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Advances in the Regulatory Mechanisms of Senescence-Associated Secretory Phenotype in Osteoporosis (Postprint)

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Abstract

Senescence-associated secretory phenotype (SASP) constitutes a crucial hallmark of cellular senescence and exerts significant roles in regulating the disease microenvironment. Currently, mechanistic understanding of SASP-mediated interference with bone metabolism and induction of bone loss remains limited. Therefore, this article investigates the regulatory mechanisms of SASP in osteoporosis models and delineates its key characteristics: SASP is robustly expressed in senescent bone cells, transmitting senescence effects to mesenchymal stem cells via autocrine/paracrine signaling, thereby impairing osteogenic differentiation; SASP activates immune cells and promotes their senescence, fostering an inflammatory tissue microenvironment that exacerbates bone loss; dysregulation of mitochondrial homeostasis, pathological hyperglycemia, and obesity-induced adipose accumulation all enhance SASP expression, disrupting microenvironmental homeostasis and propagating senescence effects to bone tissue. Consequently, a comprehensive understanding of SASP' s role in osteoporosis is essential to inform the development of anti-SASP therapeutic strategies for osteoporosis treatment.

Full Text

Preamble

Review and Monograph
Research Progress on the Regulatory Mechanism of Senescence-Associated Secretory Phenotype in Osteoporosis
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Abstract

Senescence-associated secretory phenotype (SASP) is an important characteristic of cellular senescence that plays a crucial role in regulating the disease microenvironment. Current understanding of how SASP regulates bone metabolism and contributes to bone loss remains limited. Therefore, this paper explores the regulatory mechanisms of SASP in osteoporosis models and summarizes its regulatory features: (1) SASP is fully expressed in senescent bone cells and transmits aging effects to mesenchymal stem cells through autocrine/paracrine mechanisms, thereby interfering with their osteogenic differentiation; (2) SASP activates immune cells and promotes their senescence, inducing the formation of an inflammatory tissue microenvironment that exacerbates bone loss; (3) Mitochondrial homeostasis imbalance, pathological hyperglycemia, and obesity-induced fat accumulation all promote SASP expression, disrupting microenvironmental homeostasis and transmitting aging effects to bone tissue. In conclusion, a deeper understanding of SASP' s role in osteoporosis is necessary to provide insights for developing anti-SASP therapies for osteoporosis treatment.

Keywords: Osteoporosis; Senescence-associated secretory phenotype; Cell senescence; Metabolic disorders; Immunomodulation

1. SASP: Intervening in Mesenchymal Stem Cell Osteogenic Differentiation and Regulating Tissue Regeneration and Repair in Osteoporosis

While age-related bone loss is an important factor reducing bone formation, it is not the sole determinant. Persistent DNA damage and post-traumatic stress responses trigger massive SASP factor release, which mediates systemic chronic sterile inflammation and significantly disrupts bone metabolic balance. Specifically, DNA damage-induced permanent cell cycle arrest impairs mesenchymal stem cell activity and proliferative differentiation capacity, causing irreversible damage to bone tissue regeneration and repair. Therefore, regulating MSCs through SASP to maintain stable proliferative and differentiation capacity is essential for effective osteogenic differentiation.

SASP factor release in the bone microenvironment critically affects MSC activity. One study demonstrated that senescent osteocytes influence BMSC differentiation potential through paracrine pathways. This process manifests as: (1) stress-induced activation that destroys chromatin structure within osteocyte

nuclei, disrupts nuclear integrity, and forms senescence-associated heterochromatin foci (SAHF), leading to accumulation of γ-H2AX (a DNA double-strand break marker); (2) senescent osteocytes losing division capacity and undergoing growth arrest while maintaining metabolic activity and secreting SASP, resulting in accumulation of cytokines such as IL-6, IL-1α, MMP-3, and resistin; (3) mildly impaired BMSC colony-forming ability with reduced osteogenic and adipogenic differentiation potential; and (4) significantly decreased mineralized nodule formation and increased adipogenic capacity in BMSCs induced in vitro, ultimately causing skeletal aging and bone loss.

