	(Feng et al., 2019)
Curcumin	SRT1	Decreases the ER stress response to slow down the deterioration of articular cartilage and prevents chondrocyte apoptosis	(Qiu, Luo, and Chen, 2018)
Fisetin	SRT6	Reduces the oxidative stress and DNA damage response in chondrocytes.	(Wang et al., 2024)
Honokiol	SRT3	Improves the phenotype of senescent chondrocytes and promotes the healing of degenerative cartilage.	(Xie et al., 2023)
Safflower yellow	SRT1/AMPK	Mitigates ER stress, thus safeguarding chondrocytes and suppressing inflammation.	(Wang et al., 2020)
Cyanidin	SRT3	Maintaining mitochondrial homeostasis in chondrocytes	(Jiang et al., 2019)
Irisin	SRT3	Retained mitochondrial biogenesis in chondrocytes	(Wang et al., 2020)
Dihydromyricetin	SRT3	Maintaining mitochondrial homeostasis	(Wang et al., 2018)
Hydroxytyrosol	SRT1	Modulate the level of micro-RNA-9, resulting in protective action on chondrocytes.	(D'Adamo et al., 2017)
Metformin	SRT3	Promote mitophagy, which would result in the suppression of inflammation in chondrocytes.	(Wang et al., 2018)
Silymarin	SRT1	Protective effects on chondrocytes by enhancing ECM homeostasis.	(Wu et al., 2021)

SRT: Sirtuin; AMPK: Activated protein kinase; OA: Osteoarthritis; RA: Rheumatoid arthritis DNA: Deoxyribonucleic acid; ER: endoplasmic reticulum; RNA: Ribonucleic acid; ECM: extracellular matrix.

substances to regenerate damaged cartilage, and investigates the potential synergistic effect when using these substances with other present therapies in the management of cartilage diseases.

7. Conclusions

SRTs are crucial for cartilage homeostasis by modulating ECM balance, chondrocyte metabolism, and reducing both apoptosis and senescence. Furthermore, SRTs are involved in antioxidant pathways, mitophagy, and mitochondrial biogenesis, which are essential for proper mitochondrial function. Additionally, recent research has indicated that numerous SRT-activating substances may enhance chondrocyte viability and cartilage anabolism, providing a potential therapeutic option for managing cartilage-related diseases.

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Conflicts of interest

The authors declare no conflicts of interest.

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