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# Exploiting senescence as a therapeutic target in osteoarthritis

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**Abstract**

Osteoarthritis (OA) is a complex degenerative joint disease with significant socioeconomic impact worldwide. Senescence, marked by permanent cell cycle arrest and acquisition of a pro-inflammatory senescence-associated secretory phenotype (SASP), affects chondrocytes, synovial cells and stem cells alike, disrupting cartilage homeostasis and integrity, ultimately contributing to OA pathogenesis and progression. Therapeutic strategies that target cellular senescence to mitigate OA include senolytics, senomorphics and stem cell rejuvenation approaches. Senolytics, such as navitoclax and dasatinib-quercetin combinations, selectively induce apoptosis in senescent cells, alleviating their detrimental effects on joint tissues. Emerging senolytic approaches involve sirtuin activation, autophagy induction, and leveraging natural compounds like resveratrol, metformin, and vitamin D3 to restore chondrocyte function. Senomorphics, in contrast, aim to modulate the SASP to reduce inflammation and tissue degradation while preserving cartilage integrity. Cell-rejuvenation therapies, such as exosome-based treatments and gene therapy, show promise in rejuvenating senescent mesenchymal stem cells to mitigate OA progression. Despite promising preclinical advancements, challenges remain in translating these therapies into clinical applications due to the complexity of senescence-driven mechanisms and potential side effects. This review explores the detrimental role of senescence in OA and the evolving senescence-targeted therapeutic landscape that holds potential to revolutionize OA management and improve patient outcomes.

**Key words** osteoarthritis, senescence, therapeutic target, senescence-associated secretory phenotype

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## Introduction

Osteoarthritis (OA), a prevalent degenerative joint disease, causes significant pain and disability, affecting half the population over 65 [1]. In the United States, OA impacts over 27 million people, with an annual cost exceeding $200 billion [2]. The disease is marked by the degeneration of articular cartilage and abnormal bone remodeling, and is influenced by risk factors such as gender, genetics, and obesity (mechanical overload) [3]. Although aging is a crucial etiologic factor as individuals above 50 years of age face up to a fourfold increased risk of post-traumatic OA, the mechanisms linking age to OA pathogenesis are still evolving [4]. Cellular senescence, a key hallmark of aging, denotes a sustained and irreversible growth arrest state where cells, despite optimal conditions and mitogenic stimuli, lose the ability to proliferate. Senescent cells exhibit heightened resistance to apoptotic cell death even under external stress conditions [5, 6]. While senescent cells play beneficial roles in tissue development and repair, their excessive accumulation is implicated in various age-related diseases, including atherosclerosis, macular degeneration, sarcopenia, and OA [7, 8]. Like other organs, joint tissues also undergo senescence and degeneration over time, with the prevalence of senescent chondrocytes and synovial fibroblasts strongly correlating with age [9, 10]. Given the crucial role of bone–cartilage crosstalk, age-related increased osteocyte senescence may also contributes to OA pathogenesis [11]. In addition, senescence is apparent during post-traumatic OA, where joint injury exacerbates chondrocyte senescence and prompts cartilage degradation [12]. Catabolic shear stress due to abnormal mechanical loading has been identified as a potential trigger for premature senescence after joint injury [13]. Moreover, OA-related phenotypic changes in joints often resemble senescent signatures, such as the induction of urokinase plasminogen activator surface receptor (uPAR) in chondrocytes [14]. Emerging evidence suggests varied stressor-specific induction and release of SASP-factors in OA [15, 16] contribute to a feed-forward loop with immune response, thereby promoting inflammation and senescence through paracrine and autocrine signaling [17].

Regenerative therapies for OA are riskier in older patients, contrasting with focal cartilage defects where phenotypic stability of chondrocytes is crucial for success [18]. A senescent microenvironment may also hinder stem cell implantation for joint repair [19]. Therefore, understanding and exploring senescence-related complexities may offer potential therapeutic insights for OA and related conditions. In this context, various treatment approaches are emerging to target cellular senescence in OA. First and foremost are senolytic drugs that induce apoptosis and clear senescent cells by countering anti-apoptotic pathways. On the other hand, senomorphic drugs that modulate the SASP are being actively investigated for their role in OA treatment [22]. In addition, stem cell rejuvenation is also being explored as a tool to circumvent senescence in OA [20]. In this review, we discuss the detrimental impacts of senescence in OA and how therapeutic options targeted towards senescence are changing the landscape of management and treatment options for OA.