Bone homeostasis regulation depends on interactions between MSC and hematopoietic stem cell (HSC) lineages, particularly during aging. During senescence, these lineages undergo dramatic changes, leading to imbalance between myeloid-lymphoid hematopoiesis and adipogenic-osteogenic differentiation, with increased myelopoiesis and adipogenesis at the expense of lymphopoiesis and osteogenesis. From a SASP perspective, senescent and reduced osteocytes produce SASP factors that alter MSC lineage commitment, promoting osteoclast formation. This process involves: (1) MSCs and HSCs undergoing multiple passages, which leads to cellular senescence and SASP secretion. Increasing SASP factors (TNF-α, IL-1β, IL-6, etc.) circulate, promoting bone marrow maturation and progressively inducing senescence phenotypes and even ablation of osteocytes, reducing their numbers; (2) osteocyte-secreted SASP factors acting back on MSCs to downregulate osteogenic pathways (Wnt, Hedgehog, Notch) and increase MSC adipogenic differentiation and fat accumulation; and (3) increased circulating RANKL, decreased osteoprotegerin (OPG), reduced RANKL/OPG ratio, increased serum type I C-terminal peptide (CTX) secretion, and enhanced osteoclast formation, ultimately causing bone loss.

Since senescent osteocytes can induce MSC senescence through SASP production, stable application of MSC-based regenerative medicine for osteoporosis requires addressing senescence issues arising from MSC passaging. Numerous studies confirm that late-passage MSCs secrete SASP factors that promote early-passage MSC senescence, significantly impacting stem cell transplantation strategies for tissue regeneration. Moreover, late-passage MSCs show diminished osteogenic and adipogenic differentiation potential, yet their homeostasis maintenance depends on SASP production. Specifically, extracellular vesicles containing lipid metabolites produced by senescent MSCs exhibit toxicity that induces cellular senescence and apoptosis, paradoxically accelerating the aging process.

Small-sized mesenchymal stem cells demonstrate higher growth potential and lower senescence rates, though SASP maintains senescence progression through autocrine/paracrine positive feedback loops. Research confirms that small cells from umbilical cord blood-derived MSCs (UCB-MSC) possess stronger proliferative capacity and exhibit lower levels of cellular senescence. UCB-MSC small cells produce low-dose SASP factors (primarily GROα and IL-8) during multi-

ple passages, which bind to CXCR2 receptors to accelerate cellular senescence. This process is promoted by Toll-like receptors 2 (TLR2) and TLR5, and inhibited by si-RNA secreted from MSC small cells. Late-passage MSCs can induce early-passage MSC senescence through paracrine release of inflammatory factors such as IL-1α and IL-8 in an NF- B-dependent manner.

The signaling protein WNT3 can attenuate MSC senescence by inhibiting SASP factor paracrine pathways. It supports MSC proliferation and developmental potential not by directly regulating proliferation and differentiation, but by protecting cells from the detrimental effects of senescence. Silencing the transcription factor TWIST1 in MSCs increases senescence and causes metabolic abnormalities, specifically increased cellular oxygen consumption rates. Nuclear lamina defects represent another cause of MSC premature senescence. Abnormal prelamin A triggers paracrine senescence in MSCs through a GATA4-dependent pathway, while GATA4 deletion eliminates SASP-dependent senescence by inhibiting NF- B and MCP-1 via progerin or prelamin A. BMI-1 is an important factor regulating MSC self-renewal, and elevated SASP factor IL-1α in senescent MSCs leads to decreased BMI-1 expression, representing another cause of MSC premature senescence.

