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Molecular basis of senescence in osteoarthritis

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Abstract

Osteoarthritis (OA) is a multifaceted degenerative joint disorder with substantial global socioeconomic implications. Cellular senescence, defined by permanent cell cycle arrest, has been identified as a critical contributor to OA progression, driving the disruption of cartilage homeostasis and structural integrity. Here, we first delve into the molecular triggers of senescence in OA, including impaired DNA damage response, telomere shortening, mitochondrial dysfunction, oxidative and autophagic stresses, epigenetic modifications, and dysregulated sirtuins and noncoding RNAs. These factors collectively contribute to the establishment of a senescent phenotype in joint tissues, perpetuating the degenerative processes observed in OA. Later, we present the pro-inflammatory senescence-associated secretory phenotype (SASP) as a driving force behind senescence-mediated OA progression that fuels chronic inflammation via the release of pro-inflammatory cytokines, chemokines, and matrix-degrading enzymes, disrupts tissue repair mechanisms, and alters the microenvironment to favor catabolic processes, further exacerbating joint degeneration. The interplay between these factors highlights the complexity of senescence-driven degeneration in OA, underscoring the need for deeper insights into molecular basis of the disease. This review aims to illuminate these mechanisms, providing a foundation for understanding the cellular and molecular pathways that drive senescence in OA and identifying knowledge gaps to guide future research on this pervasive disease.

Key words osteoarthritis, senescence, DNA damage, pro-inflammatory cytokines, epigenetic modifications

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Introduction

Osteoarthritis (OA), a prevalent degenerative joint disease, represents a significant health challenge, causing pain and disability. It affects nearly half of individuals aged 65 and older [1]. The disease is characterized by articular cartilage degeneration and abnormal bone remodeling, influenced by risk factors such as gender, genetic predisposition, and obesity-induced mechanical overload [2]. Aging plays a critical role in OA onset, with individuals over 50 being up to four times more likely to develop post-traumatic OA [3]. Age-related alterations in joint tissues disrupt molecular pathways, impair extracellular matrix (ECM) balance in cartilage, and weaken biomechanical properties over time [4]. Furthermore, aging reduces tissue regenerative capacity, particularly in non-vascularized areas like articular cartilage, compounding the progression of the disease [5]. Nevertheless, the precise mechanisms linking aging to OA pathogenesis are still being uncovered, offering opportunities to better understand the disease and develop targeted interventions.

Senescence, a natural aging-related response to stressors like DNA damage, telomere dysfunction, mitochondrial dysfunction, oxidative stress, autophagic stress, that introduces epigenetic, transcriptional and translational changes limiting cellular proliferation and inducing senescence associated secretory phenotype (SASP) [6, 7]. Of note, senescent joint cells express biomarkers like telomere erosion, increased expression of p53 and cyclin-dependent kinase (CDK) inhibitors p21 and p16, enhanced reactive oxygen species (ROS) generation via mitochondrial dysfunction, and senescence-associated heterochromatin, though the impact of senescence on OA is intricate and still evolving as extent and nature of senescence varies by cell types in the joint that includes the infiltrating cells from innate immune system as well [8-10]. Rather than undergoing apoptosis, these senescent cells activate pro-survival pathways like ephrins, PI3K-AKT, BCL-2 family proteins, p53-associated pathways, and FOXO4, presenting potential drug targets for OA and other senescence-related pathologies [11]. Recent findings also suggest that the establishment of cellular senescence may involve autonomous reprogramming of epigenetic mechanisms [12]. Joint tissue inflammation, a hallmark of OA, involves senescent cells contributing to the inflammatory state through the release of SASP-factors, including pro-inflammatory cytokines (interleukin-1 (IL-1), IL-8, tumor necrosis factor-alpha (TNF-α)), matrix metalloproteinases (MMPs), microRNAs (miRNAs), growth factors, and metabolites, into the tissue microenvironment [13]. Alternatively, inflammation and injury-driven immune response may also drive senescence in the affected tissue. For instance, increased Th17 T cell infiltration induces senescence through perturbation in Wnt signaling and tissue remodeling in OA [14]. Therefore, the process of senescence establishment in OA is dynamic, engaging overlapping yet distinct molecular pathways. In this review, we discuss senescence-related molecular mechanisms such as impaired DNA damage response, telomere shortening, mitochondrial dysfunction, oxidative and autophagic stresses, epigenetic modifications, and dysregulated sirtuins (SIRTs) and noncoding RNAs, contributing to the adversity of OA (**Figure 1**) and highlight the role of SASP as the driving force behind senescence-mediated OA progression.

DNA damage response and senescence in OA

Numerous stressors can instigate the induction of cellular senescence. A frequently implicated factor is nuclear DNA damage, notably in the manifestation of DNA double-strand breaks (DSBs) [15], which triggers the activation of the DNA damage response (DDR) pathway. The DDR operates as a critical checkpoint mechanism, impeding cell cycle progression and forestalling the dissemination of aberrant genetic material to progeny cells. Specific components of the DDR accrue at loci of DNA damage, forming cytologically discernible nuclear foci characterized by extensive chromatin modification events, such as histone H2AX phosphorylation. This chromatin restructuring involves proteins like MDC1, 53BP1, and the activated form of the kinase ataxia telangiectasia mutated (ATM) [16], collectively contributing to the reinforcement of the checkpoint and the imposition of cell cycle arrest until the reparative processes are completed. Persistent DNA damage leads to prolonged DDR signaling and protracted proliferative arrest, culminating in cellular senescence [17]. Recent demonstrations highlighting persistent DDR foci containing unrepaired DSBs [18] in cultured senescent cells underscore the conceptual alignment of cellular senescence with sustained checkpoint activation. Downstream in the DDR cascade, the tumor suppressor p53, a target of ATM and its paralogue ATR, undergoes activation, instigating the expression of the cyclin-dependent kinase inhibitor p21—a pivotal mediator orchestrating senescence-associated cell cycle arrest. Another integral component in various senescence modalities [19], p16—an inhibitor of CDK4 and CDK6—is activated subsequent to p21, possibly serving to sustain the senescent phenotype [20]. Concurrently, in addition to DDR cascade activation, the tumor suppressor ARF stabilizes p53, contributing to the initiation of senescence [21]. Interference with DDR signaling kinases (ATM, ATR, CHK1, and CHK2) enables senescent cells to re-enter the cell cycle [22, 23]. Increased heterogeneity in gene expression and genomic DNA damage in OA chondrocytes, indicating a unique form of age-related degeneration termed "progressive/stress-induced senescence." This degeneration, driven by accumulated DNA damage and chaotic gene activation, leads to cellular dysfunction and loss of homeostasis, contributing to OA pathogenesis [24].

