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REVIEW

Cellular senescence in age-related musculoskeletal diseases

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Abstract **Aging is typically associated with decreased musculoskeletal function, leading to reduced mobility and increased frailty. As a hallmark of aging, cellular senescence plays a crucial role in various age-related musculoskeletal diseases, including osteoporosis, osteoarthritis, intervertebral disc degeneration, and sarcopenia. The detrimental effects of senescence are primarily due to impaired regenerative capacity of stem cells and the pro-inflammatory environment created by accumulated senescent cells. The secreted senescence-associated secretory phenotype (SASP) can induce senescence in neighboring cells, further amplifying senescent signals. Although the removal of senescent cells and the suppression of SASP factors have shown promise in alleviating disease progression and restoring musculoskeletal health in mouse models, clinical trials have yet to demonstrate significant efficacy. This review summarizes the mechanisms of cellular senescence in age-related musculoskeletal diseases and discusses potential therapeutic strategies targeting cellular senescence.**

Keywords cellular senescence; aging; musculoskeletal disease; degenerative diseases; senotherapy

Introduction

Aging is a gradual and irreversible biological process characterized by the deterioration of tissue and cell function, ultimately leading to organ impairment and degenerative diseases [1–3]. One of the commonly accepted hallmarks of aging is cellular senescence, which involves irreversible cell cycle arrest and the secretion of senescence-associated secretory phenotype (SASP) proteins [1,4]. Various factors can induce cellular senescence, including but not limited to telomere shortening, DNA damage, mitochondrial dysfunction, activation of tumor suppressor genes, and inflammatory responses [5–9]. Senescent cells are typically characterized by enlarged cell size, elevated expression of cell cycle inhibitors ($p16^{INK4a}$, $p19^{ARF}$, *p53*, and *p21*), loss of nuclear proteins lamin-B1 and high mobility group box 1 (*HMGB1*), and increased expression of senescence associated-β-galactosidase (*SA-β-gal*) and *γ-H2AX* [10–12]. In the physiological context, senescent cells play a beneficial role by engaging in embryogenesis, preventing cancer, and promoting tissue regeneration and wound healing. However, these protective effects are based on the transient presence of senescent cells. The accumulation of senescent cells with age can result in various chronic age-related diseases [13–16]. Although the unique role of cellular senescence in the body remains to be fully elucidated, therapies aimed at reducing the burden of senescent cells have been shown to improve the overall aging profile [17,18].

The musculoskeletal system supports the body, manages movements, and protects internal organs. It is composed of bone, muscle, and connective tissue. The aging of the musculoskeletal system has become an important factor for human health, and it plays a crucial role in the onset of age-related musculoskeletal diseases, including osteoporosis, osteoarthritis (OA), intervertebral disc degeneration (IDD), and sarcopenia [19]. Maintaining musculoskeletal health is crucial for improving the functional ability and quality of life of the elderly. As discussed in detail below, emerging *in vitro* and *in vivo* models, along with human samples, indicate that cellular senescence plays an active role in the onset and progression of these musculoskeletal diseases. In this review, we primarily focused on the mechanisms of cellular senescence in musculoskeletal disorders and therapeutic strategies targeting senescence in these diseases.

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Mechanisms of cellular senescence

Cellular senescence can be categorized into replicative

senescence, premature senescence, and oncogene-induced senescence based on their underlying mechanisms [20]. Replicative senescence occurs as cells lose their ability to proliferate due to progressive telomere shortening during cell division. Premature senescence is induced by stress factors such as reactive oxygen species (ROS), mechanical stress, and cytokines, which disrupt the normal cell cycle, leading to the generation of senescent cells in pathological conditions [21]. The irreversible cell cycle arrest in senescence is primarily regulated by the *p53/p21/*retinoblastoma protein (*RB*) and $p16^{INK4a}/RB$ pathway [22–24]. Mechanistically, in replicative senescence, DNA repair reactions triggered by telomere shortening or DNA double-strand breaks activate DNA damage response kinases such as ataxia telangiectasia mutated protein kinase and Rad3-related protein kinase, which can increase the phosphorylation level of p53 [25]. Elevated phosphorylated p53 promotes the expression of the tumor suppressor gene *p21*, which in turn inactivates *CDK2*, leading to reduced phosphorylation and cell cycle arrest [26]. This permanent arrest is also associated with the upregulation of $p16^{INK4a}$, which inhibits cyclin-dependent kinase 4/6 (*CDK4/6*), reducing the phosphorylation of RB and consequently halting the cell cycle at the S phase [27]. The senescence of cells can be mediated by $p16^{INK4a}/RB$ alone or by the combined effort of the *p53/p21/RB* and $p16^{INK4a}/RB$ pathways [28]. Although $p16^{INK4a}$ is one of the most commonly used senescence markers in research, not all senescent cells exhibit upregulated $p16^{INK4a}$ expression. Cellular senescence is a heterogeneous process, and senescence phenotypes can evolve with time. The increase in p21 typically occurs earlier than that of $p16^{INK4a}$, indicating a stepwise progression in senescence, and cells at different stages of senescence can vary in phenotype [9]. As the stimuli of senescence can usually trigger cell death, we must understand what determines different cell fates. Some studies suggested that inner mitochondrial membrane peptidase subunit 2 (IMMP2L) plays a critical role in cell fate. A high ROS environment will shut down the IMMP2L-glycerol-3-phosphate dehydrogenase 2 (*GPD2*) pathway, which is essential for phosphatide production and cell membrane stability [29]. In this context, cell fates are influenced by apoptosis inducing factor (AIF), another substrate of IMMP2L. AIF can be cleaved by IMMP2L, inducing cell death, whereas the shutdown of IMMP2L-AIF directs cells toward senescence [29].

Mitochondria dysfunction and autophagy impairment play intriguing roles in cellular senescence. Dysregulated mitochondria metabolism leads to the accumulation of damaged mitochondria and ROS, and the subsequent oxidative stress plays an essential role in such process. Recent research has highlighted the role of methylation in ROS-mediated senescence. Under oxidative stress, coactivator-associated arginine methyltransferase 1 (CARM1) moves to cytosol, where CARM1 promotes the mitochondria localization of dynamin-related protein 1 (DRP1) and triggers mitochondrial fission and ROS production. Excessive ROS further promotes the cytoplasmic localization of CARM1, forming a positive feedback loop that strengthens ROS production and mitochondrial fission [30]. Although mitochondrial dysfunction can induce senescence through ROS accumulation and impaired mitophagy, considering that mitochondrial dysfunction can also be the consequence of cellular senescence, their relationship needs further investigation. Notably, ROS from mitochondrial and mitochondrial-independent sources can induce and maintain the senescent phenotype [31,32]. Similarly, autophagy is found to prevent senescence but may also sustain the production and secretion of SASP. Unstrained activity of mechanistic target of rapamycin (mTOR), leading to suppressed autophagy, has been found to promote senescence, whereas inhibiting mTOR with everolimus delays the onset of senile pathologies in mice [33]. However, Narita *et al*. discovered that mTOR and autophagy are spatially coupled to support the active metabolic turnover, underscoring the significance of autophagy in sustaining active SASP production and secretion [34].