Mi-RNAs are considered important targets for regulating MSC behavior, with small extracellular vesicles encapsulating mi-RNAs serving as cell-free therapies for bone regeneration and repair. The SASP perspective suggests that mi-RNAs transported via exosomal vesicles induce senescence phenotypes in MSCs through paracrine pathways. Additionally, mi-RNAs produced by MSCs can accelerate senescence progression by regulating specific target genes. MiR-29c-3p promotes MSC senescence by targeting CNOT6 through p53-p21 and p16-pRB pathways. MiR-31 is elevated in plasma from elderly individuals and osteoporosis patients, transported via senescent cell-derived exosomal vesicles, and absorbed by MSCs to inhibit osteogenic differentiation by knocking down its target frizzled-3. MiR-335 significantly regulates MSC proliferation and differentiation and increases in response to stimuli that induce cellular senescence. MiR-335 overexpression acts on MSCs via exosomal vesicle transport, reducing their chondro-osteogenic potential. P65 can prevent MSCs from producing SASP factors and block paracrine senescence between MSCs as well as transmission of pro-inflammatory messages through small extracellular vesicles.

2. SASP: Mediating Chronic Inflammatory Responses in Osteoporosis and Regulating Bone Immunity

The bone microenvironment in osteoporosis patients contains numerous pro-inflammatory factors that mediate systemic chronic inflammatory responses. The SASP perspective posits that establishment of this chronic inflammatory state significantly exacerbates cellular senescence. Pro-inflammatory factors constitute important SASP components released by senescent cells throughout the body, and resistance to this inflammatory state largely depends on the immune system—particularly immune cell behavior. This section uses SASP

factors as a bridge to explore connections between the immune system and bone metabolic balance, as well as changes occurring in senescent immune cells, aiming to establish bone immune regulatory mechanisms and investigate how immune pathways might improve bone loss induced by pro-inflammatory states in osteoporosis patients.

2.1 Macrophage Polarization and SASP

Monocytes serve as cellular reserves that can differentiate into osteoclasts, macrophages, and dendritic cells, and produce chemokines that recruit immune cells to bone remodeling sites. Monocyte clusters exhibit heterogeneity and are divided into three subsets based on CD14 and CD16 expression: classical (CD14 high/CD16-), intermediate (CD14 high/CD16+), and non-classical (CD14 low/CD16+). SASP factors induce the non-classical CD16+ subset to exhibit the most pronounced pro-inflammatory state and high miR-146a expression (a mi-RNA that negatively regulates TLR pathways), which is considered a senescence state of monocytes. Furthermore, NF- B and IL-1α may be key targets mediating senescence phenotypes in monocytes, while elevated TNF-α and IL-8 levels in plasma progressively deepen this senescence phenotype. Additionally, SASP factor GDF-15 can induce monocytes to produce more CD16+ phenotypes and promote senescence by inhibiting mitochondrial respiratory capacity.

In the senescent microenvironment, macrophages can be recruited by various cytokines, including SASP factors and NK cell secretomes, creating functional links. NK cells produce interferon-γ (IFN-γ) through interaction with senescent cells, thereby recruiting macrophages. Macrophages also respond to recruitment by SASP factors such as CCL2, CXCL1, CXCL16, and IL-8, with SASP-related CCL2 causing accumulation of pro-inflammatory M1 macrophages. As senescence progresses, macrophages exhibit a hyper-inflammatory, low-immune-activity state with senescence characteristics: (1) macrophages respond to aging by activating low-level innate immune pathways marked by sCD163 and CXCL10, leading to dysfunction; (2) SASP factor release acts on macrophages, increasing TNF-α levels; and (3) macrophages develop senescence features, shift toward the M2 phenotype, downregulate IL-10, and significantly reduce phagocytic capacity.

Senescent cells are difficult for macrophages to eliminate and can inhibit macrophage ability to recognize SASP signals and clear apoptotic cell debris through paracrine pathways. Senescent cell-mediated efferocytosis suppression (SCES) causes macrophage functional paralysis due to enhanced CD47 expression and increased CD47-modifying enzymes QPCT/L in senescent cells. SCES inhibits macrophage capacity by interfering with the SIRPα-CD47-SHP-1 axis or QPCT/L activity. Increased CD47 and CD24 expression represent components of senescent cell-mediated homeostatic dysfunction (such as efferocytosis), which must occur effectively to maintain tissue homeostasis and suppress autoimmunity. CD38 is an important regulator of macrophage function

