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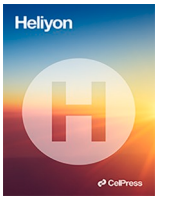

Review article

Recent advances in senescence-associated secretory phenotype and osteoporosis

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ABSTRACT

The worldwide elderly population is on the rise, and aging is a major osteoporosis risk factor. Senescent cells accumulation can have a detrimental effect the body as we age. The senescence-associated secretory phenotype (SASP), an essential cellular senescence hallmark, is an important mechanism connecting cellular senescence to osteoporosis. This review describes in detail the characteristics of SASPs and their regulatory agencies, and shed fresh light on how SASPs from different senescent cells contribute to osteoporosis development. Furthermore, we summarized various innovative therapy techniques that target SASPs to lower the burden of osteoporosis in the elderly and discussed the potential challenges of SASPs-based therapy for osteoporosis as a new clinical trial.

1. Introduction

For decades, aging has been recognized as a significant risk factor for many long-term and lethal diseases, such as atherosclerosis, diabetes, cataracts, memory loss, sarcopenia, osteoarthritis, and osteoporosis. Although aging is an uncontrollable process, it is possible to mitigate age-related disorders by modifying the fundamental aging mechanisms. Cellular senescence is one of the mechanisms that can manifest in various biological processes via SASPs [1]. SASPs contribute to releasing cytokines and chemokines that promote local and systemic inflammatory responses, immune system activation, tissue damage, fibrosis, apoptosis, and malfunction. In addition, SASP can cause amplification of localized and systemic senescence via paracrine or endocrine pathways [2].

Osteoporosis (OP) is an emerging medical and socioeconomic hazard characterized by bone loss and unpredicted osteoporotic fractures as the population ages [3,4]. Osteoporosis has emerged as a significant health risk for individuals aged 50 and beyond. As the population ages, there are more instances of osteoporosis and fragility fractures, which puts an increasing strain on the health system [5]. Osteoporosis formation and occurrence in aging are associated with deficient hormone levels, imbalanced bone remodeling, and a restricted number of osteoblasts, osteocytes, and their progenitor cells [6]. Connecting the dots directly to osteoporosis, it is clear that the build-up of senescent cells (SCs) and the overexpression of SASPs in the bone microenvironment are closely linked to the etiology of

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this illness [7]. In addition, senescent cells have also been shown to be present in the setting of radiotherapy-induced bone loss [8,9], and bone biopsy samples from elderly postmenopausal women [7]. Current studies have found that targeting senescent bone cells in the bone and modulating SASP activity can promote bone remodeling and alleviate the symptoms of OP [10,11]. Despite mounting evidence that SASPs play a vital part in OP, the mechanism between cellular senescence, SASPs, and OP pathology is still obscure.

This review highlights the most recent results on cell senescence in bone and the role of SASPs in primary and secondary OP and discusses the new treatment approaches for OP.

2. Methods

The Pubmed database was utilized to search all pertinent publications published before October 2023 comprehensively. Keywords and their combinations that were used were “bone remodeling,” “Osteoporosis,” “Cellular Senescence,” and “SASP,” and they were limited to the titles or abstracts of articles. The articles were restricted to the English language. Independently, two researchers conducted the first screening based on abstracts and titles. Articles deemed irrelevant were removed. The full-text review further established the studies’ eligibility.

2.1. Cellular senescence and SASP

Cellular senescence is a cell fate, characterized by irreversible proliferation arrest, activation of tumor suppressors, altered chromatin architecture, and apoptosis resistance [12]. In the early 1960s, Leonard Hayflick discovered this phenomenon when he noticed that normal cells had a limited ability to grow in culture with prolonged continuous culture while remaining alive. This period of growth cessation is known as senescence [13]. Decades later, Hayflick’s observations were confirmed. This limiting of proliferation was linked to the gradual shortening of telomeres after cultured cells grew in number, which is called “replicative senescence” [14]. The age-related increase of senescent cells enhances the relationship between replicative senescence and senescence [15]. As studies on cell senescence proceeded, it became evident that senescence and aging are not synonymous and that SCs can be caused by multiple stressful stressors regardless of age [16]. Excessive stress can activate or accelerate cellular senescence, including telomere shortening, DNA damage, genotoxic stress, mitochondrial damage, reactive oxygen species (ROS) and oncogene activation (Fig. 1) [17].