Interferon regulatory factor 1 (IRF1) plays a critical role in DNA repair in chondrocytes, and its absence leads to increased DNA damage and accelerated cellular senescence, exacerbating OA development [25]. Decline in estrogen receptor-α (ERα) levels ensues increased DNA damage and senescence markers in OA chondrocytes. Overexpression of ERα effectively reduces DNA damage and senescence in both normal and OA chondrocytes. Mechanistically, ERα overexpression partially reversed the DNA damage-induced activation of the NF-κB pathway induced by DNA damage, highlighting the critical role of ERα in maintaining chondrocyte health by inhibiting DNA damage and senescence in OA [26]. Oxidative stress induces heightened DDR that leads to senescence of chondrocytes in OA. In such scenario, knocking down IKB kinase alpha (IKKα) reduces microsatellite instability and promotes mismatch repair (MMR) proteins for better DNA damage recovery compared to what observed in IKKα deficient cells during OA development [27]. Mitochondrial DNA (mtDNA) variability serves as prognostic factor in OA, with its manipulation having potential to increase autophagy and limit oxidative stress and senescence, thereby reducing joint damage [28]. In addition, mitochondria-targeted DNA repair enzymes, like 8-oxoguanine DNA glycosylase 1 (OGG1), protect chondrocytes from mtDNA damage, promote mitochondrial transcription and maintain energy homeostasis, thereby reducing senescence and apoptosis. Pro-inflammatory cytokines often disrupt this balance by causing mitochondrial DNA damage [29]. This emphasizes the importance of maintaining mitochondrial DNA integrity, in addition to that of genomic DNA, to counteract senescence in OA.

Telomere shortening and senescence in OA

One of the initial and well-explored mechanisms for inducing cellular senescence is telomere shortening. Due to the limitations

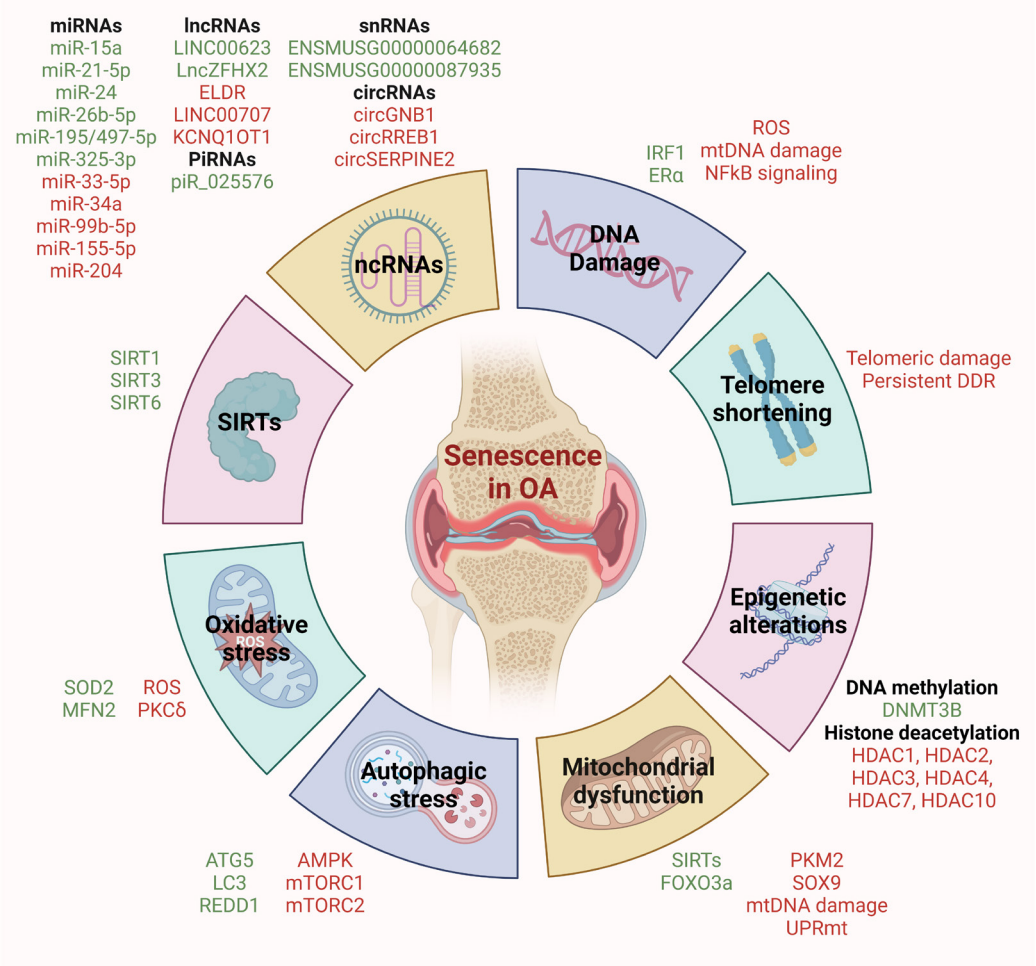

Figure 1. Molecular mechanisms driving senescence in OA. DNA damage, telomere shortening, mitochondrial dysfunction, oxidative stress, autophagic stress, epigenetic stress, and dysregulation of SIRTs and non-coding RNAs contribute to senescence in OA. Key molecular events associated with these hallmarks are listed. Red indicates upregulated/promoter factors, while green indicates downregulated/suppressor factors.

of the standard DNA replication machinery in fully duplicating chromosomal DNA ends, telomeres undergo shortening with each round of DNA replication unless maintained by mechanisms like telomerase expression or telomere recombination. In the absence of such maintenance, critically short telomeres resemble one-ended double-strand breaks (DSBs), eliciting a DNA damage response (DDR) similar to that triggered by DNA DSBs [30, 31]. Replicative cellular senescence can be triggered by just one or a few telomeres with DDR signaling, and the enforced expression of telomerase prevents senescence, allowing unlimited cell proliferation [32, 33]. Persistent DDR activation occurs not only in critically shortened telomeres but also in non-dividing cells subjected to exogenous genotoxic treatments and in non-dividing aging cells. Repair efficiency is notably reduced when DSBs are localized within telomeres [34, 35]. As telomeric DSBs persist, cellular senescence is established and sustained. Therefore, the persistent activation of DDR at telomeres, a key trigger for cellular senescence, can occur during telomere shortening in proliferating cells and also due to telomeric DNA damage in non-proliferating (quiescent or terminally differentiated) cells, independent of telomere length [36].