that modulates cellular Ca2+ metabolism and possesses anti-osteoclastogenic properties. Enhanced CD38 expression can reduce osteoclast number and bone resorption, while SASP factors can induce CD38 expression in macrophages. These M1-like macrophages express high levels of CD38 and enhance CD38-dependent NAD+ enzymatic activity, thereby reducing tissue NAD+ levels. Age-related NAD+ reduction decreases SASP factor production and alleviates pathological effects. Moreover, regulating CD38 expression through Ca2+, cAMP, and TNF-α helps coordinate the high metabolic activity of osteoclasts and osteoblasts with their respective bone resorption and remodeling functions.

2.2 Pro-inflammatory Networks of Multi-immune Cell Crosstalk and SASP

In response to SASP factors, multiple immune cells integrate and crosstalk to generate complex pro-inflammatory networks that greatly influence bone microenvironment stability. Often, individual immune cell clusters have minimal effect, while multiple clusters are regulated by one or several pro-inflammatory factors. Therefore, investigating how multi-immune cell integration regulates SASP networks is particularly important.

Monocytes can differentiate into osteoclasts, and NK cells can induce monocyte differentiation into osteoclasts through M-CSF and RANKL production, thereby exacerbating bone loss, though their own osteoclastogenic capacity is limited. The SASP perspective suggests that senescent cells secrete various chemokines (such as CXCL10) that enhance NK cell proliferation and migration through CXCR3 binding, mediating clearance of senescent cells. Additionally, CD158d expression can stimulate resting NK cells to induce NF- B signaling by recruiting TRAF6 to activate TAK1, leading to NK cell senescence and SASP development. This secretome can significantly promote angiogenesis.

T cells can respond to microenvironmental stimuli with refined reactions unmatched by other immune cells, and different T cell subpopulations play crucial roles in bone balance. T cell function depends on synergistic effects between CD4+ and CD8+ T cell subsets. Among them, Th17 cells derived from CD4+ differentiation primarily stimulate osteoclast production to mediate bone resorption, while Tregs effectively inhibit bone resorption. The dynamic balance between them is key to maintaining bone metabolic stability. CD8+ T cells can inhibit osteoclastogenesis by secreting osteoprotegerin (OPG) and IFN-γ. The SASP perspective posits that both T cell subsets develop senescence phenotypes and are regulated by SASP factors, exhibiting metabolically active hyper-inflammatory states that significantly enhance bone loss. Senescent CD4+ T cells display PD-1+ memory phenotypes. These cells do not proliferate upon T cell receptor stimulation and produce large amounts of SASP factors such as osteopontin, TNF-α, and IL-6, associated with upregulated C/EBPα expression. Unlike senescent CD4+ T cells, senescent CD8+ T cell subsets exhibit the greatest heterogeneity, producing more IL-6, IL-1β, and proteases (cathepsins and serine proteases, including ADAM family members and metalloproteinases),

regulated by p38/MAPK.

In B cells, only memory B cell subsets express SASP, particularly late-stage/exhausted memory B cells (LM B cells). The LM B cell subset spontaneously activates AMPK through endosomes, induces p38/MAPK expression, and releases pro-inflammatory factors (TNF-α, IL-6, IL-8, etc.) and inflammatory mi-RNAs (miR-155, 16, 93, etc.), transmitting senescence signals to surrounding tissues through paracrine pathways. SASP-mediated hyper-inflammatory states stimulate B cells to produce RANKL and granulocyte colony-stimulating factor (G-CSF), thereby activating osteoclastogenesis and converting B cell-mediated bone remodeling into bone resorption.

3. SASP: Regulating Multiple Metabolic Responses in Osteoporosis

A notable characteristic of osteoporosis patients is systemic metabolic dysregulation, with SASP believed to mediate secondary damage following metabolic abnormalities and contribute to formation of adverse tissue microenvironments. This section explores relationships between metabolic dysregulation and SASP regulation and their potential harm to bone metabolic balance, aiming to construct a more comprehensive and detailed SASP control network.