The secretory characteristics of senescent cells are regarded as a primary distinction between senescent cells and other cells with arrested cell cycles, such as quiescent cells or terminally differentiated cells. In contrast to quiescent and apoptotic cells, senescent cells exhibit heightened metabolic activity, which may be explained by active SASP production. SASP is mainly composed of cytokines, chemokines, oxidative factors, growth factors, exosomes, and extracellular matrix (ECM) components [35–39]. Studies have shown that the blood of old mice can induce cellular and tissue senescence in young mice [40]. However, if elderly animals are treated with anti-aging drugs before blood exchange, the pro-aging effect of old blood on young mice is attenuated, indicating a modified secretory profile of senescence [40]. Additionally, old mice can benefit from circulating components of young mice. A recent heterochronic parabiosis (HP) research demonstrated that shared circulation between old and young mice can rejuvenate old mice [41]. The protective effect even persists at 2 months after HP. Small extracellular vesicles (SEVs) from the blood of young mice have been identified as beneficial circulating components, and treatment with young SEVs ameliorates the functional decline of muscle, skeletal, heart, and brain in aged mice [42]. Although most studies have focused on the protein components of SASP, lipid components of SASP are also involved in cellular senescence. Recent research has identified the role of intracellular prostaglandin in promoting cell cycle

arrest and SASP production [43]. However, this study was limited to three cell types, and whether lipid components of SASP play similar roles in other cell lineages remains unclear.

As a double-edged sword, the effect of SASP depends on its components and exposure time. On the one hand, SASP promotes tissue repair by attracting immune cells to eliminate senescent cells and recruiting progenitor cells for regeneration [44]. Failure in immune cell recruitment can result in the long-term persistence of senescent cells, leading to tissue dysfunction, senescent phenotype, and tumorigenesis. Therefore, SASP relies on a properly functioning immune system to take effect. However, immunity function also declines with age, which may distort the protective effect of SASP. On the other hand, if the accumulated senescent cells exceed the clearance capacity, as seen in the aging process, the secreted SASP can lead to sterile inflammation or "inflammaging" [35]. Notably, the senescence of a small portion of cells can induce senescence on a large scale through either SASP-dependent or SASP-independent approaches, and this process is termed as the bystander effect of senescence [45,46]. Reactivated endogenous retroviruses (ERVs) through epigenetic alterations in senescent cells induce cellular senescence and inflammation; these senescent cells can effectively transmit and amplify senescence signals in young cells by releasing ERV particles, providing further explanation for the enlarged scale of senescence [47].

Osteoporosis

Osteoporosis is a chronic skeletal disease characterized by reduced bone density and altered bone microstructure. It is a comparatively slowly progressing disease affecting more than 200 million people worldwide [48]. Primary osteoporosis is thought to be age-related, resulting from an imbalance between bone formation and bone resorption. Several cells, including osteocytes, osteoblast and their progenitors, osteoclasts, lymphoid cells, and myeloid cells, undergo senescence with age [49]. The effect of eliminating senescent cells on osteoporosis varies across different mice models. Currently, there are several methods for the elimination of senescent cells: the p16-3MR model, which uses ganciclovir to clear p16 cells; the INK-ATTAC model, which uses AP20187 to induce caspase-dependent apoptosis in p16 cells; and the INK-NTR model, in which the injected metronidazole is converted into toxic metabolites by NTR, thereby clearing p16 cells. Clearance of p16 senescent cells in INK-ATTAC mice, or the inhibition of SASP through the Janus kinase (JAK) pathway, can alleviate age-related osteoporosis in mice [17,50]. Notably, while the INK-ATTAC mouse model effectively reduces osteoporosis by genetically eliminating p16 senescent cells, the activation of p16-3MR fails to eradicate senescent osteocytes and alleviate age-related bone loss, potentially due to the efficiency and selectivity of animal models in removing senescent cells [17,51]. Furthermore, using the p21-ATTAC system to clear p21 cells fails to alleviate age-related bone loss [52]. However, p21-ATTAC mice show improvement in fracture healing, partly facilitated by decreased p21 osteochondroprogenitors and neutrophils [52]. Future studies may investigate whether a predominant senescent cell type exists in different pathological processes.

Bone marrow mesenchymal stem cells (BMSCs) are multipotent cells capable of proliferating and differentiating into osteoblasts, chondrocytes, adipocytes, and even myoblasts [53,54]. BMSCs play a critical role in maintaining tissue integrity, bone repair, and regeneration. As age increases, BMSCs experience a decline in quantity and proliferative capacity. The decreased osteogenic ability and increased adipogenic ability contribute to bone aging and the onset of senile osteoporosis [55,56]. The sirtuin (SIRT) family has emerged as an important regulator of aging over the last two decades. As a group of nicotinamide adenine dinucleotide (NAD^+)-dependent protein deacetylases, they mainly participate in cell senescence, energy metabolism, cell cycle regulation, and inflammatory responses. The SIRT family is composed of seven genes (*Sirt1–Sirt7*) with different subcellular localizations. Sun *et al*. demonstrated that overexpressing SIRT1 in mesenchymal stem cells (MSCs) inhibits BMSC senescence and promotes their differentiation into osteoblasts, thereby restoring bone mass but not completely correcting bone defects [57]. Specifically activating SIRT1 in senescent MSCs improves their osteogenic capacity and rejuvenates bone regeneration [58]. Nucleosome assembly protein 1-like 2 (NAP1L2) was found to facilitate BMSC senescence and inhibit its osteogenic capacity, probably by recruiting SIRT1 to diacetylate osteogenic gene promoters [59]. The expression of NAP1L2 in BMSC from patients with osteoporosis is higher than that in healthy controls. Additionally, nicotinamide mononucleotide (NMN), a precursor of NAD^+ and a potential anti-aging health product, was found to alleviate BMSC senescence *in vitro*, providing further explanation for the rejuvenating effect of NMN [59,60]. As another member of the SIRT family, SIRT3 is mainly localized in mitochondria and has been reported to participate in mitochondrial homeostasis and metabolic regulation. SIRT3 can interact with lamin-B1 and KRAB-associated protein 1 (KAP1) to maintain the stability of the heterochromatin structure. By consolidating heterochromatin stability and maintaining mitochondrial function, SIRT3 combats the senescence of BMSC and alleviates osteoporosis [55].