Chondrocytes in OA patients exhibit telomere shortening and short telomere load in chondrocytes has been proposed as a significant marker for OA diagnosis and prognosis [37]. Chronic pain in OA patients also correlate with telomere length, with patients experiencing chronic severe pain showing shorter telomeres [38]. In addition, ultra-short telomere load, mean telomere length, and proximity to lesions significantly correlates to senescence level and disease severity in OA [39]. Chondrocytes from OA patients also exhibit increased chromosomal aberrations, in addition to reduced telomere length, compared to control chondrocytes, suggesting local advanced senescence in OA joints [40]. The same study also established that peripheral blood leukocytes (PBL) from OA patients exhibit increased chromosomal abnormalities, indicating a more generalized accelerated senescence phenotype associated with OA [40]. Similarly, multiple studies have also established a link between telomere shortening in PBL and OA. For instance, relative telomere length is significantly shorter in PBL from knee OA patients compared to healthy controls, and associates with high oxidative stress and inflammation [41]. In addition, individuals with knee OA at recruitment and those who developed knee OA during the follow-up have shown higher telomere loss in PBL compared to those without knee OA in a 6-year follow-up study. Telomere loss in PBL was independently associated with incident knee OA, suggesting it as a potential risk factor for accelerated cartilage degeneration in OA [42]. Furthermore, another study has correlated telomere size with age, hypertension, BMI, and waist circumference in OA patients, while affirming PBL telomere size as an independent risk factor for knee OA [43]. Meanwhile,

a significant sex-by-disease-status interaction of telomere length in leukocytes, with females having greater differences than males compared to controls, has also been observed [44]. Physiological premenopausal levels of estrogen limit telomere attrition in chondrocytes, while postmenopausal estrogen levels do not do so, suggesting a potential link between estrogen decline in postmenopause and OA onset in women [45]. Severe and moderate pain in OA patients is also associated with shorter telomere length in leukocytes, highlighting sex and pain as factors influencing telomere length in OA. Moreover, cartilage telomere length in severely affected areas corresponded to disease severity, showing telomere attrition. It is noteworthy that telomeres in both severely and less affected cartilage are significantly shorter than leukocytes from the same patient [44]. Accelerated telomere loss in PBLs may indicate a systemic senescence phenotype linked to mitochondrial function, increasing the risk of developing knee OA [46]. Lastly, a meta-analysis of six studies has revealed that OA patients do present shorter telomere length in PBLs compared to healthy controls, confirming the link between telomere length in PBLs and OA pathogenesis [47]. Overall, these findings highlight the contribution of telomere shortening in driving senescence in OA.

Mitochondrial dysfunction and senescence in OA

Senescent cells exhibit alterations in mitochondrial mass, membrane potential, and mitochondrial morphology, indicating a connection to dysfunctional mitochondria [48]. The establishment of senescence may be influenced significantly by dysfunctional mitochondria, as evidenced by senescence induction upon the depletion of mitochondrial SIRTs, a group of evolutionarily conserved proteins involved in regulating aging across various species. Additionally, selective chemical inhibition of mitochondrial function has been demonstrated to trigger senescence [49]. Remarkably, mitochondrial dysfunction-associated senescence, manifests a unique cell-non-autonomous program, potentially contributing to the metabolic alterations observed in aged and diseased individuals [49]. In addition, reciprocal interactions between nuclear DNA damage and mitochondrial dysfunction further exacerbate the scenario [50], as mitochondrial dysfunction leads to mtDNA damage and impaired mitochondrial respiratory chain functions [51]. Chondrocyte senescence is marked by several characteristic changes, including cellular hypertrophy, shortened telomeres, elevated expression of p21, p16, and p53, increased ROS levels, and heightened SA-β-Gal activity [52]. This process involves an upregulation of the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS) in mitochondria to meet the increased demands for acetyl-CoA and activated pyruvate dehydrogenase complexes, crucial for membrane biogenesis [53]. In OA chondrocytes, the upregulation of PKM2 and increased oxygen consumption indicate enhanced glycolysis and oxidative phosphorylation to maintain ATP levels, with a positive correlation observed between PKM2 and SOX9 in senescent chondrocytes [54].

Perturbations in proteostasis and mitochondrial metabolic functions can trigger the activation of the mitochondrial unfolded protein response (UPRmt) during stress leading to cellular senescence [55]. UPRmt activation can propagate deleterious mtDNA rearrangements, impacting oxidative phosphorylation and cellular function. Hence, controlled UPRmt activation is crucial for maintaining mitochondrial homeostasis under stress conditions [56]. At molecular level, inner mitochondrial membrane depolarization activates OMA1, leading to DELE1 cleavage. The resulting fragment activates HRI, phosphorylating eIF2α and slowing cellular protein synthesis. ATF4 and ATF5 levels increase, along with C/EBP homologous protein (CHOP), mediating the integrated stress response. SIRT1 restoration may hamper this pathway and promote chondrocyte function to alleviate osteoarthritis progression [57, 58]. SIRT1 regulates SIRT3 through PGC-1α, activating FOXO3a, that later induces SOD2 and catalase expression, reducing mitochondiral stress [59]. FOXO3a may also promote autophagy-related genes, impacting inflammatory mediators and cartilage degradation [60].

Mechanical stress-induced mitochondrial dysfunction may trigger low-grade chronic inflammation-related senescence response [61]. In turn, inflammatory factors like IL-1β and TNF-α further impair mitochondrial function, reduce energy production, and hinder mitochondrial DNA repair in chondrocytes [29, 62]. Additionally, altered redox environments in OA inhibit anabolic signaling pathways, leading to decreased cartilage matrix synthesis [63, 64]. Overall, disruptions in mitochondrial homeostasis and quality control mechanisms contribute significantly to the persistence of chondrocyte senescence and hinder recovery processes.