## Detrimental role of senescence in OA

The impact of senescence in driving and fostering OA encompasses a wide range of observations that collectively contribute to the progression and manifestations of the disease. In this section, we discuss the detrimental impacts of senescence across various cell types within joint morphology contributing to OA (**Figure 1**), which is critical for developing targeted interventions aimed at preserving joint health, reducing inflammation, and improving outcomes for OA patients.

### *Chondrocyte senescence*

Senescence in chondrocytes, the key cells responsible for maintaining cartilage integrity, and other joint tissues, contribute to significant clinical outcomes in OA patients [7]. While chondrocytes are typically hypo-replicative during homeostasis, they may proliferate in specific contexts. For instance, chondrocytes form 'clusters' as an apparent effort to repair damaged matrix during the early stages of OA [21]. In this scenario, the interplay between quiescence and senescence is complex, as mitogenic stimulation of damaged, quiescent cells can trigger the induction of senescence they re-enter the cell cycle [22]. Unfortunately, the prevalence of senescent chondrocytes along with acquisition of SASP increases with age, serving as a pivotal contributor to the initiation and progression of OA [23]. One of the primary clinical observations related to chondrocyte senescence is the progressive damage to the cartilage matrix. Senescent chondrocytes exhibit reduced capacity for ECM synthesis and repair, leading to the gradual degradation of cartilage [24]. This degradation is clinically evident through joint pain, stiffness, and reduced joint function, as the loss of cartilage integrity compromises joint stability and mobility. Patients often report difficulty in performing daily activities and experience limitations in range of motion due to chondrocyte-related cartilage damage [25]. Moreover, senescence-related changes in chondrocytes contribute to alterations in the ECM composition marked by increased production of degenerative enzymes like MMPs [26]. These changes are clinically visible through imaging modalities such as X-rays and MRIs, which show joint space narrowing, osteophyte formation, and structural deformities indicative of cartilage damage and joint degeneration [27]. Additionally, extracellular vesicles (EVs) secreted by OA-related senescent chondrocytes induce senescence in neighboring non-senescent cells and suppress chondrogenesis through a para-senescent effect [28]. In summary, altered ECM composition, inflammatory responses, and acquisition of SASP are key events linking chondrocyte senescence to disease progression and clinical manifestations in OA.

### *Synovial senescence*

Senescence in synovial fibroblasts, along with synovial macrophages, osteoblasts, and adipocytes, contributes to the production of SASP and acquisition of inflammatory environment [29, 30], that plays a crucial role in cartilage degeneration, subchondral bone remodeling, and ultimately leads to cartilage loss, OA development and progression [31, 32]. Synovial tissue contributes significantly to the senescence burden in OA knee joints [12], with SASP levels markedly upregulated in isolated synovial tissue from human OA patients, exacerbating synovial inflammation [33]. Senescence can disrupt the synovial microenvironment and drive OA-like degeneration, as demonstrated by mouse knee joints transplanted with senescent fibroblasts which exhibited cartilage erosion, osteophyte formation, and loss of mobility [34]. Synovial cells are responsible for producing approximately 55% of cytokines, and interactions between synoviocytes and chondrocytes are vital in the pathogenesis of OA [35]. These interactions can lead to the degradation of ECM in articular cartilage, which subsequently exacerbates synovial inflammation [36]. This inflammation promotes MMP13 production, and resulting build-up of matrix debris aggravates synovial inflammation, creating a vicious cycle that ultimately results in total joint destruction. Key proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 are pivotal in driving synovial inflammation and cartilage destruction [37]. Elevated levels of cytokines such as IL-6 in the