Osteoporosis is especially prevalent in post-menopausal women, because of the sharply decreased estrogen levels

in this population. Mechanistically, by binding to estrogen receptor beta (ERβ), estrogen suppresses the senescence of BMSC by upregulating special AT-rich sequence binding protein 2 (SATB2) [61,62]. Transplan ting SATB2-modified BMSCs to ovariectomized rats attenuates bone loss and osteoporosis [61]. Vitamin D deficiency is highly prevalent in post-menopausal women, and it is a global health problem that further deteriorates osteoporosis. Vitamin D receptor (VDR) is crucial for the osteogenic function of BMSCs. VDR is downregulated in high-fat diet (HFD)-induced osteoporosis, but activating VDR alleviates BMSC senescence and bone loss by reducing ROS and restoring mitochondrial function [63]. The active form of vitamin D, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), can improve the mineralization and turnover rates of bone [64,65]. Recent research uncovered the role of $1,25(OH)_2D$ in preventing BMSC senescence and SASP by upregulating enhancer of zeste homolog (*Ezh2*), a histone methyltransferase that epigenetically suppresses $p16^{INK4a}$ [66]. Furthermore, the increased Ezh2 represses the ubiquitin–proteasome degradation of nuclear factor erythroid 2-related factor 2 (Nrf2), a key regulator of cellular redox homeostasis, inhibiting BMSC senescence [67]. As an inhibitor of Nrf2 degradation, oltipraz has emerged to be a possible reagent for age-related osteoporosis [67].

The senescence of BMSC also entails altered autophagy and alternative splicing. Autophagy is mainly thought to protect cells against senescence, and most autophagy modulation therapies in osteoporosis aim to enhance autophagy activity, among which rapamycin is the most widely studied treatment [68]. Although the increased autophagy resulting from rapamycin treatment can effectively reverse BMSC senescence and alleviate bone loss, the side effects of rapamycin restrict its clinical use [69]. Splicing factor Y-box binding protein 1 (YBX1), a transcriptional and translational regulator known to participate in the senescence of hypothalamic neural stem cells, regulates the fate of BMSCs during aging [70]. Age-related reduction of YBX1 in BMSCs leads to false splicing of the senescence-related gene *Sirt2* and other osteogenic genes. The knockout of YBX1 in mice BMSCs accelerates the loss of bone, and vice versa [71]. Concerning its therapeutic potential, sciadopitysin has been identified to reduce the degradation of YBX1 and attenuate bone loss [71].

Osteoblasts are bone-forming cells derived from BMSCs. The proliferation, mineralization, and functional activity of osteoblasts become compromised with aging, resulting in reduced bone density and increased fracture risk [72]. The impaired function of osteoblasts can result from alterations in the surrounding microenvironment or cellular senescence. With aging, the accumulation of ROS can lead to reduced peptidyl arginine deiminase 2 (PADI2), which activates the nuclear factor kappa-B (NF-κB) signaling pathway and then promotes SASP expression in osteoblasts [73]. siRNA and neutralizing antibodies targeting these SASP factors protect osteoblasts against ROS-induced senescence [73]. As another mechanism of osteoblast senescence, ferroptosis considerably affects the pathology of age-related osteoporosis [74]. The activation of VDR can attenuate ferroptosis by activating the *Nrf2/GPX4* pathway, thereby correcting the cellular senescence of osteoblasts and osteoporosis triggered by D-gal [74].

SASP factors play an active role in bone remodeling and senile bone diseases. Senescent osteocytes and senescent myeloid cells seem to predominantly contribute to the secretion of SASP within aged bone tissue, and the SASP secretion capacity of osteocytes may be attributed to their abundance in bone [49]. Recently, Ambrosi *et al*. revealed that senescent skeletal stem cells (SSCs) possess strong pro-inflammatory capacity, mainly affecting the local bone niche. These senescent SSCs present with upregulated expression of pro-inflammatory cytokines. Moreover, they skew the differentiation of hematopoietic stem cells (HSCs) toward osteoclasts and inflammatory myeloid cells, further strengthening SASP signals in aged bone [75]. Interestingly, the role of SASP in propagating senescence has been proposed recently. Current research focused on the transmission of senescence from bone marrow adipocytes (BMADs) and immune cells to bone-related cells (Fig. 1). Liu *et al.* found that senescent BMAD intensifies aging signals via inducing the senescence of osteoblasts during glucocorticoid-induced bone loss [76]. A similar phenomenon has been observed in age-related bone loss, during which macrophages secrete PCNA clamp-associated factor (PCLAF), inducing BMAD senescence and a reduction in bone mass [77]. Furthermore, PCLAF-treated senescent BMAD impairs the bone of healthy mice, highlighting the role of senescent cells on skeletal health [77]. A recent study demonstrated that the activation of the β-catenin/forkhead box protein O1 (FOXO1)/regulated in development and DNA damage response 1 (REDD1) pathway induced by lipoteichoic acid (LTA) promotes macrophage senescence and accelerates bone degeneration in mice [78]. In addition, an age-related subpopulation of $CD8^+$ T cells has been identified to promote “inflammaging” [79]. Considering that immune cells are spatially close to bone cells, and senescent immune cells also exhibit SASP, the crosstalk between these cells may contribute to the progression of osteoporosis [49,80,81].

Osteoarthritis

OA is the most prevalent joint disease in the elderly, and it is characterized by cartilage destruction, aberrant