Oxidative stress and senescence in OA

Mechanical stress and aging stand out as primary risk factors contributing to OA, with both capable of generating ROS and inducing oxidative damage [65]. This oxidative stress is elevated in senescent cells and correlates with the accumulation of impaired mitochondria as stress-induced mtDNA damage fosters telomere shortening and ROS production, that, in turn, hinders mtDNA repair [62, 66]. In OA, ROS exacerbate mitochondrial dysfunction, trigger DNA damage and DDR, and accelerate premature senescence, matrix degradation, and subchondral bone loss [67]. Furthermore, oxidative stress contributes to membrane damage, extracellular component degradation, and cartilage destruction. ROS also hinder proteoglycan synthesis in cartilage via nitric oxide and ATP formation, along with inhibiting mitochondrial oxidative phosphorylation through H2O2 production [68, 69]. Mechanistically, chondrocytes experience heightened mitochondrial superoxide production alongside decreased levels of superoxide dismutase 2 (SOD2) under mechanical stress, leading to mitochondrial superoxide accumulation. This imbalance between antioxidants and prooxidants contributes to cartilage degeneration [70]. Reduced levels of antioxidant enzymes correlate with accelerated senescence, as evidenced by SOD2 knockout (SOD2−/−) mice displaying shortened lifespans, early aging cellular phenotypes, and increased expression of p16 and p21 at both mRNA and protein levels [71]. Notably, SOD2 deletion exacerbates OA severity, while its overexpression or antioxidant use mitigates OA progression. Peroxiredoxins serve as antioxidants by clearing excess H2O2; however, under oxidative stress, they become hyperoxidized and lose their function, dampening survival signaling through Akt pathway inhibition and promoting p38 signaling in chondrocytes [63, 72], underscoring the detrimental impact of ROS on cartilage health.

Oxidative stress may promote cellular senescence by instigating DNA damage and DDR [73]. In the context of OA, oxidative stress contributes significantly to disease progression by inducing genomic instability, particularly telomere instability, replicative senescence, and dysfunction in human chondrocytes [74]. For instance, hypertrophic ligamentum flavum is a characteristic of OA in spine, that is directly linked to higher levels of oxidative stress and associated telomere shortening compared to non-hypertrophic ligamentum flavum [75]. Upon exposure to oxidative stress, redox-sensitive PKCδ activates IKKα, leading to p53 phosphorylation and activation, thereby modulating DDR and influencing cell cycle arrest and senescence [76]. Despite this, the role of P53 in chondrocytes is controversial as PKR/p38 MAPK/p53/AKT/PGC-1α pathway has been shown to cause abnormal mitochondrial biosynthesis and increased oxidative stress in chondrocytes under

TNF-α stimulation, wherease AMPK-SIRT-p53 signaling has been reported to protect against chondrocyte senescence [77, 78]. The latter is further supported by the findings that AMPK activation in OA chondrocytes alleviates increased mtROS associated with mtDNA4977 deletion and reduced SIRT3 expression, enhancing mitochondrial function and potentially offering chondroprotective benefits [79]. Further research is needed to clarify P53's involvement in the mitochondria of senescent chondrocytes.

During aging and OA, MFN2 expression increases in chondrocytes, promoting protective mitochondrial fusion that maintains mitochondrial function under stress [80]. However, prolonged stress disrupts mitochondrial dynamics, leading to mitochondrial dysfunction, their excessive division and compromised removal of damaged mitochondria [81]; thereby worsening chondrocyte damage induced by ROS. The interplay between inflammation and oxidative stress further exacerbates senescence-related cartilage damage in OA, with ROS playing a pivotal role in overproducing SASP components such as IL-1, IL-6, and MMPs. Inflammatory changes are associated with decreased antioxidant enzyme levels in biological fluids and cartilage, coupled with elevated oxidative agent levels, contributing to cartilage matrix protein impairment and subsequent damage [73, 82].

Autophagic stress and senescence in OA

Autophagy, a crucial mechanism for cellular homeostasis during which damaged organelles and proteins are sequestered and broken down by lysosomes, conserves energy and provides protection in response to cellular stress, such as nutrient deprivation, hypoxia, ROS exposure, and DNA damage [83]. Evidence from normal human articular cartilage indicates that autophagy is constitutively active in chondrocytes, as shown by the expression of markers such as ULK1, LC3, and Beclin1. The avascular and hypoxic conditions within cartilage likely contribute to this ongoing autophagic activity that eventually plays a protective role in chondrocytes by mitigating cell death [84]. Notably, aging is associated with diminished autophagic activity in knee articular cartilage, marked by reduced autophagic vesicles and lower levels of ATG-5 and LC3, alongside elevated levels of the apoptosis marker p85 [85, 86]. Similarly, reduced levels of autophagy markers alongside increased apoptosis have been observed in chondrocytes from OA patients and surgery-induced OA mouse models [84]. In addition, studies have also highlighted the beneficial effects of autophagy in chondrocytes, with Regulated in Development and DNA Damage Response 1 (REDD1), an endogenous mTOR inhibitor, demonstrating protective effects in OA models [87]. Moreover, autophagy plays a role in regulating cellular senescence by overseeing protein degradation processes. Chaperone-mediated autophagy (CMA) is a key component of the lysosome-autophagy proteolytic system and is implicated in maintaining proteostasis. Dysfunctional CMA can lead to the accumulation of misfolded proteins and oxidative products, contributing to senescence [88]. DNA damage further exacerbates senescence by impeding the autophagic degradation of GATA4, a transcription factor involved in senescence and the SASP factor production through NF-κB activation. Under normal conditions, GATA4 is degraded via p62-mediated selective autophagy, a process that is compromised during senescence [89]. AMPK triggers chondrocyte autophagy in a HIF-1α-dependent fashion, with a documented reduction in AMPK expression observed in chondrocytes from individuals with knee OA [90]. AMPK, along with PI3K/Akt pathway, in chondrocytes may also inhibit mTORC1; thereby regulate mitophagy [91], a process specifically targets and degrades faulty mitochondria, safeguarding mitochondrial function in human chondrocytes [92]. Unfortunately, expression and activity of REDD1 and AMPK decrease in chondrocytes with age and OA, opening gateway for poor autophagic response, cell cycle arrest and senescence [81].