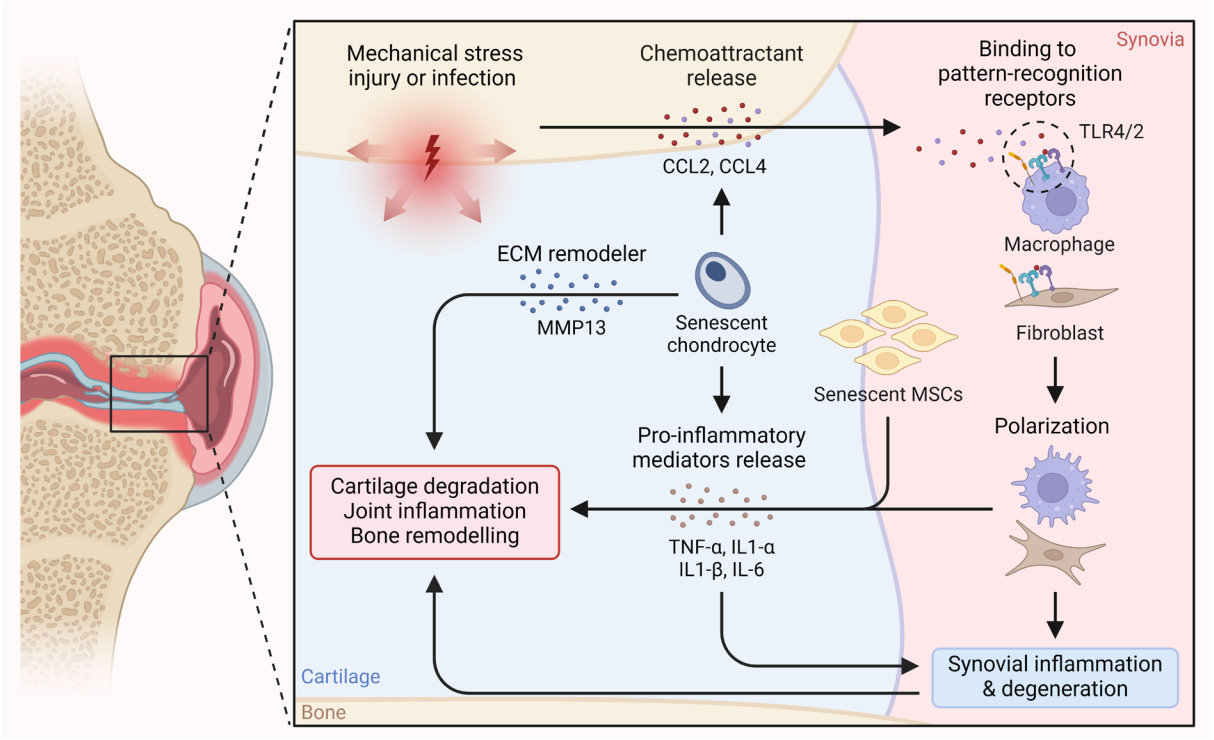


**Figure 1. Detrimental role of senescence in OA. Chemoattractants released in response to mechanical stress and from senescent chondrocytes in OA lead to immune cell polarization and infiltration into cartilage, resulting in the release of pro-inflammatory cytokines. Simultaneously, the release of pro-inflammatory mediators from senescent chondrocytes and MSCs exacerbates the situation, ultimately leading to cartilage and synovial degeneration, joint and synovial inflammation, and bone remodeling.**

synovial fluid of OA patients indicate their potential involvement in triggering senescence and SASP in surrounding cells [38]. These cytokines also promote the formation of SASP in senescent chondrocytes, with IL-1β notably enhancing the production of other proinflammatory cytokines and MMPs in chondrocytes [39]. Similarly, TNF-α induces the expression of MMPs and ADAMTS, contributing to further degradation of the cartilage matrix [40]. Cytokines, released in SASP, can also, in turn, upregulate MMPs, such as MMP13 and ADAMTS-5, which contribute to ECM degradation in cartilage [41]. This cartilage degeneration, along with synovitis and joint inflammation, leads to clinical symptoms such as joint swelling, and tenderness observed in OA patients [42]. In summary, senescence in synovial fibroblasts and associated release of SASP profoundly aid in disease progression in OA.