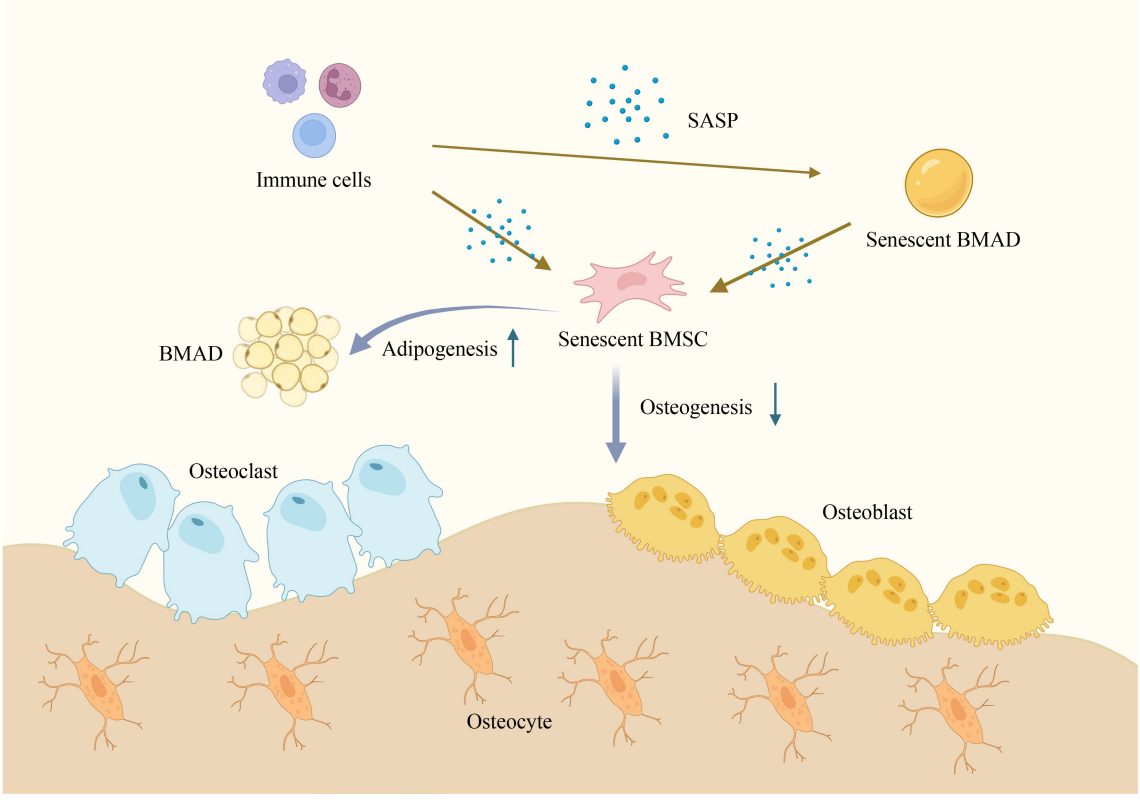

Fig. 1 Induction of senescence among different cell types in osteoporosis. The senescence of BMSCs is influenced by their neighboring cells. Senescent BMAD augments aging signals via inducing osteoblast senescence during glucocorticoid-induced bone loss. The PCLAF secreted by macrophages leads to BMAD senescence, which then impairs bone homeostasis. Additionally, an age-related subpopulation of $CD8^+$ T cells has been identified to promote inflammation in bone tissue. BMSC, bone marrow mesenchymal stem cell; PCLAF, PCNA clamp-associated factor; BMAD, bone marrow adipocyte.

mineralization of the subchondral bone, and synovial inflammation [82]. It is a whole-joint disease that includes impairment in hyaline articular cartilage, synovium, ligaments, capsule, and subchondral bone [83,84]. As the only cell type in articular cartilage, chondrocytes determine the anabolism and catabolism of the abundant ECM in articular cartilage. In addition to senescent chondrocytes, senescent fibroblast-like synoviocytes and adipocytes also participate in OA progression. Despite residing in different tissues, the SASP from these senescent cells forms an inflammatory environment that promotes cartilage degeneration. Swahn *et al*. identified a senescent population shared by cartilage and meniscus in arthritis [85]. This population participates in ECM signaling and is regulated by transcription factor zinc finger E-box binding homeobox 1 (*ZEB1*) and fibroblast activating protein (*FAP*), a gene that promotes ECM degradation. Given that arthritis affects all joint tissues, common pathways among these tissues may be a promising target for treatment. The selective elimination of senescent cells ameliorates injury-induced OA in aged mice, and the clearance of $p16^{INK4a}$ cells also decreases age-related cartilage degeneration, indicating the potential relationship between senescent cells and spontaneous OA with age [86].

Chondrocyte are normally quiescent with low mitosis. In response to joint injury, chondrocytes proliferate to maintain joint homeostasis. Although chondrocytes have a relatively low proliferation rate, chondrocytes from patients with OA exhibit impaired telomeres; activated chondrocytes after injury are highly susceptible to senescence, indicating that intrinsic factors may be critical for the limited proliferation capacity and senescence of chondrocytes. Several factors have been identified as protecting chondrocytes from telomere and DNA damage during senescence. The upregulation of lncRNA (LncZFHX2) by hypoxia-inducible factor-1α (HIF-1α) prevents DNA damage, whereas its knockdown induces cellular senescence and ECM disturbance in OA cartilage [87]. Furthermore, HIF-1α alleviates OA via regulating mitophagy [88]. Nagai *et al*. found that SIRT6 can prevent DNA damage and telomere dysfunction in chondrocytes. When suppressing SIRT6 with siRNA, chondrocytes display reduced proliferation and elevated expression of senescence marker SA-β-gal [89,90]. SIRT6 deficiency exacerbates chondrocyte senescence and OA. In particular, SIRT6 can deacetylate signal

transducer and activator of transcription (STAT5), thereby inhibiting the *IL-15/JAK3/STAT5* signaling pathway and promoting the progression of OA [91].

Aging and aberrant mechanical load, two leading causes of OA, can both result in excessive intracellular ROS, and accumulated ROS in cartilage is closely related to the onset of OA [92,93]. Interferon regulatory factor 1 (IRF1) promotes the transcription of DNA repair genes, protecting chondrocytes from oxidative stress-induced senescence and alleviating OA development [94]. Deficiency of IRF1 results in accumulated DNA damage in chondrocytes, predisposing them to senescence [94]. The downregulation of Sirt4 in chondrocytes hinders their ability to remove damaged mitochondria by inhibiting Pink, which leads to increased ROS accumulation and promotes chondrocyte senescence [95]. Another study revealed the significance of selenium metabolism in maintaining cartilage health. Decreased selenophosphate synthetase 1 (SEPHS1) in OA cartilage impairs the oxidoreductase capacity of selenoproteins, thereby mediating oxidative damage and chondrocyte senescence [96]. Senescent chondrocyte also impairs ECM integrity. miR-204 is significantly upregulated in oxidative stress-induced senescent chondrocytes, and the upregulation of miR-204 disrupts articular matrix homeostasis via inhibiting the synthesis of sulfated proteoglycan [97].

Age-related ECM stiffness is also an important cause of OA [98]. As a novel mechanosensitive mechanism proposed recently, aged ECM epigenetically regulates α-Klotho, a longevity gene, and accelerates chondrocyte senescence [99]. Another research revealed the role of mitophagy in EMC stiffness-mediated chondrocyte senescence. ECM stiffening downregulates histone deacetylase 3 (HDAC3), prompting Parkin acetylation and mitophagy in chondrocyte senescence and cartilage degeneration [100]. Changes in the ECM are related to the chondrocyte–mesenchymal transition, which promotes the participation of chondrocytes in ECM remodeling, inflammation, and senescence [101]. JNK signaling is thought to promote OA by activating pro-inflammatory and ECM degradation pathways [102,103]. Increased JNK phosphorylation has been found in human OA cartilage [104]. However, the deletion of JNK1 or JNK2 leads to severe OA, accompanied with increased cellular senescence in synovium and cartilage of aged mice, indicating the dual roles of JNK signaling in maintaining articular homeostasis and suppressing cellular senescence [105].