Despite being in a growth-arrest state, senescent cells are metabolically active. Senescence can modify the internal mechanisms of cells and influence the surrounding environment through the secretion of a complex mixture of substances that can affect the activities of non-senescent cells [18]. This hypersecretion phenotype is defined as the senescence-associated secretome (SASP)or the senescence-message secretome (SMS) [19], which is one of the main characteristics of senescence [20].

Initial research on SASP indicated that it consists primarily of proinflammatory factors. Based on mounting evidence, SASP also includes proteases, hemostasis factors, ceramides, bradykinin, extracellular matrix (ECM) components, vesicles, exosomes, various microRNAs and non-coding RNAs, DNA fragments, other nucleotides, protein aggregates, and lipid components. Due to the SASP’s complexity, senescent cells impact various biological processes involving cell proliferation, angiogenesis, inflammation, epithelial-interstitial transformation (EMT), wound healing, tissue repair, immune clearance, and senescence reinforcement [21,22]. Many SASP components, including IL-6, IL-8, Wnt16B, and GRO, function autocrinely in the context of oncogene-induced senescence (OIS) and may contribute to the induction of prolonged growth arrest. Intriguingly, SASP can create a complicated pro-inflammatory milieu that varies by senescent cell type [23–26] and may have multiple activities with both beneficial and detrimental outcomes depending on the environment [22,27–30].

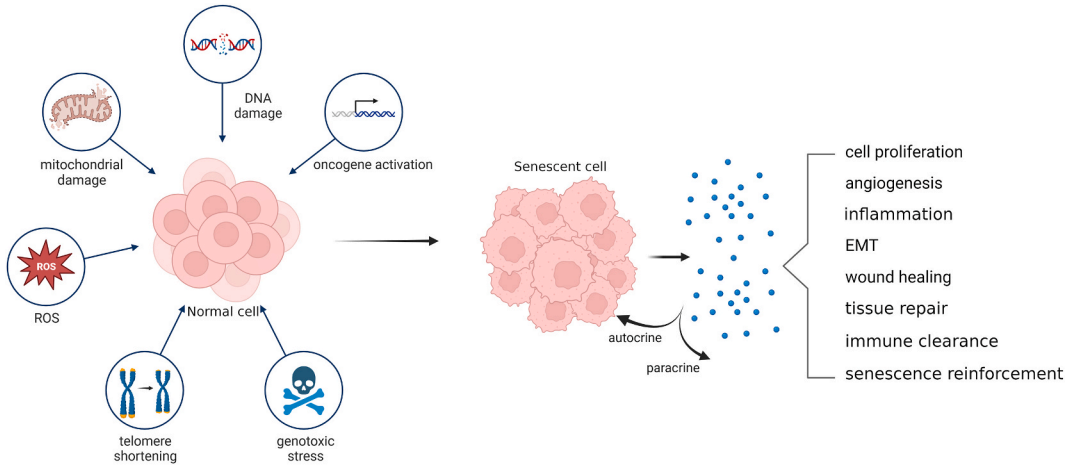

Fig. 1. Various stressors trigger the formation of senescent cells and the release of SASP, resulting in different pathological and physiological processes.

2.2. The SASP regulator

SASP varies in senescent cells rely on the cell type, the triggers and their responses to hormones, therapies, and other variables [31]. The different biological processes induced by various SASP components suggest they communicate with local and nearby cells and serve as microenvironment-regulating mechanisms. Moreover, its toxicity relies on secretory parameters, cell type, length, and stimulation produced by secretion [32]. According to earlier studies, numerous processes are involved in the control of SASP factors (Fig. 2).

SASP is regulated at the transcriptional level. C/EBPβ and NF-κB are the two primary transcription factors that activate SASP in senescent cells. It is reported that they are essential to the senescent process and SASP secretion. Activating modifications induced by oncogenic RAS signaling and other forms of stimuli regulate the DNA binding activity and homodimerization of C/EBPβ, and these modifications trigger cell cycle arrest in OIS [33]. Evidence has shown that C/EBPβ increases the expression of numerous known SASP cytokines and properties, such as IL-1, IL-6, IL-8, IGFBP3, CXCl1, CXCl2, CCR1and NAP2 [34–36]. Intriguingly, C/EBPβ and IL-8 expression decreased rapidly following the depletion of IL-6 [34]. C/EBPβ is regulated by its 3′ untranslated region (3′ UTR), which governs C/EBPβ post-transcriptional translation and DNA binding ability to limit SASP secretion [37]. Moreover, C/EBPβ plays an essential function in androgen deprivation-induced senescence [38].