*Stem cell senescence*

In addition to senescent chondrocytes and synovial cells, age and/or stress related senescence in MSCs play crucial role in overproducing SASP factors such as chemokines, cytokines, and MMPs, resulting in detrimental effects on cell responses to growth factors and their proliferative capacities [43]. One notable marker of senescent MSCs is the elevated expression of p16INK4a, a potent cell cycle inhibitor. Studies using animal models have shown that p16INK4a-positive senescent MSCs, particularly those residing in the articular osteochondral region, can contribute significantly to cartilage damage and the progression of OA [44]. Within the synovial tissue of OA joints, the p16INK4a protein regulates the production of SASP factors, which have a catabolic effect on tissues [45]. Furthermore, analyses of synovial fluid from OA patients have revealed elevated levels of SASP factors like IL-6 [46]. Prolonged exposure to IL-6 in synovial fluid derived MSCs hinders their differentiation into chondrocytes [47], a critical process for cartilage regeneration. Similarly, IL-6 inhibits the differentiation of murine bone marrow-derived MSCs into chondrocytes, highlighting its dose-dependent regulatory role in cartilage maintenance [48]. Articular cartilage repair and rejuvenation rely heavily on the functional capacity of chondrocytes and resident MSCs, particularly synovial MSCs, which possess superior chondrogenic potential compared to other MSC populations [49]. Their ability to produce hyaline cartilage matrices is crucial for cartilage regeneration. However, an excessive presence of senescent synovial MSCs can impede these regenerative processes. Notably, senescent synovial MSCs are resistant to apoptosis and exhibit prolonged survival. Their accumulation in joints, cartilage, synovial tissue, and synovial fluid is a common observation in various pathological conditions [50]. Although inflammatory environments can activate and promote the proliferation of synovial MSCs, OA-related persistent inflammation can deplete these cells and induce replicative senescence. A significant population of senescent synovial MSCs resides in OA synovium, characterized by features such as cellular senescence, heightened production of pro-inflammatory molecules, and diminished chondrogenic potential [51]. Despite all this, the precise molecular mechanisms that resident senescent synovial MSCs employ to disrupt homeostasis and impair cartilage function remain a subject of ongoing research and exploration.

**Senescence as a therapeutic target for OA**

Senolytics and senomorphics are two distinct classes of therapeutics targeting senescence that have shown promise in alleviating age-related pathologies in animal models and are currently being tested in humans. Senolytics trigger apoptosis

specifically in senescent cells, while senomorphics suppress SASP factors, associated paracrine inflammatory signaling and tissue damage [52]. Considering the connections between senescence and OA, these medications present compelling options for addressing OA pathogenesis and impeding its advancement (**Figure 2**).

*Senolytics – Killing senescence*

In a groundbreaking preclinical investigation, a novel inducible transgene was engineered to selectively eliminate senescent cells expressing elevated levels of p16 [53]. Mice carrying this transgene exhibited an extended median lifespan and delayed onset of age-related pathologies compared to their wild-type counterparts. Notably, there was a substantial reduction in the development of post-traumatic OA, when a similar transgenic approach was employed to clear senescent cells specifically in mouse articular cartilage [12]. While these experiments primarily utilized transgenic mice to induce apoptosis in senescent cells, other studies explored whether senolytics could replicate these effects therapeutically. For instance, a study investigating gene expression profiles of senescent versus proliferating cells revealed upregulation of genes associated with anti-apoptotic signaling networks during senescence, including BCL-2 family members and proteins in the PI3K–AKT pathway [54]. Many senolytics selectively trigger apoptosis in senescent cells by inhibiting pro-survival pathways that are activated in senescent cells but not in healthy ones. Notably, navitoclax (ABT-263), a dual inhibitor of BCL-2 and BCL-XL, administered to irradiated or naturally aged mice, depleted senescent haematopoietic stem cells and muscle stem cells, fostering cellular rejuvenation [55]. Navitoclax reduced the senescence burden in cartilage explants by inducing apoptosis in p16-expressing chondrocytes, effectively eliminating them. [56]. Another example is the senolytic combination of dasatinib and quercetin, currently under investigation in clinical trials for treating idiopathic pulmonary fibrosis associated with senescence [57, 58]. Dasatinib inhibits various tyrosine kinases, while quercetin, a plant flavonol, inhibits PI3K and serine proteinase inhibitors (serpins) [59]. Treatment with dasatinib and quercetin in mice attenuated the detrimental effects of senescence, improving healthspan and lifespan by reducing senescent osteocytes in bone and enhancing bone microarchitecture [60]. While these drugs await human trials for joint tissue diseases, several senolytics, including UBX0101, are currently under investigation for OA treatment [23]. UBX0101 inhibits the interaction between p53 and mouse double minute 2 homologue (MDM2), selectively clearing senescent cells in post-traumatic OA, decreasing proteoglycan loss, and alleviating OA-related symptoms [12].