3.1 Mitochondrial Homeostasis Disorder: Energy Metabolism Abnormalities, Oxidative Stress, and SASP

Mitochondrial homeostasis is crucial for maintaining cellular energy supply and mediating systemic anti-oxidative metabolism. Conversely, mitochondrial homeostasis disorder leads to energy metabolism abnormalities and cellular oxidative stress—important triggers for SASP. Senescence causes mitochondrial dysfunction (SAMD) and promotes SASP production. SIRT4 is expressed exclusively in mitochondria and negatively regulated by miR-15b. In senescent cells, increased SIRT4 expression inhibits miR-15b production. Targeted inhibition of miR-15b enhances SIRT4 expression, promoting mitochondrial ROS generation and reducing mitochondrial membrane potential, leading to mitochondrial dysfunction. Moreover, miR-15b inhibition causes SASP release in a SIRT4-dependent manner and prevents normal miR-15b-mediated suppression of SASP factors IL-6 and IL-8 through IRAK2.

GRSF1 is a protein essential for maintaining mitochondrial oxidative phosphorylation, and its levels decrease in senescent cells due to reduced protein stability. This leads to mitochondrial stress, increased superoxide production, increased DNA damage foci, reduced cell proliferation, and development of senescence phenotypes, including increased senescence-associated β-galactosidase activity and SASP factor IL-6 production and secretion. Notably, SAMD-induced ROS can regulate SASP production, but SASP cannot reverse mediate SAMD. SASP transmits senescence effects to surrounding tissues through paracrine mechanisms. This indicates that for SAMD-ROS effect-induced senescence, we cannot

control it by inhibiting SASP factor production, suggesting that antioxidants and mitochondrial activity-enhancing drugs may be effective strategies.

Senescence reduces mitochondrial respiratory capacity, shifting cells to rely primarily on glycolysis for energy supply with accompanying SASP production. Nicotinamide phosphoribosyltransferase (NAMPT) is the rate-limiting enzyme in the NAD+ salvage pathway, regulated by HMGAs during senescence. The HMGAs/NAMPT/NAD+ signaling axis regulates SASP factor release by enhancing glycolysis and mitochondrial respiration.

Recombinant human ubiquitin-conjugating enzyme UBE2E3 depletion causes senescence with a unique SASP. Unlike mitochondrial dysfunction-induced aging (MiDAS), UBE2E3 depletion represents a senescence mode of disrupted mitochondrial network maintenance, causing mitochondrial homeostasis disorder (affecting mitochondrial distribution, quality, and susceptibility to toxins) and increasing IL-1β nearly six-fold. Meanwhile, common SASP factors like IL-10 show minimal increase, suggesting UBE2E3 depletion may couple with other senescence pathways.

Cytoplasmic chromatin fragments (CCFs) extruded from senescent cell nuclei also mediate cellular senescence. Dysfunctional mitochondria cause downregulation of nuclear-encoded mitochondrial oxidative phosphorylation genes and trigger ROS-JNK retrograde signaling, driving CCF formation and resulting in SASP factor production. Aneuploidy (chromosomal numerical imbalance) mediates cellular senescence in a c-Jun N-terminal kinase (JNK)-dependent manner, causing ROS production, accumulation of dysfunctional mitochondria, and SASP factor release. Additionally, deletion of endoplasmic reticulum-resident disulfide reductase ERdj5 causes intracellular Ca2+ imbalance and activates Drp1 (a cytosolic GTPase involved in mitochondrial fission), ultimately leading to abnormal mitochondrial fragmentation, reduced cell viability, and SASP factor release.

Mitochondrial homeostasis disorder-mediated SASP effects can trigger widespread bone tissue senescence through autocrine/paracrine pathways. More specifically, SASP-induced abnormalities in mitochondrial fusion and fission also impair osteogenic capacity and enhance osteoclastogenesis, exacerbating osteoporosis progression. Under oxidative stress conditions, Drp1 expression and phosphorylation increase in osteoblasts, causing mitochondrial fragmentation, deformity, and vesiculation. SASP factor TNF-α can induce high Drp1 expression, triggering mitochondrial membrane potential collapse, reducing mitochondrial function, and inhibiting osteogenic activity. Moreover, Drp1-mediated mitochondrial hyperfission facilitates osteoclast proliferation. RANKL, widely generated under inflammatory conditions, promotes osteoclast differentiation by regulating Drp1 and its receptor proteins Fis1, Mid49, and Mid51, thereby aggravating bone loss.