The NF-κB signaling system is a major regulator in initiating cellular senescence and SASP production by functioning as the primary regulator for immune and stress responses [39,40]. It can be caused by immunological activation, DNA damage and several forms of cellular stress related to senescence and the senescence process. Cellular stress, specifically DNA damage, oxidative stress and immune responses can activate the NF-κB system via various signaling pathways [41,42], especially the NEMO shuttle and the p38MAPK and RIG-1 pathways. In addition, NF-κB signaling is strengthened by other signaling pathways, including TLR, mTOR, HMGB1, STING, and inflammasomes, as well as signals from kinase cascades of numerous conventional and nonclassical routes [43].

Moreover, C/EBPβ and NF-κB have a reciprocal regulatory connection. Capello et al. found that C/EBPβ overpression enhanced NF-κB activity by suppressing the production of IκB-α, an NF-κB inhibitory [44]. Apart from this, several gene promoter sites obtain both NF-κB-like and a C/EBPβ-like binding site, the interaction between NF-κB and C/EBPβ governs these genes' expression [45,46]. While the strong association between NF-κB and C/EBPβ has been heavily reported, C/EBPβ harms the function of NF-κB in a given situation. Zwergal A et al. found that, in TNF-tolerant cells, the binding of C/EBPβ to p65 inhibited NF-κB-dependent IL-8 gene expression [47].

GATA factors are a set of transcription regulators that are ubiquitous in eukaryotic cells and regulate development and differentiation [48]. When intracellular DNA damage occurs, GATA4 activated by the ATM and ATR pathways triggers NF-κB, resulting in the development of SASP. Generally, GATA4 is degraded by autophagy after binding with the autophagy receptor protein SQSTM1/p62. However, this regulation is suppressed in aging cells, thereby stabilizing GATA4. The stability of GATA4 was adequate to promote fibroblast senescence and the development of SASP. GATA4 appears to regulate SASP, at least in part, by inducing TRAF3IP2 and IL1A expression to form a feed forward activation circuit with NF-κB [49].