While the potential of targeting autophagy to modulate senescence is recognized, several complexities warrant further investigation. Autophagy's role in senescence regulation appears multifaceted, with instances where autophagy inhibition, such as through rapamycin-mediated mTOR inhibition, can prevent certain aspects of senescence like SASP induction but may not affect oncogene-induced cell cycle arrest [93]. Moreover, conflicting evidence exists regarding autophagy's overall impact on senescence, with studies suggesting both promoting and protective roles in different contexts [94]. Notably, sustained p53 activation, characteristic of senescent cells, can influence the expression of various autophagy-related proteins, indicating a potential constitutive activation of autophagy during senescence [94]. Recent studies have also linked autophagy to senescence induction via mTORC2, highlighting the intricate interplay between autophagy and senescence pathways [95]. The dual nature of autophagy in senescence underscores the need for a comprehensive understanding before considering autophagy-targeting interventions for senescence modulation in OA.

Epigenetic alterations and senescence in OA

Epigenetics encompasses heritable changes in gene expression induced by external factors rather than genetic alterations. The majority of cells in a senescent state exhibit profound alterations in both the epigenome and chromatin organization. These changes have implications for both the cell's autonomous functions and its influence on surrounding cells in the context of senescence-associated proliferation arrest [6]. Accelerated epigenetic aging in articular cartilage of OA patients highlights the specific involvement of premature aging processes in OA pathogenesis [96]. DNA methylation, and acetylation, and histone modifications serve as key epigenetic marks in human biology, diseases and aging, as these alterations can regulate gene expression by influencing chromatic structure and accessibility [97]. Regarding DNA methylation, it is a reversible process catalyzed by DNA methyltransferases (DNMTs), leading to the formation of 5-methylcytosine (5 mC) at CpG dinucleotides [98]. Overall, DNA methylation levels are diminished in OA [99]. In addition, substantial demethylation occurs during cartilage development, particularly at sites with enhancer modifications [100]. Altered DNA methylation of inflammatory genes is associated with OA in human chondrocytes. For instance, IL8 exhibits significantly higher expression in hip OA patients than in controls, with methylation reducing basal IL8 promoter activity in vitro. Upregulated IL-8 decreases DNMT3B expression in OA chondrocytes [101], resulting in decreased DNA methylation. Additionally, the pro-inflammatory cytokine IL-1β may downregulate DNMT3B in chondrocytes via NFκB [102]. Prolonged exposure to inflammatory cytokines induces demethylation of specific CpG sites in the proximal promoter of IL-1β, leading to increased and sustained IL-1β expression [103]. This dysregulation of inflammatory factors contributes to an imbalance in joint cartilage metabolism through the NFκB pathway. Furthermore, epigenetic changes in the methylation state of CpG sites in promoter regions of cartilage-degrading enzymes may underlie increased enzyme levels in advanced OA [104]. Moreover, hypermethylation of specific CpG sites on the SIRT1 gene promoter reduces SIRT1 expression in OA chondrocytes, inducing matrix-degrading enzymes and pro-inflammatory SASP;, thereby impacting disease progression [105]. Aging MSCs also produce numerous pro-inflammatory factors, potentially influencing OA by impacting DNA methylation [106], linking epigenetic alterations

to senescence in OA.

Histones are highly conserved proteins with the primary function of stabilizing, organizing, and concentrating DNA within the nucleus's limited space. They are composed of duplicate octamers that contain dimers of four core histones (H2A, H2B, H3, and H4), effectively encapsulating genomic DNA on their outer surface [99]. Acetylation plays a crucial role in modulating histone function by neutralizing the positive charge on histones, converting the amine residue into an amide. This process reduces the histone's affinity for DNA, preventing chromatin shrinkage and facilitating access for the gene transcription machinery to transcribe DNA. Conversely, deacetylation restores a positively charged histone tail, leading to high-affinity binding with the DNA backbone and resulting in chromatin condensation that blocks transcription [107]. The family of histone deacetylases (HDACs) and histone acetyltransferases are enzymes responsible for histone and non-histone deacetylation and acetylation, respectively [108]. HDAC1 and HDAC2 expression is increased in chondrocytes and synovial membranes of OA patients compared to controls. The carboxyl-terminal domain of HDAC1 and HDAC2 collaborates with the transcriptional inhibitor SNAIL to inhibit the expression of collagen α1(II) gene (COL2A1) and aggrecan, contributing to OA pathology [109, 110]. Knocking down HDAC3 in human chondrocytes results in altered expression of cartilage-related genes, potentially impacting OA progression [111]. Additionally, HDAC4, HDAC7 and HDAC10 play roles in regulating gene expression associated with cartilage degradation and inflammation, linking histone modifications to senescence in OA [112-114]. Histone methylation marks also play important role in OA pathology. For instance, knocking down Jun, whose expression is found to be reduced in senescent chondrocytes in vivo, induces micronuclei formation, reduces H3K9 trimethylation, and decreases levels of heterochromatin protein 1gamma, indicating chromatin destabilization that fosters senescence phenotype in chondrocytes [115]. Overall, epigenetic alterations play key role in acquisition of senescence in OA.

Dysregulated sirtuins (SIRTs) and senescence in OA

SIRTs, a family of highly conserveHDACd NAD+-dependent histone and non-histone deacetylases, regulate cellular energy output in response to energy demands by sensing cytoplasmic NAD+ levels [116]; thereby playing pivotal roles in cellular processes such as senescence, DNA repair, inflammatory response, metabolism, apoptosis, and cell survival [117]. The discovery of Sir2 in Saccharomyces cerevisiae marked the beginning of understanding sirtuins' role in aging and longevity [118], with seven known homologs in mammals known as SIRT1-SIRT7 [117, 119]. Recent investigations highlight the protective role of SIRTs, specifically SIRT1, SIRT3 and SIRT6, in mitigating chondrocyte senescence [73]. For instance, SIRT1 impedes the onset of chondrocyte senescence by suppressing the expression of SASP factors, including IL-1β, IL-6 and IL-8 [120]. Additionally, SIRT1 interacts with Sox9, a cartilage-specific transcription factor, promoting collagen 2 transcription and potentially benefiting cartilage by upregulating genes encoding ECM components [121]. Conversely, the absence of SIRT1 in cartilage accelerates OA progression, primarily through the aberrant activation of the p53/p21-mediated SASP [122]. Under pro-inflammatory stress, SIRT1 undergoes cleavage into an inactive N-terminal polypeptide and a C-terminal fragment in chondrocytes, with the increased serum ratio of N/C terminal fragments serving as an indicator of early OA and chondrocyte senescence [123]. Moreover, SIRT1's influence on circadian rhythm, including its inhibition leading to reduced expression of the clock gene Bmal1, underscores its association with circadian rhythm disruptions, heightened vulnerability to aging, cartilage damage and OA progression and [124].