Reduced mitophagy mediated by mitochondrial homeostasis disorder is a key factor exacerbating bone loss. Under oxidative stress, ROS and superoxide

accumulation destroy mitochondrial structure, alter mitochondrial membrane potential, and prevent PINK1 from coupling with Parkin signals to clear damaged mitochondria and inhibit SASP effect transmission. Studies have found reduced PINK1 expression in osteoporosis patients, which leads to decreased bone mass and represents a key factor inhibiting osteogenic differentiation and aggravating bone loss.

OPA1 plays a critical role in mitochondrial homeostasis regulation, connecting mitochondrial function with SASP effect transmission and glucose metabolism. OPA1 exists in long (L-OPA1) and short (S-OPA1) forms that regulate mitochondrial division and fusion. Under oxidative stress, L-OPA1 cleaves into S-OPA1, significantly reducing mitochondrial function and inducing osteoblast apoptosis. OPA1 overexpression activates the p38MAPK pathway, reducing mitochondrial ATP generation and promoting bone marrow cell apoptosis, thereby accelerating osteoporosis development. p38MAPK activation is accompanied by massive SASP release, amplifying this effect in bone tissue. Under pathological hyperglycemia, advanced glycation end products (AGE) accumulate, enhancing S-OPA1 while inhibiting L-OPA1 expression, accelerating ROS generation, and inducing osteoblast apoptosis, thereby linking abnormal glucose metabolism, mitochondrial homeostasis disorder, and osteoporosis.

3.2 Glucose Metabolism Abnormalities and SASP

Abnormal glucose metabolism mediates pathological hyperglycemia and advanced glycation end product accumulation, severely compromising skeletal system stability. The SASP perspective suggests that hyperglycemia mediates chronic inflammation, induces cellular senescence, and generates massive pro-inflammatory SASP factors. In this inflammatory bone microenvironment, bone metabolism shifts from formation to resorption.

Senescent pancreatic β cells induce pathological hyperglycemia and produce massive SASP factors, destroying the osteogenic microenvironment through high-glucose and high-inflammatory stimuli. Senescent β cells secrete core SASP factors including CCL2, IL-1α, IL-6, and Tnfa, inducing senescence in adjacent non-senescent β cells through paracrine pathways. Senescence impairs adult pancreatic β cell proliferation and response to growth stimuli, with enhanced p16Ink4a expression initiating β cell senescence, reducing proliferative capacity, and causing massive SASP factor release. This paracrine effect also disrupts pancreatic α cell function, causing glucagon secretion disorders and subsequently reducing insulin secretion.

Pathological hyperglycemia induces low-grade inflammation, with endothelial cells and macrophages serving as primary transmission cells mediating SASP effects and playing crucial roles in propagating diabetic low-grade inflammation. Studies show that GLUT1 functions as a facilitative glucose transporter in macrophages, intimately involved in SASP effect mediation. In high-glucose environments, bone marrow-derived macrophages (BMDM) exhibit strong GLUT1

mRNA responses, driving elevated glucose uptake and triggering mTOR phosphorylation, which induces p16/p21-mediated SASP factor release. Furthermore, high glucose induces macrophage senescence and SASP factor secretion through NLRC4 phosphorylation, stimulating NF- B/Caspase-1 cascades via IRF8-dependent pathways and causing broader SASP effects. Under these multiple regulatory mechanisms, inflammatory bone loss worsens and senescent bone cells accumulate.