Treatment with SIRT-activating compounds exhibit chondroprotective effects in OA. Resveratrol, a natural anti-oxidant and a potent SIRT1 inducer, has been shown to inhibit MMP-13 expression in human OA chondrocytes through SIRT1 activation [61]. Additionally, it protects against articular cartilage destruction in OA mice by suppressing the NF-κB and HIF-2α pathways in a SIRT1-dependent manner [62]. Studies in preclinical models have highlighted resveratrol's ability to reduce serum levels of inflammatory cytokines such as IL-1β, IL-6, and TNF-α, alleviating pain and stiffness and potentially improving knee joint function in OA patients, with favorable safety and tolerability profiles [63]. Metformin, an anti-diabetic medication, has recently been shown to suppress the expression of p16, IL-6, and MMP-13 while promoting the expression of Collagen type II and Aggrecan in OA chondrocytes by regulating the miR-34a/SIRT1 axis [64]. Vitamin D deficiency accelerates age-related knee OA development, characterized by cartilage surface destruction, proteoglycan loss, and chondrocyte senescence with SASP acquisition. Supplementation with vitamin D3 reverses OA phenotypes rescuing chondrocyte proliferation, matrix protein synthesis, and reducing oxidative stress via upregulating SIRT1 expression [65]. Since an elevated serum ratio of SIRT1 N-terminal to its C-terminal fragments correlates with early-stage OA and chondrosenescence, the concomitant administration of systemic navitoclax and intra-articular UBX0101 reduced the ratio by

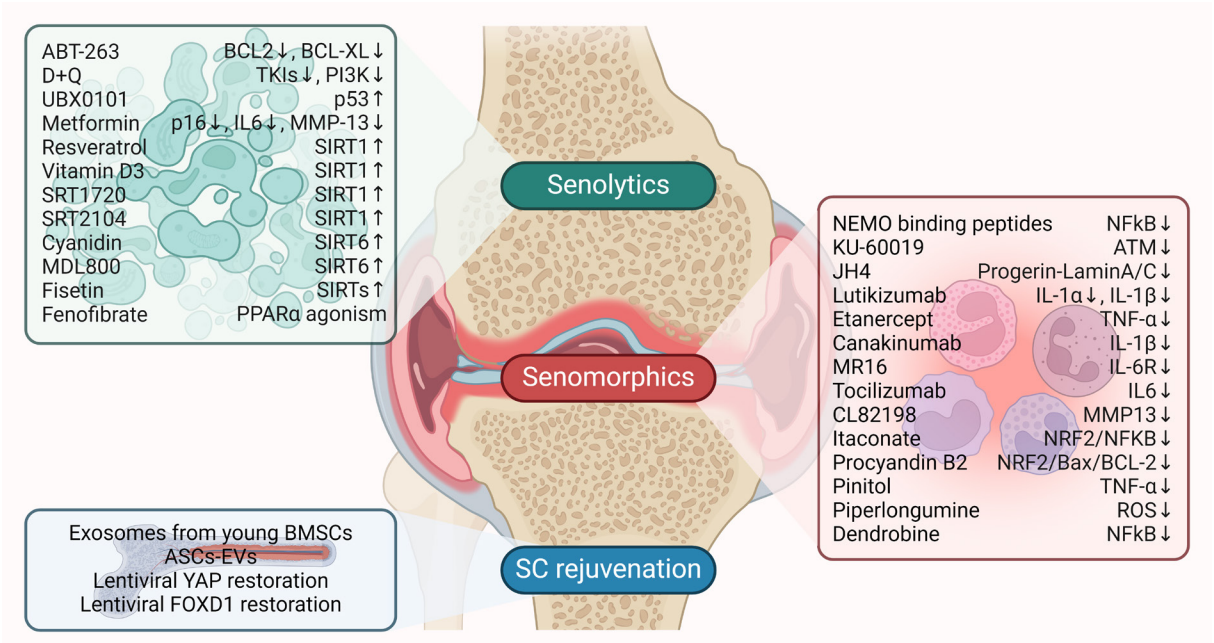


**Figure 2. Therapeutic targeting of senescence in OA. Senolytics, senomorphics, and stem cell (SC) rejuvenation are key therapeutic options currently being investigated to target senescence in OA. Senolytic and senomorphic drugs are listed along with their impact on molecular targets. Arrows indicate the effect on the target: ↑ (upregulation) and ↓ (downregulation).**