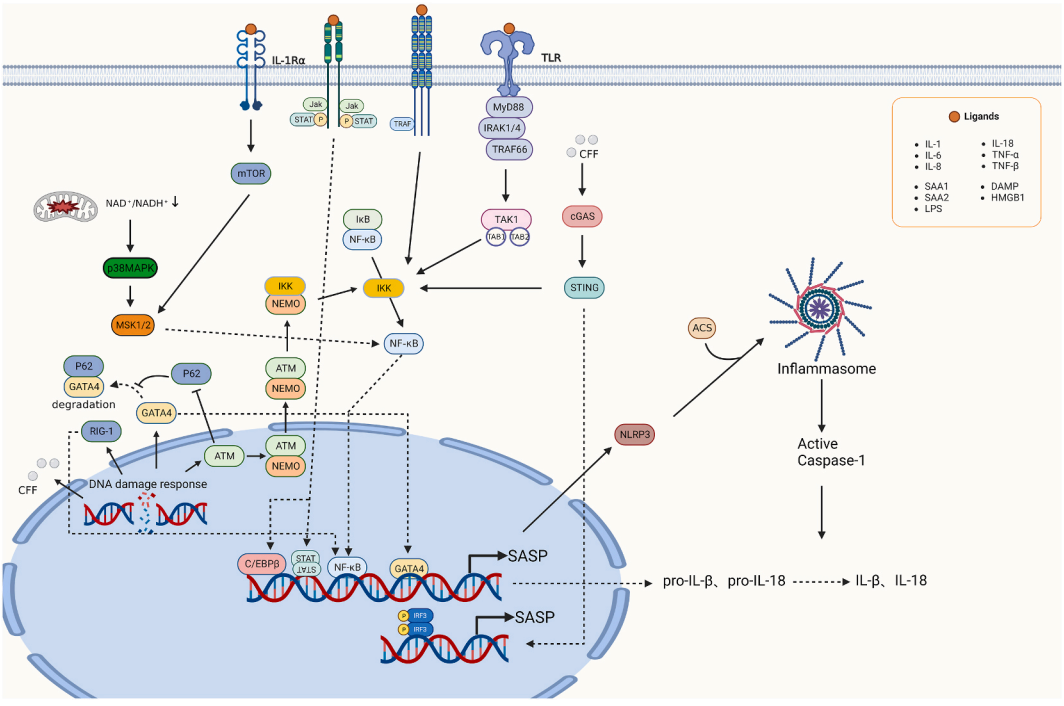

Fig. 2. Signal pathways to regulate SASP.

Epigenetics mechanisms also affect SASP factor expression. Epigenetics is the process of inducing heritable changes in gene expression without altering the DNA nucleotide sequence, including DNA methylation, histone modification, and non-coding RNA. Persistent DNA damage resulting to the loss of H3K9me2, G9a, and GLP stimulates the expression of IL-6 and IL-8 in OIS [50]. Several epigenetic regulators, including H2A.J, histone deacetylase 4 (HDAC4), high mobility group protein 2 (HMGB2), scaffold-attachment factor A (SAFA), mixed lineage leukemia 1 (MLL1), and Sirtuin-1 (SIRT-1), have an impact on the production of SASP factor genes [51–55].

The innate immune system receptor, Toll-like receptor (TLR), also affects the transcription of SASP genes. As a pattern recognition receptor, TLRS can identify exogenous pathogens and endogenous ligands and cause SASP after a series of inflammatory reactions [56, 57]. Moreover, it is shown that some bacteria, can trigger TLR-dependent NF-κBsystem to induce the production of SASP factors, hence encouraging the development of hepatocellular carcinoma (HCC) [58,59].

Cyclic guanosine phosphate (GMP) - adenosine monophosphate (AMP) synthase (cGAS) is a typical DNA sensor. After detecting cytosolic DNA, cGAS triggers the formation of cGAMP and subsequently activates protein STING. The transcription factors IRF3 and NF-κB are stimulated by STING via the kinases TBK1 and IKK, respectively [60]. When ROS-JNK signaling is activated by laminB1-dependent nuclear layer disruption or malfunctioning mitochondria, cGAS recognizes endogenous cytoplasmic chromatin fragments from damaged, senescent nuclei and mediates SASP component formation via the cGAS-STRING pathway [18,61].

Metabolic diseases predominantly impact SASP secretion [62]. When a mitochondrial malfunction occurs, NADH accumulates, the oxidation of NADH to NAD+ is inhibited, and the NAD+/NADH ratio decreases, resulting in cell cycle arrest. Yet, the decrease in NAD+/NADH induces mitochondrial dysfunction-associated senescence (MiDAS) by activating the AMPK-p53 axis, ultimately eliciting the IL-1-deficient SASP [25]. Similarly, mitochondrial dysfunction increases ROS generation. Mitochondrial ROS can control the formation of cytosolic chromatin fragments and the activation of SASP through activating JUN N-terminal kinase [63].

Recent research has demonstrated that mTORC1 is crucial in regulating the SASP. Through variably holding the translation of MK2/MAPKAPK2 kinase via 4EBP1, mTOR modulates the phosphorylation level of the phosphorylated RNA-binding protein ZFP36L1. This phosphorylation reduces ZFP36L1's capacity to degrade several SASP component transcripts [64]. By cooperating protein synthesis and autophagy in the TOR-autophagy spatial coupling (TASCC) compartment, cells experiencing OIS increase their secretory phenotype. The mTOR inhibitor rapamycin suppresses senescent cells' release of IL-6 and IL-8. In addition, rapamycin reduces SASP by preventing senescent cells from generating the positive IL-1A- NF-κB feedback loop through the suppression of IL-1A.

In general, although the understanding of SASP regulation is inadequate, it affords us numerous opportunities to target it for therapeutic benefit.