3.3 Lipid Metabolism Disorder and SASP

Lipid metabolism disorder leading to fat accumulation is a key factor driving progressive cellular senescence. The SASP perspective suggests that fat accumulation induces cellular senescence, triggers SASP effects, and accompanies low-grade inflammation formation. In this inflammatory tissue microenvironment, osteogenesis weakens while bone resorption strengthens, and BMSC differentiation shifts from osteogenic to adipogenic.

Senescent cells accumulate in adipose tissue of obese patients, mediating SASP effects and inflammation formation. Obese individuals show increased memory B cell generation frequency and decreased naive B cell generation frequency in adipose tissue, with mature B cells (memory B) exhibiting high metabolic activity accompanied by massive release of inflammatory SASP factors (IL-6, IL-8, TNF-α), exacerbating systemic inflammatory states. Obesity also induces accumulation of senescent macrophages, which display low phagocytic and high secretory activity. CD9+ macrophages promote adipose progenitor cell expression of PDGFRα and PDGFRβ by secreting osteopontin and PDGF-BB, thereby inhibiting adipose tissue generation through promoting extracellular deposition and fibrosis. This represents a rare anti-aging process. Additionally, obesity causes accumulation of senescent adipose progenitor cells, activating the NOTCH pathway and leading to SASP factor SFRP4 and INHBA release, thereby converting adipogenesis to fibrogenesis and suppressing obesity. Senescent adipose progenitor cells also express SASP via JAK pathways, mediating systemic inflammatory responses. Furthermore, SPRY1 in adipose progenitor cells can inhibit MAPK activity to suppress transcription factors NF B and C/EBPβ, thereby reducing SASP factor IL-6 release.

Obesity induces senescence in mesenchymal stem cells and reduces their proliferative differentiation capacity, which is detrimental to bone remodeling. Obesity induces adipose-derived mesenchymal stem cells to downregulate PPAR-γ and upregulate p16 and p53 levels, promoting inflammatory SASP factor expression (IL-6, MCP-1, etc.) that inhibits adipogenic capacity and transmits senescence effects. Long-term exposure to SASP environments also reduces angiogenic potential of adipose-derived mesenchymal stem cells, impairing vascularized bone regeneration. Studies identify SASP factor IL-6 as a key inflammatory mediator inducing bone loss during obesity. IL-6 induces BMSC senescence through STAT3 activation and p53/p21 pathways, and antibody antagonism of IL-6 helps maintain balance between bone marrow osteogenesis and adipogenesis

while inhibiting obesity-induced BMSC senescence and bone loss. Another important SASP factor, TNF-α, primarily expands senescence effects by transmitting inflammatory effects to healthy adipocytes. Obesity-mediated inflammatory SASP signals also regulate bone marrow adipose tissue (BMAT) content to intervene in adipose-derived BMSC differentiation. In obesity-induced osteoporosis models, increased BMAT volume significantly elevates fracture risk and shifts BMSC differentiation from osteogenic to adipogenic. Long-term glucocorticoid administration also induces BMAT accumulation: glucocorticoids increase synthesis of oxidative lipids such as 15d-PGJ2 to activate PPAR-γ, which stimulates expression of key SASP genes and promotes oxidative lipid synthesis in bone marrow adipocytes, forming a positive feedback loop that induces glucocorticoid-induced osteoporosis.

SASP effects demonstrate that cellular exposure to excessive damage can be "translated" into senescence, which is associated not only with age but also with oxidative stress, inflammation, and dramatic tissue microenvironment changes. This provides an opportunity to explore osteoporosis pathogenesis from a deeper perspective. The SASP-related viewpoint suggests that osteoporosis development is driven by three mechanisms: (1) insufficient bone formation—related to SASP effects transmitted between senescent bone tissue, microenvironment, and BMSCs, with the core factor being insufficient osteogenic capacity of senescent BMSCs; (2) suppressed bone turnover—related to SASP effects transmitted between senescent tissue and immune cells, with the core driver being immune cell senescence forming inflammatory SASP that aggravates bone loss; and (3) impaired bone metabolism—related to SASP effects transmitted between tissues mediated by mitochondrial damage, lipid metabolism disorder (obesity), and glucose metabolism dysregulation (diabetic pathological hyperglycemia), with core factors being pathological product accumulation (such as advanced glycation end products, BMAT) and inflammatory bone microenvironment formation. Therefore, anti-SASP strategies can be designed based on SASP' s broad regulation of the bone microenvironment and inflammation mediation to optimize osteoporosis treatment.