clearing senescent cells [66, 67]. One notable synthetic SIRT-activating compound, SRT1720, a robust SIRT1 activator, has demonstrated significant reduction in MMP-13 and ADAMTS-5 expression in chondrocytes, mitigating articular cartilage degeneration and osteophyte formation while attenuating synovial inflammation, thus delaying OA progression in murine models [68]. Similarly, SRT2104, a selective SIRT1 activator, exhibits efficacy in preventing knee OA progression in mice by lowering MMP-13, ADAMTS-5, IL-1β, IL-6 levels, acetylated NF-κB p65, and enhancing Col-II synthesis within cartilage [69]. Its systemic benefits include anti-inflammatory and antioxidant effects linked to reduced NF-κB activity, mirroring the physiological improvements seen with SRT1720 [70]. Notably, non-therapeutic clinical studies confirm the excellent safety profile and tolerability of SRT2104 [71]. Cyanidin, an activator of SIRT6, increases SIRT6 expression in a dose-dependent manner. It significantly reduces IL-1β-induced expression of pro-inflammatory mediators like TNF-α, IL-6, COX-2, MMP-13, and ADAMTS-5, thereby mitigating synovial inflammation and cartilage degradation. In OA mouse models, cyanidin downregulates MMP-13 expression and upregulates Col-II expression, preserving articular cartilage matrix integrity [72]. Chondrocytes from younger donors repair damage more efficiently than those from older donors. Activation of SIRT6 with MDL-800 improved repair, reduced baseline DNA damage in older chondrocytes and aging murine cartilage, indicating a potential role in mitigating DNA damage and delaying senescence, which could impact OA progression [73]. Flavonoids like fisetin, known for activating SIRTs and linked to longevity, has demonstrated efficacy in inhibiting IL-1β-induced inflammation in osteoarthritic chondrocytes, mitigating cartilage erosion, ECM degradation, apoptosis, and senescence in OA. These compounds are currently undergoing clinical trials for OA symptom alleviation [74-76].

The exploration of high-throughput drug screening for senolytics targeting chondrocytes and synovial cells, along with the identification of novel mechanisms contributing to OA pathology, has gained significance. In a specific study, over 1,000 compounds were screened for senolytic activity in a human chondrocyte cell line, revealing that fenofibrate, a flavonoid and peroxisome proliferator-activated receptor-α (PPARα) agonist used to treat dyslipidaemias, induced apoptosis in SA-β-gal-positive chondrocytes [77]. This finding prompted an investigation into reduced PPARα expression in the blood and knee cartilage of OA patients.

Concerns regarding the use of senolytics in OA treatment arise from potential side effects and variations in drug potency. The impact of promoting cell death on tissue integrity, exacerbating cartilage and bone loss in OA patients, remains uncertain. Notably, a study in mice using diphtheria toxin on superficial zone proteoglycan-expressing cells did not induce further cartilage damage but rather improved injury outcomes [78]. This challenges assumptions about the consequences of promoting cell death in OA treatment and suggests a potential benefit in preventing injury-induced cartilage loss by eliminating senescent chondrocytes. Another consideration in employing senolytics for OA is the conflicting evidence regarding the role of senescence in physiological processes. While senescence is often implicated as a driver of aging and disease, studies suggest a beneficial role in tissue remodeling and wound healing [79]. For instance, senescent cells accumulated during limb regeneration in salamanders but were naturally cleared before full regrowth. Efficient immunosurveillance of senescent cells might play a crucial role in tissue repair, as demonstrated in studies involving macrophage-mediated clearance and secretion of growth factors by senescent cells near wound sites [80, 81]. Consequently, further research is essential to determine if wholesale elimination of senescent cells from joints could lead to side effects contributing to tissue loss in OA.

*Senomorphics – modulating SASP*

The strategic targeting of pathways and molecules associated with inflammation and disease has long been a therapeutic approach. A diverse range of senomorphic candidates has emerged, demonstrating the ability to suppress SASP-related mechanisms without inducing apoptosis [23]. These include inhibitors of IκB kinase and NFκB, such as NEMO-binding domain peptides [82], JAK inhibitors like ruxolitinib [83], ATM inhibitors exemplified by KU-60019 [84], compounds disrupting progerin–lamin A/C binding, for instance, JH4 [85], activators of PDGF and fibroblast growth factor signaling [86], TGFβ receptor type 2 and p21 inhibitors [87]. The link between SASP factor expression and OA highlights the potential of inhibiting these factors in OA. However, selecting appropriate target is crucial to guarantee therapeutic efficacy and specificity.