2.3. Bone modeling

The skeletal system of mammals has different functions, from daily movement support to organ protection. Apart from that, it is also a regulator of mineral homeostasis [65]. A healthy skeleton system must be constantly remodeled throughout life to maintain its functions [66]. Reconstruction of bones includes the resorption and formation of bone tissue. It requires the coordination of four primary bone cells: bone lining cells, bone cells, osteoclasts, and osteoblasts [67–69].

In the quiescent state, a single layer of bone-lining cells derived from osteoblasts covers the surface of the bone [70,71]. Under mechanical stress, bone lining cells are transformed into osteoblasts, and PTH can promote this process. Osteocytes are the primary cells in mature bone tissue. They are scattered throughout the mineralized matrix, used to sense and transmit mechanical stress in bone, and initiate bone remodeling [72]. By activating the Wnt signaling pathway, they promote the stability and nuclear entry of β-catenin and induce the transcription of osteogenesis-related genes [73]. Moreover, osteocytes are capable of producing and secreting sclerostin, a Wnt signaling pathway inhibitor that suppresses osteoblast development and bone production [74]. Osteoblasts can transform into osteocytes with the expression of dentin matrix protein 1 (DMP1) and matrix metalloproteinase (MMP) [75,76].

Osteoclasts derive from hematopoietic stem cells and are a major regulators of bone homeostasis.

Macrophage colony-stimulating factor (M-CSF) and receptor activator of NF-κB ligand (RANKL), a member of the TNF family, are the major regulators for osteoclast maturation, activation, and survival. M-CSF is a cytokine involving the generation and growth of the monocyte/macrophage lineage. RANKL is highly enriched in osteoblasts, osteocyte, bone marrow stromal cells (BMSCs), T and B lymphocytes. RANKL-RANK binding and the combination of M-CSF and C-fms promote osteoclast differentiation, proliferation, activation, and survival by boosting the action of numerous essential regulatory transcription factors and enzymes [77,78]. RANKL expression can be modulated by TNF-α, prostaglandin E2, parathyroid hormone (PTH), calcitriol, interferon, glucocorticoids, and several pro-inflammatory compounds of SASP. Furthermore, it is blocked by TGF-β [79,80]. These findings shed light on how senescent cells in the bone marrow microenvironment influence bone density.

Osteoblasts are bone-forming cells that differentiate from pre-osteoblasts derived from mesenchymal stem cells (MSC) [81]. Several signaling pathways, including Wnt, PTH, BMP, TGF, fibroblast growth factor (FGF), and hedgehog (Hh), govern osteoblast formation [82]. The key molecular route regulating osteoblast differentiation is the conventional Wnt/β-catenin pathway [83]. Wnt signaling activation enhances osteoblasts proliferation and differentiation, inhibits pre-osteoblasts and osteoblasts cell death, and increases osteoprotegerin (OPG) synthesis. OPG is a decoy receptor that competitively binds to RANKL with RANK. By boosting the production of OPG, in osteoblasts and osteocytes [84], it also improves osteoblast development and survival and suppresses osteoclast formation. Moreover, numerous cytokines regulate osteoblasts. IL-10, IL-11, IL-18, IFN-γ, corticotrophin-1 (CT-1) and oncostatin M (OSM) can stimulate the development of osteoblasts. In addition, IL-1α, IL-4, IL-7, IL-12, IL-13, IL-23, TNF-α, TNF-β, IFN-α, IFN-β, leukemia inhibitory factor (LIF), corticotrophin-like cytokines (CLC), and ciliary neurotrophic factor (CNTF) limit the production and differentiation of osteoblasts and accelerate their death [85]. By binding to osteoblast surface receptors, PTH can enhance the expression of

M-CSF, RANKL, and monocyte chemotactic protein 1 (MCP-1) by osteoblasts, efficiently attracting monocyte progenitors of osteoclasts and promoting the development and fusion of osteoclasts [86]. Exogenous injection of PTH-related protein (PTHrP) inhibits the induction of senescence markers and IL-6 release by IL-1 in osteoarthritis (OA) osteoblasts [87]. Low-dose PTH increases bone trabeculation by increasing osteoblast activity but not quantity in Samp6 mice [88].

Skeletal modeling Optimizes the shape and structure of developing bones in response to prevailing mechanical forces. Unfortunately, these benefits are compromised with age, resulting in decreased bone creation relative to resorption (more old bone is eliminated) and finally a negative bone balance. Over time, these unfavorable occurrences can lead to osteoporosis by causing substantial bone mass loss.