Note: CTX = C-terminal telopeptide of type I collagen β special sequence, RANKL = receptor activator of nuclear factor- B ligand, OPG = osteoprotegerin, G-CSF = granulocyte colony-stimulating factor, cAMP = cyclic adenosine monophosphate, AMPK = AMP-dependent protein kinase, p38/MAPK = p38 mitogen-activated protein kinase pathway, C/EBPα = CCAAT enhancer-binding protein α, sCD163 = soluble CD163, CXCL10 = C-X-C motif chemokine 10, IL = interleukin, miR = microRNA, WNT = Wingless/Integrated protein, GATA4 = GATA binding protein, BMI-1 = polycomb ring finger gene, MCP-1 = monocyte chemoattractant protein-1, Hedgehog = hedgehog protein, frizzled-3 = frizzled class receptor-3 protein, CNOT-6 = transcription regulatory complex CNOT-6, TAK1 = transforming growth factor-β-activated kinase 1, γ-H2AX = γ-histone H2AX (a DNA

damage marker), NF- B = nuclear factor B, TNF-α = tumor necrosis factor-α, MMP-3 = matrix metallopeptidase-3, p16/pRB = multiple tumor suppressor gene-16/retinoblastoma protein gene pathway, p53/p21 = tumor suppressor protein p53 gene/activated kinase-1 gene pathway.

Figure 1 [Figure 1: see original paper] Bone immune regulatory network of SASP

Note: NOTCH = transmembrane receptor protein NOTCH-1, JAK = non-receptor protein tyrosine kinase, GLUT1 = facilitated glucose transporter 1, NLRC4 = nucleotide-binding oligomerization domain-4, mTOR = mammalian target of rapamycin, IRF8 = interferon regulatory factor 8, STAT3 = signal transducer and activator of transcription-3, JNK = c-Jun N-terminal kinase, SFRP4 = secreted frizzled-related protein-4, PDGFR = platelet-derived growth factor receptor, INHBA = inhibin β subunit A, Tnfa = tumor necrosis factor α, CCL2 = monocyte chemoattractant protein 1, p16Ink4a = a cyclin-dependent kinase inhibitor, PPARγ = peroxisome proliferator-activated receptor γ, PDGF-BB = platelet-derived growth factor-BB, IRAK2 = interleukin-1 receptor-associated kinase 2, OPA = optic atrophy 1 protein, SIRT4 = sirtuin-4, PINK1 = PTEN-induced putative kinase 1, Drp1 = dynamin-related protein 1, GRSF1 = G-rich RNA sequence binding factor 1, HMGAs = high mobility group AT-hook proteins, NAMPT = nicotinamide phosphoribosyltransferase, UBE2E3 = ubiquitin-conjugating enzyme E2 E3, ERdj5 = a protein disulfide isomerase, CCFs = cytoplasmic chromatin fragments, MOTS-c = a mitochondrial-derived peptide encoded by the mitochondrial genome 12S rRNA region consisting of 16 amino acids, SHLP-2, -6 = small human-like peptide-2, -6, MCP-1 = monocyte chemoattractant protein-1, p16-p21 = multiple tumor suppressor-16-multiple tumor suppressor-21 pathway, p53-p38MAPK = p38 mitogen-activated protein kinase pathway, JAK/STAT = JAK/STAT pathway, P53/P21 = multiple tumor suppressor gene-53/multiple tumor suppressor gene-21 pathway, ROS-JNK = reactive oxygen species-c-Jun N-terminal kinase pathway, NF- B/Caspase-1 = nuclear factor B/IL-1β converting enzyme pathway.

Figure 2 [Figure 2: see original paper] SASP regulatory network of mitochondrial homeostasis disorders, lipid metabolism disorders, and glucose metabolism abnormalities

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