Despite the increased interest in exploring cytokine inhibitors and neutralizing antibodies approved by the FDA for inflammatory conditions like OA, In vivo experiments using IL-1 blockade and IL-1 knockout in mice did not show a reduction in cartilage destruction or synovial inflammation in collagenase-induced OA [88]. Nevertheless, such inhibitors present intriguing prospects for OA therapies due to their established safety and efficacy in different hereditary autoinflammatory conditions [89], though pre-clinical and clinical studies targeting cytokines for OA treatment have yielded mixed results. For instance, the combined blockade of IL-1α and IL-1β using monoclonal antibodies prevented the development of pain and reversed established pain in a preclinical model of OA [90]. Alternatively, Lutikizumab, a dual inhibitor of IL-1α and IL-1β, showed limited pain improvement and no impact on synovitis in a phase II trial for knee OA patients [91]. Similarly, etanercept, a TNF inhibitor, failed to alleviate pain and had minimal effects on structure in a trial for inflammatory hand OA [92]. Canakinumab, a selective IL-1β neutralizing antibody currently undergoing phase 2 clinical trials for knee OA patients (NCT04864392), has shown significant reductions in serum C-reactive protein (CRP) levels and a lower risk of cardiovascular events in patients with a history of myocardial infarction and elevated baseline CRP. These findings were observed in the large Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) [93]. Notably, a post-hoc analysis of the CANTOS study suggested that participants randomized to canakinumab exhibited lesser OA symptoms and underwent fewer OA-related joint replacements compared to the placebo group [94]. IL-6 is a potential target for OA therapy, and systemic administration of an IL-6 neutralizing antibody has been shown to decrease cartilage lesions and subchondral bone sclerosis in experimental OA model in vivo [95]. Additionally, Systemic administration of the anti-IL-6-receptor neutralizing antibody (MR16) resulted in the improvement of cartilage damage, reduction in synovial inflammation, and inhibition of osteophyte formation in vivo [96]. Despite this, IL6 knockout mice exhibit more severe OA in response to aging than wild-type mice, suggesting the complexity of OA pathogenesis requires a multifaceted treatment approach [97]. In line with this, tocilizumab, an IL-6 neutralizing antibody approved for RA treatment, did not show benefits in a phase 3 clinical trial for hand OA, as it indicated no improvement in pain or secondary outcomes, while slightly more frequent adverse events were observed [98]. IL-17 significantly contribute to the pathogenesis of OA and is strongly linked to joint pain in OA patients [99]. In addition, IL-17 producing Th17 cells are known to induce senescence in fibroblasts. Underscoring the roles of these cells and IL-17 in OA development and cartilage senescence, intraarticular injection of an IL-17-neutralizing antibody has

been shown to alleviate cartilage degeneration and reduce the senescence marker p21 in vivo [15]. However, the effectiveness of IL-17 neutralizing antibodies in human OA remains to be tested. Given their catabolic impact on cartilage, MMPs represent an additional category of SASP factors that should be considered as promising therapeutic targets. Specifically, MMP13 stands out as the highly expressed MMP in connective tissue [100] and serves as the key enzyme for the degradation of type-II collagen [101]. Chondrocytes from individuals with OA were observed to exhibit elevated MMP13 levels compared to chondrocytes from those with healthy cartilage [102]. Moreover, transgenic mice overexpressing MMP13 develops OA-like arthropathy, suggesting MMP13's pivotal role in OA pathogenesis [103]. A separate study demonstrated that the chondrocyte-specific deletion of MMP13 reduces OA severity. In addition, treating wild-type mice with a selective MMP13 inhibitor, CL82198, reduces OA severity, increases type II collagen levels, and inhibit chondrocyte death [104].

Exogenous supplementation with itaconate, an anti-inflammatory metabolite activates Nrf2, inhibits the STING-dependent NF-κB pathway, and reduces SASP-driven inflammation, ECM degeneration, and chondrocyte senescence. Itaconate also regulate macrophage polarization, decreasing chondrocyte apoptosis [105]. Supplementation with naturally occurring falvonoid, procyanidin B2, dampens IL-1β-triggered SASP factors expression, preserving the extracellular matrix (ECM), reducing chondrocyte apoptosis, and attenuating senescence via repressing Nrf2/NF-κB pathway. Additionally, procyanidin B2 exhibited anti-apoptotic properties through the Nrf2/BAX/Bcl-2 pathway and alleviated knee cartilage degeneration in an OA rat model [106]. Pinitol, is a natural compound that counteracts the effects of TNF-α-induced cellular senescence and cell cycle arrest by rescuing NRF2 signaling in chondrocytes, thus alleviating OA [107]. Piperlongumine, an amide alkaloid constituent of long pepper, reduces senescence markers and SASP, preserves cartilage matrix components, mitigates oxidative stress and DNA damage, and decreases inflammatory markers associated with OA [108]. Dendrobine, an alkaloid found in orchids, effectively combats OA by inhibiting ECM degradation and SASP factors expression, improving mitochondrial function, and suppressing NF-κB activation in chondrocytes [109]. Similarly, supplementation with antioxidant, pyrroloquinoline quinone, prevents articular surface collapse, reduces cartilage matrix protein loss, and inhibits oxidative stress, DNA damage, cellular senescence, and inflammatory cytokine secretion associated with OA development, highlighting its potential as a preventive measure against OA progression [110]. Collectively, these findings suggest that inhibiting SASP factors through senomorphics holds promise for OA treatment. However, further research is essential to identify specific SASP factors contributing to OA pathology and determine if their inhibition can effectively slow or prevent disease progression.