The inflammatory reaction in OA is not accompanied with massive infiltration of immune cells, indicating the pro-inflammatory role of resident cells [106]. Bone and cartilage degradative particles and IL-1β are primary inducers of the inflammatory phenotype of chondrocytes, which involve the expression of inflammatory and SASP genes (Fig. 2) [106]. The SASP phenotype is also found to be associated with accumulated cholesterol in lysosomes, and regulating lysosomal cholesterol alleviates senescence-induced inflammation in OA progression [107]. Although senescent cells are arrested in cell cycle, they maintain metabolic activity; thus, senescent cells are typically hypertrophic and have active SASP [108]. Senescent cells consistently maintain high mechanistic target of rapamycin complex 1 (mTORC1) activity, which integrates nutrient and growth signals to regulate cell growth and proliferation [109,110]. The accumulated cholesterol in lysosomes activates mTORC1 and promotes SASP in OA. However, evidence to support the relationship between cholesterol and cell cycle arrest is lacking [107]. The fat tissue can also regulate osteoporosis through SASP. Infrapatellar fat pad (IPFP) is the primary fat tissue that functions as a buffer against mechanical force in the knee joint. IPFP regulates OA progression by secreting cytokines and adipokines. Small extracellular vesicles from IPFP can also promote chondrocyte senescence via let-7c-5p and let-7b-5p [111]. Synoviocytes are thought to participate in the pathogenesis of OA by secreting proinflammatory cytokines and matrix metalloproteinases (MMPs). A significant increase in senescent synoviocyte occurs after the medial meniscus surgery, which happens ever before the senescence of chondrocytes and cartilage degradation, indicating that senescent synoviocytes are not merely the result of OA [112]. Damaged autophagy in synoviocytes was found to promote SASP. The excessive m^6A modification of autophagy-related 7 (*ATG7*) through methyltransferase-like 3 (*METTL3*) impairs autophagy flux and exacerbates cartilage destruction. Senescent fibroblast-like synoviocytes interfere with the function of chondrocytes. Inhibiting *METTL3* can alleviate the senescence of fibroblast-like synoviocytes and limit OA progression by improving autophagy [112]. Senescent cells and Th17 cells increase with OA. Senescent cells can induce naïve T cells to differentiate into Th17 cells, which induce fibroblast senescence *in vitro* [113]. A decline in IL-17 combined with upregulated IL-4 expression within joints can rescue damaged cartilage of OA mice [113]. The abundant ECM and limited vascularization in the articular joint limit senescent cell clearance and inflammation resolution, and the interaction between Th17 cells and senescent cells further promotes chronic inflammation in joints.

Intervertebral disc degeneration

IDD is the chief cause of lower back pain in middle-aged and elderly people. Aging is the primary driver of IDD, and other risk factors include injury, mechanical loading, genetic predisposition, and certain metabolic disorders [114]. Intervertebral disc is composed of nucleus pulposus (NP) and annulus fibrous (AF), as well as

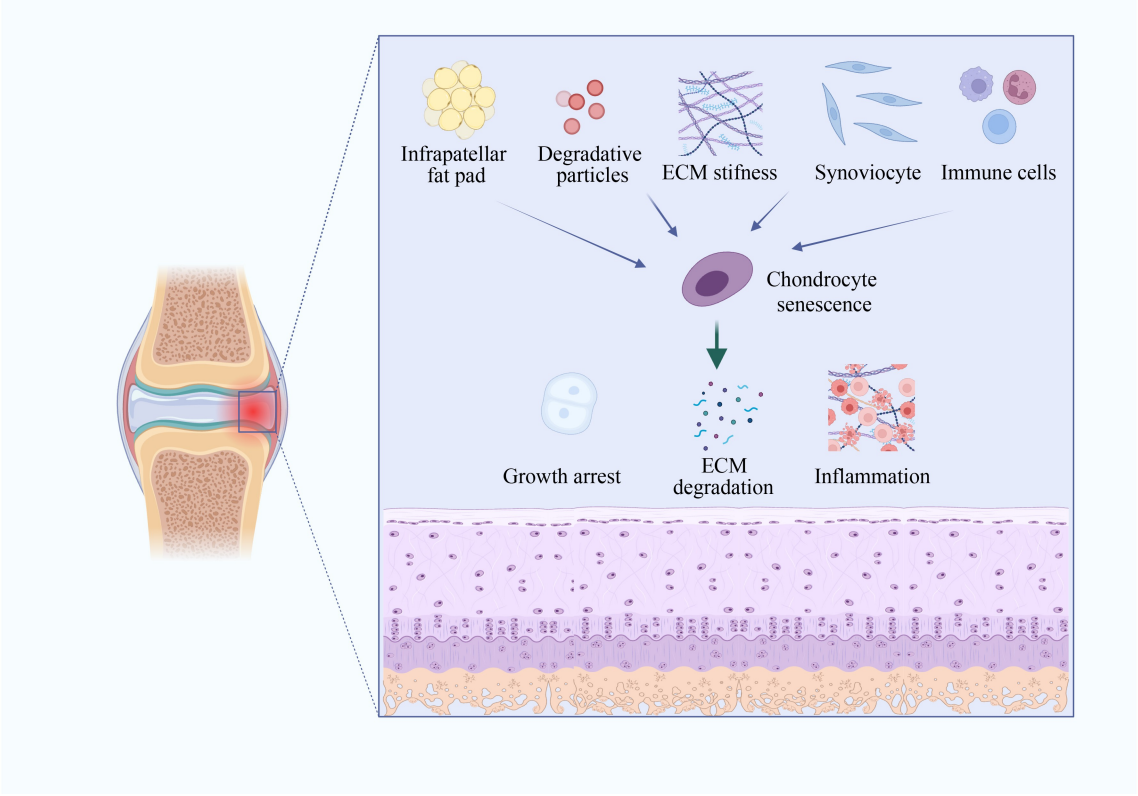

Fig. 2 Factors promoting chondrocyte senescence and mechanisms by which senescent chondrocytes mediate osteoarthritis. Despite intrinsic alterations in chondrocyte with age, SASP secreted by adipocytes, synoviocytes, and immune cells forms an inflammatory environment that promotes chondrocyte senescence. Age-related ECM stiffness epigenetically modulates chondrocytes and accelerates their senescence. Bone and cartilage degradative particles and IL-1β are primary inducers for the inflammatory phenotype of chondrocytes. Chondrocyte senescence results in damaged repair capacity, increased ECM degradation, and pro-inflammatory cell recruitment, thereby promoting osteoarthritis progression. SASP, senescence-associated secretory phenotype; ECM, extracellular matrix.

cartilaginous endplates. NP acts to dissipate compressive forces, and AF protects it from outward expansion. The main components of NP are proteoglycans and type II collagen, which help retain water and bear loads [115]. The limited vascularization of intervertebral disks limits their repairment capacity, which leads to reduced cell function and degraded ECM with age. The loss of proteoglycans and water with aging in NP results in fibrotic alternation, and the organized fibrous framework in AF is also damaged in time [116,117]. The reduction in nutrient supply to the intervertebral disc caused by cartilaginous endplate calcification further deteriorates IDD [118]. Other mechanisms that exacerbate degeneration include cellular senescence, chronic inflammation, and cell apoptosis [119–121]. An increase in senescent cells expressing senescence makers $p16^{INK4a}$ and SA-β-gal has been witnessed in IDD. Senescent cells primarily accumulate in the protruding NP and correlate positively with the degree of IDD, suggesting the significant role of cellular senescence in IDD [122].