SIRT3, predominantly located in mitochondria, maintains mitochondrial homeostasis and regeneration, a phenomenon that protects against OA development [125]. In particular, SIRT3 deacetylates SOD2, a protective factor against oxidative stress, thereby increasing SOD2-specific activity and safeguarding against chondrocyte senescence and OA progression [126]. SIRT3, at the downstream of ubiquitin-specific protease 3 (USP3), also attenuates inflammation-driven chondrocyte senescence by directly deacetylating FOXO3; thereby alleviating disease progression [127]. On the other hand, SIRT6 inhibits replicative senescence and retards OA progression by reducing inflammatory responses and chondrocyte senescence [128]. Unfortunately, SIRT6 levels in chondrocytes and cartilage tissue from OA patients are substantially lower than those in normal individuals [128, 129]. This loss of SIRT6 can contribute to increased DNA damage, telomere dysfunction, and premature senescence in chondrocytes [130, 131]. Notably, IL-1β downregulates SIRT6 expression while increasing MMP13 expression, resulting in the accumulation of DNA damage and telomere dysfunction, leading to cellular senescence. SIRT6 prevents premature senescence in human chondrocytes by coordinating DNA repair mechanisms and preserving appropriate telomere function [131]. Notably, SIRT6's involvement extends to promoting DNA repair under stress and safeguarding against telomere dysfunction through its deacetylation activity [132]. In particular, SIRT6 inhibits the acetylation of p27, a protein highly acetylated with an extended half-life during cellular senescence, leading to its degradation via the ubiquitin–proteasome pathway and delaying cellular senescence [133]. In addition, overexpressing SIRT6 facilitates DNA damage repair and inhibits senescence, potentially through the activation of the Keap1/Nrf2/HO-1 signaling pathway [129].

Dysregulated non-coding RNAs and senescence in OA

Noncoding RNAs (ncRNAs) such as miRNAs, long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), PIWI-interacting RNAs (piRNAs), small nuclear RNA (snRNA) and small nucleolar RNAs (snoRNAs) play pivotal roles in maintaining cellular homeostasis. Their regulatory functions span gene expression modulation, epigenetic regulation, and cellular signaling, contributing significantly to plethora of physiological processes in the human body such as development, immune responses, metabolism, proliferation and senescence, while their dysregulation is associated with various diseases, including OA [134, 135]. Various ncRNAs either restrain or promote senescence in chondrocytes, highlighting importance of ncRNA as potential therapeutic targets for OA [136]. For instance, miR-15a expression is low in OA cartilage whereas its overexpression through intra-articular injection inhibits senescence and cartilage degeneration in vivo by directly targeting β1,4-Galactosyltransferase-I (β1,4-GalT-I) that inhibiting NF-kB activation [137]. Similarly, upregulation of miR-21-5p decreases senescence and enhances cell viability in OA chondrocytes. Mechanistically, miR-21-5p decreases MMP13 and ADAMTS5 expression while increases COL2A1 expression [138]. miR-24 acts as a negative regulator of p16, with increased p16, MMP-1 and MMP-13 expression and decreased miR-24 levels observed in OA cartilage, linking senescence and adverse cartilage remodeling to OA [139]. miR-26b-5p is also downregulated in OA cartilage and consequent upregulation of its target, asporin, induces senescence via inhibiting TGF-β1-Smad2 pathway in chondrocytes [140]. Disrupted miR-195/497-5p expression in senescent chondrocytes affects the circadian rhythm via Per2 modulation, leading to articular cartilage degradation and OA onset during aging. Mechanistically, miR-195/497 cluster directly

targets DUSP3, impacting ERK 1/2 and CREB phosphorylation, and hindering subsequent Per2 transcription [141]. miR-325-3p expression decreases in response to overload induced senescence in OA, with miR-325-3p inhibiting chondrocyte senescence via targeting p53 [142]. miR-33-5p promotes chondrocyte senescence and OA progression by targeting SIRT6 [143]. miR-34a, on one hand, can directly target SIRT1, and upregulate p16, IL-6, and MMP-13 expression [144] whereas, on the other hand, it can also inhibit DLL1, modulating the PI3K/AKT pathway and resulting in senescence and cartilage loss [145]. miR-99b-5p mediated downregulation of MFG-E8 induces senescence in chondrocytes, resulting in cartilage damage, synovial hyperplasia, and osteophyte formation; thereby exacerbating OA pathology [146]. Chondrocytes sense mechanical overload via PIEZO1, leading to increased miR-155-5p expression downstream, and subsequent chondrocyte senescence through miR-155-5p mediated inhibition of GDF6-SMAD2/3 in OA [147]. miR-204 is significantly upregulated in osteoarthritis (OA) cartilage, induced by transcription factors GATA4 and NF-κB in response to senescence signals. In return, it targets multiple components of the sulfated proteoglycan biosynthesis pathway, leading to reduced proteoglycan anabolism and cartilage matrix imbalance, further exacerbating the scenario [148].

LncRNA ELDR plays a key role in chondrocyte senescence during OA by regulating histone modifications to activate hedgehog signaling [149]. Similarly elevated LINC00707 promotes chondrocyte senescence, ECM degradation, and inflammation in OA by rescuing FSHR via sponging-off miR-330-5p [150]. LncRNA KCNQ1OT1 potentially targets and inhibit miR-1202 to promote ETS1-driven cellular senescence in OA [151]. On the other hand, LINC00623 inhibits chondrocyte apoptosis, senescence, and ECM degradation via MAPK signaling. Mechanistically, LINC00623 rescues HRAS from miR-101 mediated inhibition, resulting in hyperactive MAPK signaling and alleviating OA progression [152]. LncZFHX2 regulates RIF1 expression by forming a transcription complex with KLF4, promoting chondrocyte DNA repair and matrix homeostasis while decelerating cellular senescence [153].