2.4. SASP and osteoporosis

The in-depth study of SASP shows that SASP plays a vital role in regulating bone remodeling (Fig. 3). Farr and colleagues identified the presence of p16Ink4a, a key mediator of cellular senescence, and many SASP factors are enriched with aged in myeloid cells, -B and T cells, osteoprogenitors, osteoblasts, and osteocytes [7]. Meanwhile, a comparison of bone resorption in healthy women of various ages indicated that age-related markers and SASP components were elevated in a group of aged women with an average age of 78 [89]. Kim and colleagues demonstrated that the population of osteoprogenitor cells in aging mice decreases significantly. The surviving osteoprogenitor cells display higher levels of DNA damage and senescence markers, including H2AX foci, G1 cell cycle arrest, p53 phosphorylation, and p21 Cip1 levels, as well as GATA4 activation and NF-κB activation, two important triggers of SASP [90]. In addition, aged mice's bone marrow stromal osteoprogenitor cells exhibited enhanced expression of SASP genes with osteoclastogenesis features, such as TNF-α, IL-1α, MMP-13, CXCL12, and the presentation of osteoclastogenesis factor RANKL [91–93]. These findings imply that bone loss in elderly humans and mice is linked to increased SCs in the bone marrow microenvironment.

Apart from age, estrogen insufficiency is also a major factor in bone loss. Farr et al. discovered that although estrogen deficiency and cellular senescence impact osteoporosis development, their mechanics have no connection. While therapy with AP20187 removes SCs in INK-ATTAC mice, it could not prevent bone loss produced by OVX or modify aging indicators [94]. However, it has been discovered that the JAK2/STAT3 axis modulates the production of SASP factors, increasing the senescent BMSCs population in ovariectomized (OVX) mice. Moreover, by reducing oxidative stress, osteocyte senescence, and SASP, administering pyrroloquinoline quinone (PQQ) or deleting the P16 gene can reverse bone loss induced by OVX [95,96].

Mounting evidence shows cellular senescence may contribute to developing diabetes-induced bone fragility associated with poor bone quality [97].In the bone tissues of T2D mice, p16 Ink4a and p21 Cip1 are overexpressed, and a more significant proportion of senescent cells is discovered. These senescent cells create a unique pro-inflammatory SASP that is dominated by matrix metalloproteinases with considerably increased expression levels (Mmp3, Mmp9, Mmp12, and Mmp13). NF-κB expression was likewise significantly upregulated in osteocyte-rich T2D bone samples. Furthermore seen in the femoral tissue of the T1D mouse model was an increase in senescent markers, which was reversed by melatonin treatment, which also ameliorated bone loss in T1D animals [98].

Radiation also promotes the senescence of BMSCs. Despite the fact that BMSCs do not lose their ability to proliferate and form colonies when exposed to low or high doses of ionizing radiation(IR), they tend to develop into adipocytes rather than osteoblasts [99–101]. Moreover, radiation stimulated the JAK1/STAT3 pathway in these cells, which then released SASP factors including IL-6, IL-8, and MMP9. The conditioned medium of senescent BMSCs harmed osteoblast differentiation. In contrast, JAK1 inhibitors prevent the secretion of SASP factors by senescent BMSCs and reverse the negative effects on osteoblast differentiation [101,102]. Chemotherapy also causes cellular senescence in a variety of tissues. Doxorubicin-treated mice have a higher proportion of p16 Ink4a, p21