Mitochondria quality is an indispensable part of NP cell survival, including mitochondria dynamics and mitophagy. Partially damaged mitochondria fuse to share their contents for complementation; mitochondrial fission helps remove damaged parts, which are then degraded by mitophagy [123]. Oxidative stress is implicated in the senescence of NP cells, as ROS damages mitochondria dynamics, causing metabolic disturbance or even cell death [124–126]. Early growth response 1 (*EGR1*), commonly upregulated under oxidative stress, is found to increase in patients with IDD, and *EGR1* knockdown restores mitophagy via modulating PINK1/parkin and protecting NP cells from senescence [127]. Additionally, an *in vitro* study revealed that *Sirt1* reduces high-magnitude compression-induced NP cell senescence by increasing PINK1-dependent mitophagy [128]. Another *in vitro* study proposed that activated PINK1/parkin in continuous compression condition results in excessive mitochondria degradation, which can accelerate NP cell senescence [129]. Song *et al*. found that the defect of NLR family member X1 *(NLRX1*), which supervises and regulates the activity of mitochondria, also promotes NP cell senescence by compensatorily activating PINK1/parkin, leading to overactivated mitophagy [130]. Restoration of *NLRX1* function was shown to reduce NP cell senescence and rejuvenate intervertebral discs

through coordinating mitochondria dynamics and mitophagy [130]. However, the *in vitro* mechanical load-bearing model and the *NLRX1* knockout model were under relatively extreme conditions, which may not be faced by *in vivo* NP cells. These conditions simply go beyond the capacity of mitophagy to respond to stress, and further research is needed to determine whether over-activated mitophagy is involved in IDD progression.

Inflammatory cytokines such as IL-6, IL-1β, and TNF-α regulate the expression of ADAMTS and MMPs, which are crucial in the breakdown of disc structure. Selectively clearing p16 senescent cells in aged p16-3MR transgenic mice reduces the secretion of ADAMTS and MMP-13, increases aggrecan content, and ultimately improves the morphology of intervertebral discs [131]. The inflammatory phenotype of senescent NP cells is partly promoted by genomic DNA damage. A recent study found that the progression of IDD is accompanied with decreased ATR, as proteasome-dependent ATR degradation increases. ATR deficiency results in genomic integrity impairment, which then activates the cGAS/STING pathway and promotes SASP production in NP cell senescence and IDD progression [132–134]. As the main signaling pathway regulating SASP production, NF-κB was found to promote senescence and SASP in IVD through positive feedback. Su *et al*. demonstrated that mechanical stress-activated NF-κB p65 increases periostin transcription; the secreted periostin would reactivate NF-κB, amplifying the senescent signal, whereas periostin neutralization was found to greatly attenuate IDD [135]. Risk factors of IDD generally lead to a pro-inflammatory environment in IVD, and degraded intervertebral disks further exacerbate inflammatory signals. The imbalanced inflammatory environment recruits inflammatory cells, including macrophages. Research has revealed that M1 macrophage-derived exosomes accelerate NP cell senescence through lipocalin-2 (LCN2), which then activates the NF-κB pathway [136]. Suppressing LCN2 inhibits the expression of MMP13 and protects ECM metabolic balance.

Sarcopenia

Sarcopenia is an age-related condition featured by a decline in skeletal muscle strength, muscle mass, and physical performance [137]. It compromises the quality of life and increases the risk of fall and death. Skeletal muscle is composed of myofibers, muscle stem cells (MuSCs), endothelial cells, immune cells and fibroadipogenic progenitors (FAPs). After a thorough analysis of aged skeletal muscle, two main senescent cell populations have been identified: FAPs that express $p16^{INK4a}$ and myofibers that express p21 [138]. FAPs are multipotent cells that can differentiate into fibroblast and adipocyte. As an indispensable part of muscle homeostasis, FAPs promote muscle repairment by recruiting immune cells and supporting the activation and differentiation of MuSCs [139,140]. A significant increase in $p16^{INK4a}$ but not p21 was observed in senescent FAPs, which is also the primary source of $p16^{INK4a}$ in aged skeletal muscle [138]. The senescent myofiber population expresses high p21 but shows no significant increase in $p16^{INK4a}$ expression, indicating two independent senescent mechanism in aged muscle. The research team further revealed that cellular senescence is the core characteristic of aged muscle [138].

Using senolytics to remove senescent cells, particularly FAPs, restores function and improves muscle health, suggesting the negative effect of cellular senescence on aging skeletal muscle [45]. Given that myofibers are terminally differentiated, MuSCs are crucial for muscle regeneration. In response to stress and damage, the normally quiescent MuSCs will be activated to proliferate and form new myofibers. Subsequently, parts of MuSCs will return to the quiescent state to maintain the stem cell pool. During aging, MuSCs experience a switch from quiescence (reversible cell cycle arrest) to senescence, promoting the depletion of MuSCs [141]. Slug is a highly expressed zinc-finger transcription factor in quiescent MuSCs, which directly represses $p16^{Ink4a}$ and inhibits cellular senescence [142]. Decreased levels of slug in aged MuSCs accelerate cellular senescence and damage their self-renewing capacity. Additionally, myofibers in aged muscle express fibroblast growth factor 2 (*Fgf2*), which breaks the quiescent state of some MuSCs. One strategy of aged quiescent MuSC to combat *Fgf2* is via strongly expressing sprouty 1, which inhibits the FGF signaling pathway and prevents MuSCs from depletion [143]. Although senescence is traditionally thought to repress regeneration in aged muscle while promoting regeneration in young muscle, a recent study challenged this idea. Moiseeva *et al*. proposed that, regardless of age, the inflammatory environment created by senescent cells hinders muscle regeneration [144]. Senescent cells suppress the proliferation capacity of stem cells even in young mice, and the upregulated SASP in injured young muscles is similar to that in uninjured aged muscles. In addition, CD36 was identified as a crucial factor for SASP. Transplanting senescent cells into skeletal muscle induces the senescence phenotype in myofibers, including muscle fiber thinning, which is a marker of sarcopenia; silencing CD36 in senescent cells diminishes the negative effects, suggesting the complex effect of senescence in the regenerative field [144].