Increased circGNB1 in stressed chondrocytes and aging cartilage blocks miR-152-3p, that no longer targets ring finger protein 2019 (RNF219). This stabilizes caveolin-1 (CAV1) by preventing its ubiquitination at the K47 residue, driving senescence OA progression [154]. CircRREB1 inhibits FASN degradation by impeding acetylation-mediated ubiquitination and promotes FASN stability via RanBP2-mediated SUMOylation. This CircRREB1-FASN axis suppress PI3K-AKT signaling by inhibiting FGF18/FGFR3, leading to increased p21 expression and senescence in chondrocytes [155]. Increased circSERPINE2 levels in long-term-cultured mesenchymal stem cells (MSCs) contributes to stem cell senescence. Mechanistically, circSERPINE2 interacts with YBX3, restraining it to cytoplasm. This leads to reduced PCNA transcription and, subsequent ubiquitin-mediated degradation of p21, resulting in acquisition of senescent phenotype [156]. Chondrocytes undergo replicative aging and exhibit significant changes in ncRNA expression profiles. A large scale ncRNA profiling study has identified that miR-132-5p promote chondrocyte senescence, whereas a piRNA named piR_025576, a snRNA named ENSMUSG00000064682 and a snoRNA named ENSMUSG00000087935 delay chondrocyte senescence upon overexpression [157]. Overall, different ncRNAs regulate chondrocyte senescence though varied molecular mechanisms, offering therapeutic avenues to target OA progression.

SASP – The driving force behind senescence-mediated OA progression

The key mechanism through which senescent cells exert their multifaceted biological functions involves the transcriptional activation of SASP (**Figure 2**). This program is characterized by the release of cytokines, chemokines, growth factors, and ECM proteases, contributing to the potential self-reinforcement of senescence or influencing the local tissue microenvironment of senescent cells and, conceivably, the entire organism. The activation of SASP is a dynamic process that coincides with the establishment of senescence [7, 158, 159]. Despite some qualitative and quantitative variations in SASP among different tissues and senescence models, a core SASP program consistently includes proinflammatory IL-6, IL-8, and monocyte chemoattractant protein 1 (MCP1, or CCL2) in all types of in vitro-generated senescent cells [7]. Chemokines like CCL2 and CCL4 play a role in recruiting macrophages and natural killer cells to the site [160]. SASP encompasses not only proinflammatory molecules but also enzymes participating in ECM remodeling, such as MMPs, serine/cysteine proteinase inhibitors (SERPINs), and tissue inhibitors of metalloproteinases (TIMPs) [161]. While both permanent cell cycle arrest and the ongoing secretion of SASP factors are hallmarks of senescence, these processes are governed by distinct yet interconnected mechanisms. It has been proposed that SASP factor production and release operate independently of cell cycle arrest, as evidenced by studies in p16INK4A knockout mouse chondrocytes which show no reduction in SASP factor release [162].

The generation of SASP factors is intricately linked to signaling pathways such as NF-κB, p38MAPK, and mTOR, operating at various levels from transcription to secretion [163]. NF-κB, a key player in inflammatory signaling, orchestrates the transcription of numerous inflammatory mediators [164] and is a pivotal pathway driving SASP factor production [165]. Cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) expression is elevated in OA tissues and chondrocytes exposed to IL-1β, promoting ECM degradation, apoptosis, and senescence. Mechanistically, STING activates the NF-κB signaling cascade, contributing to OA progression whereas its knockdown attenuates SASP production and OA development [166]. Stress-induced p38MAPK, observed in various senescent fibroblasts, plays a significant role in SASP regulation; inhibiting p38MAPK can notably reduce the secretion of most SASP factors. Moreover, p38MAPK independently induces SASP production, bypassing the DDR, thus promoting sustained SASP secretion [167]. In the context of OA, PIEZO1, and calcium ion channel component, is elevated in diseased cartilage. It increases SASP factor production, especially IL-6 and IL-1β, through activation of p38MAPK and NF-κB pathways [168]. Rapamycin, an mTOR inhibitor, modulates SASP factor production by suppressing the translation of membrane-bound IL-1α and dampening NF-κB activity [169]. Additionally, mTOR regulates the translation of MAPKAPK2 (MK2), which in turn inhibits ZFP36L1, a protein involved in degrading SASP factor transcripts, thus stabilizing SASP components [93]. Both oxidative and inflammatory stresses can induce senescence and SASP in chondrocytes with latter exhibiting a more profound impact [170]. It's important to note that the production of SASP in OA is not limited to senescent chondrocytes alone. Cells such as osteoblasts, synovial fibroblasts, synovial macrophages, and NK cells within the joints also contribute significantly to this inflammatory milieu that contributes to cartilage degradation [171]. Synovial cells, for instance, account for approximately 55% of cytokine production, and interactions between synoviocytes and chondrocytes play a critical role in OA pathogenesis [172].

SASP factors form a complex regulatory network with both upstream and downstream interactions. For instance, cell membrane-bound IL-1α enhances the DNA binding ability of