*Rejuvenation of stem cells to prevent senescence in OA*

Increasing age and pathological factors alters the extracellular environment, impacting the fate of all cells within a tissue, including resident MSCs. Understanding the mechanisms involved could aid in stem cell rejuvenation, maintaining MSC function and preserving healthy tissues in older age and disease scenarios [111]. Local administration of exosomes derived from bone marrow-MSCs of young rats significantly accelerates bone regeneration and improves mechanical properties in older rats, affirming the potential of stem cell rejuvenation in rejuvenating aged and senescent tissues [112]. In the context of OA, bone marrow derived-MSCs primed with TNF-α and IFN-γ have exhibit increased anti-inflammatory potential to reduce SASP-driven inflammation in a chemically induced OA model [113]. Notably, yes-associated protein (YAP) represses MSC senescence via promoting FOXD1 transcription. Intra-articular delivery of YAP or FOXD1 coding lentiviral particles has been shown to decrease senescent cells, while also mitigating articular inflammation and cartilage erosion. These findings suggest that gene therapy which introduces geroprotective factors to rejuvenate senescent MSCs could represent a new tool for OA therapy in the future [114]. Recently, antler stem cells (ASCs)-derived exosomes (ASCs-EVs) have demonstrated remarkable potential to induce proliferative and regenerative capacity in human senescent MSCs, thereby rejuvenating these cells. Following treatment with ASCs-EVs, human MSCs showed reduced signs of senescence, and intra-articular injection of ASCs-EVs alleviated cartilage damage in an OA mouse model [20]. These results suggest that ASCs could serve as a sustainable source of EVs for cell-free therapy. Further explorations are warranted to fully tailor stem cell rejuvenation as a tool to prevent senescence in OA.

## Conclusion and future prospect

In conclusion, developing effective OA treatment strategies is need of the hour. Senolytics and senomorphics, promising approaches in preclinical studies, hold potential in mitigating OA phenotypes. However, their efficacy in eliminating or preventing the disease in clinical settings mostly remains unverified [7]. The lack of evidence pinpointing a specific cell type as the sole driver of OA poses a significant hurdle, as various joint tissue cells exhibit senescence and secretion of SASP [29]. Therefore, determining cell specificity is paramount for evaluating drug efficacy in disease treatment. Similarly, devising targeted and personalized strategies to curtail senescence in OA is also of utmost importance. In this regard, Ceria nanoparticles have shown promise in OA treatment by inhibiting senescence and SASP biomarkers in synoviocytes, reducing ROS levels both in vitro and in vivo, and protecting cartilage from degeneration [115]. In addition, a hydrogel-based miRNA delivery system, utilizing miR-29b-5p to target chondrocyte senescence in OA showed promising results by suppressing matrix-degrading enzymes and senescence markers, offering a non-surgical therapeutic option for OA [116]. Unfortunately, these efforts are still in infancy, requiring long time to reach clinical implication. Finally, investigating the detrimental impacts of eliminating or altering senescent cells is essential. Recent findings suggest that senescence takes part in early wound healing and tissue regeneration, raising concerns that early interventions with senolytics or senomorphics could hinder the initial healing process in the damaged cartilage and surrounding tissues [117]. Rigorous studies, encompassing different treatment timings, are imperative to assess drug efficacy and comprehend the nuanced impact on disease outcomes. As research advances, unraveling these complexities will pave the way for more targeted and effective therapeutic interventions in the multifaceted landscape of OA.

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## Ethics approval

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## Data availability

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**Authors' contribution**

CL contributed to draft, critical revision of the article and approved the final manuscript; UR was devoted to to figure production and modification.

**Competing interests**

None.

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