Senescence is partly induced by decreased autophagy flux, whereas the restoration of basal autophagy in aged mice mitigates senescence and promotes muscle regeneration [145]. Mice with muscle-specific autophagy-related 7 (*Atg7*) deficiency demonstrate serious muscle

atrophy [146]. A highly active organ may need timely removal of toxic metabolites and impaired organelles. Changes in sex hormones with aging can also affect muscle function by regulating autophagy. The aging of hypothalamus can lead to systemic aging, including impaired muscle function. The hypothalamic–pituitary–gonadal axis has been found to regulate MuSC senescence through transcription factor EB (Tfeb)-mediated autophagosome clearance [147]. Reactivating autophagy in senescent myoblasts via reversine, a small-molecule drug, can promote the differentiation of myoblasts into myocytes [148]. The depletion of glycogen synthase kinase-3 (GSK-3), a key regulator of autophagy, also leads to activated mTOR, suppressed autophagy, and sarcopenia with age [33].

Although MuSCs mainly rely on glycolysis for energy, oxidative respiration is also important for MuSC function, and maintaining mitochondria health is crucial for the self-renewal capacity of SC [149]. Zhang *et al*. revealed that dietary supplementation of NAD improves mitochondrial health [150]. Specifically, increased NAD in MuSC activates prohibitin signaling, restores mitochondria homeostasis, and alleviates cellular senescence [150]. Cytoplasmic polyadenylation element binding protein 4 (*CPEB4*) affects cellular senescence by targeting mitochondrial mRNA and controlling its translational activity. During aging, the downregulated *CPEB4* in senescent MuSCs affects the function and activity of mitochondria, which in turn impairs the regenerative ability of MuSCs [151]. Loss of autophagy with age impairs mitochondria function and protein homeostasis, leading to MuSC senescence [152]. Transcription factor Nanog effectively reverses the senescence of myoblasts *in vitro* and *in vivo* and restores autophagy, energy homeostasis, genomic stability, and heterochromatin structure in myoblasts [153]. The research team further revealed that Nanog reduces methionine adenosyltransferase 2A, an enzyme catabolizing methionine to produce ammonium, thereby restoring glycolysis and promoting muscle regeneration [154].

Additional research provided evidence for the role of mechanical signals and the reactivation of embryonic genes in MuSC senescence and sarcopenia. As exercise is important for muscle health, mechanical signals may participate in maintaining muscle function. Piezo1 is a mechanosensitive ion channel. Peng *et al*. found that Piezo1 controls the quiescent state of MuSCs and prevents cellular senescence. Absence of Piezo1 activates the Ca^{2+} channel, and increased Ca^{2+} leads to excessive ROS production and p53-dependent senescence [155]. Hox are crucial regulators of stem cells during embryogenesis, and they are rarely activated after birth. However, Hoxa9 is reactivated in damaged aged MuSCs, which then activate senescence signaling pathways, leading to decreased regeneration ability of skeletal muscle [156].

Strategies targeting senescence in age-related musculoskeletal diseases

Several therapeutic strategies that interfere with the negative impacts of senescent cells have been proposed recently. Clearing senescent cells (senolytics) or inhibiting SASP (senomorphics) is found to alleviate the occurrence and progression of chronic diseases. Treatments targeting cellular senescence can slow the progression of atherosclerosis, cardiac hypertrophy, osteoporosis, OA, IDD, sarcopenia, and tumorigenesis [86,157–159]. Compared with treatments targeted at a specific disease, senotherapeutic strategies are more effective in improving the overall health status and alleviating various complications of age-related diseases at the same time [122]. Using the INK-ATTAC system to clear $p16^{INK4A}$ senescent cells in progeroid mice can greatly attenuate certain senile diseases such as muscle atrophy and spinal curvature [18]. However, the INK-ATTAC system fails to eliminate $p16^{INK4A}$ cells in organs such as liver and colon, indicating that senescence is heterogeneous, and the overall picture of senescent cells cannot be easily uncovered with one theory. Considering that the effect of a specific serotherapeutic compound differs between tissue and diseases, we mainly focus on their effect on degenerative musculoskeletal diseases in this review.

Senolytics

Senolytics induce apoptosis in senescent cells via inhibiting the anti-apoptotic pathways. These pathways are commonly upregulated in senescent cells to protect themselves against damaging effects of SASP, including the BCL-2 pathway, *MDM2/p53/p21^{Cip1}*/serpine element pathway, *PI3K/AKT*/ceramide metabolic pathway, *HIF-1α* pathway, and SP-90-dependent pathway [160–162]. As the first discovered senolytic drug, dasatinib plus quercetin (D + Q) can attenuate bone loss in osteoporosis, rejuvenate intervertebral disk, and reduce IDD progression in preclinical models, but the specific mechanism remains unclear [163]. Although D + Q has found to alleviate certain age-related diseases clinically, their performance in treating patients with degenerative musculoskeletal diseases is not ideal. A phase I trial using D + Q to treat patients with diabetes and chronic kidney disease found that this therapy can eliminate senescent cells in humans, suggesting its potential for clinical application [164]. However, a recently finished phase 2 clinical trial revealed that, after intermittently administrating D + Q on post-menopausal women, no significant improvement in bone formation and absorbent

markers has been shown at 20 weeks, but the change in serum P1NP from baseline is significantly increased at 2 weeks (+16%, $P = 0.020$) and 4 weeks (+16%, $P = 0.024$) compared with control [165]. Further analysis found that participants in the D + Q group with higher senescent T cell burden tend to benefit more than those in other groups. Therefore, when applying senolytics to clinical use, we should be careful with the frequency and interval of treatment, as well as criteria for evaluating the senescence burden of a patient. Targeted at the BCL-2 pathway, senolytic compound navitoclax or ABT263 can alleviate the burden of senescent MuSCs in mice [166,167]. However, navitoclax is accompanied with off-target effects. A study revealed that navitoclax can impair the bone formation function of osteoblasts, leading to trabecular bone loss in senile mice [168]. The combination of different anti-apoptotic suppressors may address this problem, as combination therapy decreases the dosage and adverse effects of each drug. The senolytic compound UBX0101, a suppressor of *MDM2/p53*, has been previously reported to induce apoptosis in senescent chondrocytes and improve joint function in an OA mouse model [86]. Nonetheless, UBX0101 failed to show a protective effect on patients with OA during a phase 2 clinical trial with a 12-week follow-up. Another anti-apoptotic molecule involved in senescence is FOXO4. FOXO4 protects the viability of senescent cells by sequestering p53 within the nucleus, preventing it from inducing apoptosis [169]. FOXO4-DRI is a peptide fragment that lacks the normal transcriptional activity of FOXO4 but binds to p53 stably, and treatment of FOXO4-DRI induces senescent cells to undergo apoptosis [169]. The combination of senolytic drugs with certain senescence-related miRNAs (senomiRs) improves the effectivity of senotherapy. For instance, miR-340-5p is a novel senomiRs that disturbs heterochromatin status probably via reduced lamin B receptor (LBR). The overexpression of miR-340-5p induces senescence and increases the sensitivity of senescent cells toward senolytic drugs [170].