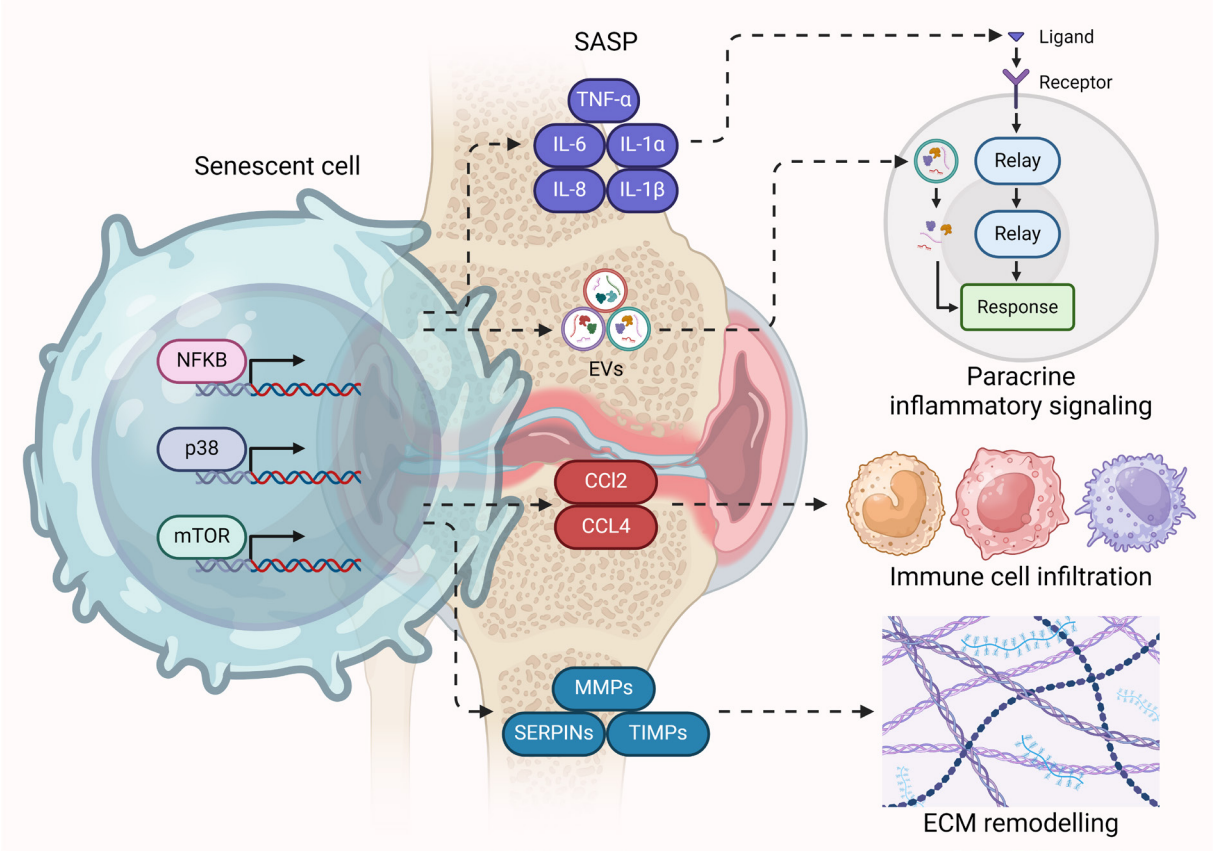

Figure 2. SASP – The driving force behind senescence-mediated OA progression. Hyperactive NF-κB, p38, and mTOR signaling in senescent cells (particularly chondrocytes) in OA drive the expression of pro-inflammatory cytokines, chemoattractants, ECM remodelers, and aberrant release of EVs as part of SASP. Pro-inflammatory cytokines and EVs promote inflammation and senescence in neighboring cells through paracrine signaling. Chemoattractants promote immune cell infiltration in the cartilage, while ECM remodelers disrupt ECM homeostasis.

NF-κB and C/EBPβ, leading to increased transcription of IL-6 and IL-8 [173]. Key SASP factors like IL-6 and IL-8 further promote SASP factor secretion, creating a positive feedback loop that reinforces senescence [174]. Lumican, an ECM glycoprotein is upregulated in OA cartilage, aggravates inflammation by enhancing proinflammatory activation via TLR4 and macrophage polarization [175]. On the other hand, ERCC1 is decreased in OA cartilage and is associated with increased expression of MMP-13 and decreased collagen type II, along with increased apoptosis and cellular senescence, highlighting ERCC1's role in protecting chondrocytes from SASP-driven disease progression [176].

Early SASP factors induce senescence in neighboring normal cells, thereby contributing to senescence expansion, whereas later SASP factors recruit immune cells and intensify the inflammatory milieu [177]. In the context of OA, EVs from human OA-derived chondrocytes, enriched with Cx43, have been shown to induce a senescent phenotype and activate inflammatory pathways in targeted cells, promoting joint degeneration through SASP. These EVs alter protein profiles and cellular plasticity, and activate pro-survival and pro-inflammatory mechanisms such as ERK1/2 and NF-κB signaling pathways, highlighting their role in disease progression by spreading senescence, inflammation, and reprogramming factors across cartilage, synovium, and bone, potentially affecting multiple joints [178]. Senescent microenvironment also impedes cartilage repair by bone marrow stem cells (BMSCs). Although BMSCs have potential to induce apoptosis in senescent chondrocytes and reduce their numbers, senescent chondrocytes inhibit BMSC proliferation, promote senescence, and suppress chondrogenic differentiation; thereby inhibiting cartilage repair by BMSCs [179]. In summary, SASP drives a complex network of inflammatory mediators, ECM remodeling enzymes, and signaling pathways, contributing to the reinforcement of senescence through systemic effects. Understanding these intricate mechanisms is crucial for developing targeted interventions to modulate the SASP-driven inflammatory milieu and promote tissue repair in OA.

Conclusion and future prospect

In conclusion, the escalating incidence of OA in the aging population underscores the urgent need to unravel the intricate molecular mechanisms linking aging and OA [65]. The accumulation of senescent cells over time, coupled with gradual changes in cellular metabolism, morphology, and function, collectively contribute to the loss of joint tissue homeostasis and integrity. The compelling evidence provided here, implicating cellular senescence in joint tissues as a primary driver of OA pathogenesis highlights the need for deeper exploration into the precise mechanisms through which senescence induces specific disease phenotypes. In addition, current reliance on common biomarkers for identifying senescence is deemed insufficient for diagnosing OA accurately [180]. Alternative biomarkers, particularly circulating ones including miRNAs and/or EVs provide promising approach, though merit further investigation to enhance specificity [181]. Bioinformatic analyses and machine learning approaches have great potential to serve the purpose of

identifying novel biomarkers [180]. Finally, developing effective senescence-targeted OA treatment strategies requires a dual-pronged approach: understanding the underlying mechanisms driving the associated cellular changes and subsequently designing therapies tailored to these mechanisms. Therefore, existing gaps in knowledge necessitate further investigations to identify novel senescence-related therapeutic targets for the treatment of OA in the elderly population.

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Data availability

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Authors' contribution

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Competing interests

None.

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