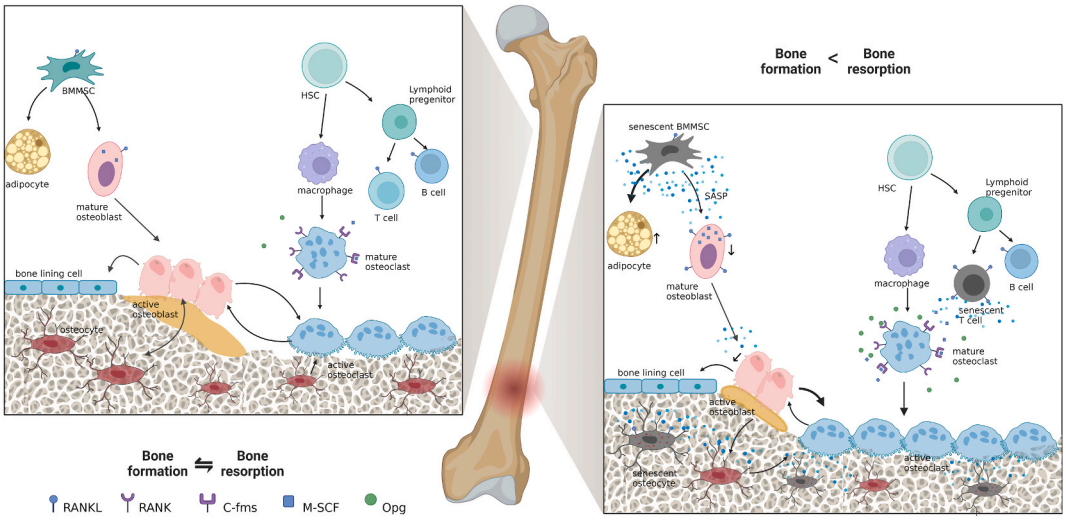

Fig. 3. Effects of senescent cells in bone remodeling.

Cip1, and SASP genes in the bone marrow samples, and targeting SASP with p38MAPK or MK2 can prevent chemotherapy-induced bone loss [103].

Recent studies have examined the impact of the heavy metal cadmium (Cd) on BMSCs. Cd caused an increase of senescent primary bone marrow-derived mesenchymal stromal cells (BMMSCs) via upregulating the NF-κB system, resulting in the transcription of IL-1, IL-6 TGF-β, GROα, and VEGF. Cd exposure can delay bone repair and regeneration after skull defect surgery. Even though Cd stimulated the mTOR system, rapamycin partly alleviated Cd-induced apoptosis but not the cellular senescence phenotype of BMMSCs. Importantly, pretreatment with melatonin partially prevented some of the senescence-related defects in Cd-induced BMMSCs, including mitochondrial dysfunction and DNA damage. This study indicated the functions of Cd in osteoporosis and may provide new therapeutic options for Cd-associated bone loss [104].

Although vascular endothelial cells also exist in the bone marrow cavity, the connection between senescent vascular endothelial cells and bone loss isunclear. Emerging evidence shows vascular endothelial cell senescence remains significant in age-related disease [105]. This implies that the mechanics of age-related osteoporosis may involve senescent vascular endothelial cells.

The accumulation of senescent cells in the bone marrow microenvironment causes chronic inflammation and bone tissue destruction via SASP. Farr discovered senescent T and B cells in the bone marrow microenvironment of mice with age-associated osteoporosis [89]. Rheumatoid arthritis is connected with premature T lymphocyte senescence. IL-15 enhanced expression of RANKL expression on senescent T cells surface efficiently stimulating osteoclast formation. Furthermore, several SASP factors such as IL-6, TNF-α, IFN-γ, and IL-1β play an important role in osteoporosis. These factors have the ability to modulate the amount of RANKL on the surface of diverse cells, trigger osteoclast development, and cause bone loss. In addition, these substances limit osteoblast function and decrease bone formation [106,107]. Furthermore, LPS promotes the development of premature osteocyte senescence and the secretion of proinflammatory factors, triggering inflammatory bone loss [108].

2.5. Targeting SASP for osteoporosis

Many evidence indicate that anti-senescence therapy drugs may have a role in treating osteoporosis associated with aging, radiation, diabetes, estrogen shortage. Nowadays, essential senescence treatment drugs can be categorized into two groups. One is the senolytic approach, which eliminates senescent cells by targeting the apoptotic pathway of senescent cells. The other one is senomorphic technique that targets SASP without influencing cell death.

Senolytic medicines such as Dasatinib (D), quercetin (Q), D + Q, Navitok, Navitoclax (ABT263), BCL-XL inhibitor, HSP90 inhibitor, and ABT-737 are utilized to decrease the number of senescent BMSCs and preosteoblasts and to increase the osteogenic capacity [109–116]. Moreover, it decreases the propensity for fat development. Remarkably, evidence showed that the anti-aging osteoclast progenitors have no connection with aged-related bone loss. Thus, other senescent cell types, such as bone cells, must be accountable for the effect [101].