Despite their therapeutic potential, most senolytic drugs have three problems. First, most drugs are designed to target a specific anti-apoptotic pathway and are ineffective in eliminating different types of senescent cells, as senescence is a heterogeneous process. Second, these senolytic drugs lack specificity and may inadvertently kill non-senescent cell. Third, small-molecule senolytic drugs should be administered repeatedly and cannot address the senescence problem in a single application. For the first two concerns, one solution is to fully utilize markers of senescent cells. Increased β-gal activity is a typical feature of senescent cells, and Deng's group has developed a prodrug that can be metabolically activated by β-gal to eliminate senescent cells. This prodrug improves physical function of aged mice and is non-toxic to normal cells exhibiting low β-gal activity [171]. For the third concern, the senolytic chimeric antigen receptor (CAR)-T cell therapy has emerged as a promising substitute. Given the longevity and memory of T cells, a single dose of senolytic CAT-T therapy can produce a significantly prolonged therapeutic effect. Urokinase-type plasminogen activator receptor (uPAR)-specific CAR-T cells were initially developed to treat senescence. uPAR was identified as an upregulated cell surface protein during aging, and uPAR CAR-T cells were shown to effectively remove senescent cells *in vitro* and *in vivo*, improving exercise capacity and metabolic function [172,173]. Another recent study identified NKG2D ligand (NKG2DL) as a promising target [174]. Anti-human NKG2DL CAR-T therapy reduces the senescence of human cells *in vitro*, and T cells with human NKG2D clear senescent cells of aged nonhuman primates, showing the potential of CAR-T in treating age-related diseases [173,174].

Notably, when performing serotherapeutic treatments, the positive role of senescent cells should be seriously considered. Cells expressing $p16^{Ink4a}$ were found to enhance the insulin secretion capacity of β cells during cellular senescence, thereby improving global glucose homeostasis, indicating that senescence can regulate the normal aging process [175]. Another research revealed that senescent cells promote epithelial repairment [176]. Senescent $p16^{Ink4a}$-positive cells are present at lung basement membrane early in life. These $p16^{INK4α}$-expressing fibroblasts were found to sense and respond quickly to inflammatory stimuli [176], and they also promote stem cell regeneration through SASP secretion. A recent study found that continuous or acute removal of $p16^{High}$ senescent cells can disrupt the blood–tissue barrier in liver and causes fibrosis of the liver and perivascular tissues, as sinus endothelial cells cannot be replenished in time [177]. This phenomenon highlights the importance of controlling the speed of clearing senescent cells.

Senomorphics

Disruption of senescent cell secretome via senomorphics is another target of senotherapeutic strategies. The suppression of SASP signals, SASP secretion, and SASP factors are three methods for senomorphics. Inhibiting the JAK/STAT signaling pathway through ruxolitinib reduces the secretion of IL-6, IL-8, and plasminogen activator inhibitor-1 (PAI-1), as well as alleviates senile osteoporosis [178]. MMP13, which degrades type-II collagen in cartilage, is a crucial promotor of OA [179,180]. Inhibiting MMP13 via CL82198 reduces chondrocyte death and alleviate articular degeneration [180]. Furthermore, metformin, quercetin, and protein DX have been found to alleviate OA in rats by activating

the AMPK pathway [181,182]. As SASP highly relies on the activity of the endoplasmic reticulum (ER), a possible way to reduce the effect of senescence is by disturbing ER. New findings suggested that using verteporfin to inhibit the YAP-TEAD pathway hinders the biogenesis of ER, leading to ER stress and apoptosis [183]. Verteporfin can also reduce the number of senescent cells in old mice and mice with induced senescence [183]. Intra-articular injection of an IL-17 neutralizing antibody mitigates cell senescence and improves tissue structure. Inhibition of IL-17 also has the potential to promote muscle regeneration [113]. Although senomorphics offer numerous benefits, inhibiting SASP may impair wound healing and tumor suppression process [184–187]. These safety problems require long-term research for validation. A potential alternative involves suppressing senescence-specific SASP without targeting the whole secretome of senescent cells. Senolytics are more promising than senomorphics, as senolytics eliminate the root of SASP and decrease the risk of tumor development, given that some senescent cells are driven by oncogenic mutation. Moreover, senolytic treatment can be administered intermittently, whereas senomorphic treatment usually requires continuous administration, thereby limiting its clinical usage.

Discussion and outlook

Musculoskeletal health is essential for the quality of life among the elderly, and musculoskeletal degenerative diseases are a global public health concern. Cellular senescence exacerbates degenerative diseases primarily by impairing the degenerative capacity of stem cells and secreting SASP to induce senescence in neighboring cells. Substantial evidence supports the relationship between cellular senescence and age-related musculoskeletal diseases, though mainly in pre-clinical models. Despite all these advances, the completed serotherapeutic clinical trials on musculoskeletal diseases failed to demonstrate significant effect. To enhance clinical translation, various issues may need to be addressed. First, the senescent phenotype in progeria or other pre-aging model differs from physiologic aging, and naturally aging models may accurately reflect the true situation. Second, extensive research relies on $p16^{INK4a}$ and p21 to identify senescent cells, although senescence is a heterogeneous process, and some senescent cells do not express either markers. To mitigate the harmful effect of senescent cells, we should develop efficient methods for identification, which involves finding new markers as well as the combination of different markers. Third, aging is associated with decreased mobility, increased body mass, and other health risk factors, so further research is necessary to determine whether senescent cells are byproducts of these risk factors or increased age itself. Senescent cells provide benefits, and their abrupt eradication has been found to be associated with adverse effects. Therefore, we should choose serotherapeutic targets cautiously and control the rate of elimination. Another objective for future research is to identify patients that can benefit most from serotherapeutic research, as the senescence load varies among different patients and diseases. Additionally, the combination of lifestyle changes, such as physical activity and nutrition, and serotherapeutic treatments may represent an effective strategy in the management of musculoskeletal degenerative diseases.

Compliance with ethics guidelines

Conflicts of interest Jinming Xiong, Qiaoyue Guo, and Xianghang Luo declare that they have no conflict of interest.

This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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