Neutralizing antibodies can also inhibit senescence by targeting specific SASP components, such as TNF-α, TGF-β, IL-1β, IL-6, and IL-8 [117–121]. These drugs effectively ameliorate bone loss in inflammation-related diseases. Unfortunately, the efficiency of these agents in clinic OP is obscure. Antibodies that neutralize IL-17 prevent bone loss and immune system aging in animal models of OVX. Mice protected from OVX-induced bone loss when the major IL-17 receptor is deleted [122,123]. These findings provide the thought that IL-17 may be a possible therapy of OP.

Existing research suggests that suppressing SASP function can aid in preventing bone loss and extending bone growth. Senescent BMSCs increases SASP factor secretion in the ovariectomized (OVX) mouse model through activating the JAK2/STAT3 axis. Treating with ruxolitinib regularly for 3 months distinctly reverse the phenotype of senescence and bone loss in OVX mice [124]. In addition, CM from JAKI-treated senescent cells had a considerably diminished capacity to stimulate osteoclast development compared to CM from untreated senescent cells [110]. Prior research has shown that the p38MAPK-MK2 pathway affects the expression of several SASP components [125]. Reduced SASP factors (CXCL2, IGFBP4) were treated with p38MAPK inhibitors (P38i) or MAPKAPK2 pathway inhibitors (MAPKAPK2i) to prevent chemotherapy-induced bone loss [103].

Reduction of oxidative stress enhances bone structure by decreasing osteocyte senescence and SASP. Astaxanthin (AST) is a potent antioxidant extracted from certain types of seafood. It has high antioxidant activity and can inhibit the production of genes related to oxidative stress. Due to its influence in inhibiting the effect of oxidative stress, AST supplementation effectively rectifies these osteoporotic phenotypes caused by IR and OXV, diminishes the secretion of SASP, and successfully promotes bone density increase [126]. A similar effect can be seen in PQQ. Surprisingly, the supplementation of OVX animals with PQQ did not alter blood E2 levels or uterine weight [95].NAC treatment prevents ORX-induced osteoporosis by decreasing bone resorption and oxidative stress in osteoclasts, preventing DNA damage, osteocyte senescence, and SASP synthesis, and boosting bone formation in osteoblasts [127]. Fisetin is a polyphenolic flavonoid that is found in plants. Through decreasing NF-κB, p38, and JNK signaling, fisetin suppressed RANKL-induced osteoclast differentiation. Fisetin inhibited oophorectomy or inflammation-induced bone loss [128].

3. Conclusion

Research indicates that cellular senescence is critical in regulating bone loss induced by age or numerous other disorders, such as diabetes, radiation, and chemotherapy. ROS, DNA damage, dysfunctional telomeres, and heterochromatin modifications can induce bone cell senescence. SASP may mediate the local or remote damaging effects of senescent cells, particularly bone marrow and bone cells. With senolytics or senomorphic, it is possible to genetically or pharmacologically reduce the number of SCs in old mice, thereby attenuating bone loss caused by senescence. Many compounds, including PTH 1–84 or its fragment (PTH 1–34), pathway inhibitors,

bisphosphonates, tetracycline, cationic peptides, and antibodies (e.g. dinoumab and romosozumab), have been used to treat osteoporosis. Unfortunately, the majority are limited due to severe side effects or the fact that they merely reduce bone resorption without diminishing bone repair. Incorporating osteoporosis treatment into the context of addressing several other aging-related illnesses may therefore revive optimism. Further clinical trials are required for the treatment of senile osteoporosis, as the existing data mainly come from animal studies.

Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Haonan Fan: Writing – original draft. **Zhi Qiao:** Writing – original draft. **Jitian Li:** Project administration. **Guowei Shang:** Project administration. **Chunfeng Shang:** Investigation. **Songfeng Chen:** Investigation. **Zikuan Leng:** Writing – review & editing, Project administration. **Huifang Su:** Investigation. **Hongwei Kou:** Writing – review & editing, Supervision. **Hongjian Liu:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Credit Author Statement: investigation, CS, HS and SC; writing—original draft preparation, HF, ZQ, and ZL; writing—review and editing, HK and HL; supervision, HK and HL; project administration, JL, GS and ZL. All authors have read and agreed to the published version of the manuscript.

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