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REVIEW

The Bidirectional Role of Obesity and Aging in the Pathogenesis of Osteoarthritis: Molecular Mechanisms, Epigenetic Insights, and Therapeutic Implications

Chuang Lin[1], Junxing Yang[1], Hang Su[2], Xinguo Zhang[1], Bo Wang[3]

[1]Department of Bone Injury, Shenzhen Hospital, Guangzhou University of Chinese Medicine (Futian), Shenzhen, 518000, People's Republic of China; [2]Department of Medicine, Guangzhou University of Chinese Medicine Shenzhen Hospital (Futian), Shenzhen, 518000, People's Republic of China; [3]Department of Bone Injury, the First Affiliated Hospital of Heilongjiang University of Chinese Medicine, Harbin, 150036, People's Republic of China

Correspondence: Bo Wang, Department of Bone Injury, The First Affiliated Hospital of Heilongjiang University of Chinese Medicine, Harbin, 150036, People's Republic of China, Tel +86-18646246661, Email wb8788000@163.com

Abstract: Osteoarthritis (OA) is a major global contributor to pain, disability, and socioeconomic burden. With the increasing prevalence of obesity and an aging population, the incidence of OA continues to rise. This review explores the bidirectional relationship between obesity and aging in the pathogenesis of OA, focusing on the underlying molecular mechanisms. Obesity contributes to aging by inducing oxidative stress, chronic inflammation, and metabolic dysregulation, thereby promoting OA development and progression. Conversely, the accumulation of senescent cells with age exacerbates obesity-induced inflammation and metabolic dysfunction by secreting pro-inflammatory cytokines and bioactive molecules. Epigenetic changes, including DNA methylation, histone modifications, and the regulation of non-coding RNAs, play pivotal roles in modulating these interactions, further influencing OA progression. The review also discusses current and emerging therapeutic strategies targeting the obesity-aging-OA axis, highlighting the potential of epigenetic interventions and novel anti-inflammatory treatments. A comprehensive understanding of the molecular interplay between obesity and aging in OA is essential for developing more effective prevention and treatment strategies. Future research should prioritize the in-depth exploration of epigenetic mechanisms, coupled with technological innovation, standardized education and training, quality control, and multidisciplinary collaboration. Targeted strategies and interventions are essential to effectively prevent and manage obesity- and OA-related diseases.

Keywords: obesity, aging, osteoarthritis, epigenetics, inflammation

Introduction

Global Burden of Osteoarthritis

Osteoarthritis (OA) is the most common joint disorder and a leading cause of chronic disability worldwide, affecting approximately 600 million individuals. With the rising prevalence of obesity and an aging global population, the incidence of OA is projected to increase further, posing substantial societal and economic challenges.[1] Beyond physical pain and functional limitations, OA imposes substantial psychological and physiological stress. Many individuals experience elevated levels of psychological distress, including anxiety and depression, which compromise disease management and form a cycle of worsening health outcomes.[2–4]

Clinical Manifestations and Disease Impact of OA

Key clinical features of OA include progressive degradation of articular cartilage, alterations in the extracellular matrix (ECM), and irreversible structural changes affecting cartilage, ligaments, joint capsules, synovium, and periarticular muscles.[5] Disease progression often results in persistent pain and loss of functional independence, leading to significant declines in quality of life.

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Risk Factors for OA

Aging and obesity are two of the most significant risk factors for OA, with approximately 73% of OA patients being over the age of 55 and around 20% of cases attributed to obesity.[6] Obesity increases mechanical loading on joint cartilage, contributing to structural damage and degeneration. In addition, obesity influences cartilage metabolism through adipocyte-derived pro-inflammatory adipokines and cytokines such as leptin, resistin, and adiponectin, further accelerating OA progression.[7,8] Although cellular senescence plays a physiological role in development, its associated pathological changes, such as chronic low-grade systemic inflammation, cartilage thinning, reduced glycosaminoglycan content, altered proteoglycan composition, accumulation of advanced glycation end-products, impaired autophagy, and apoptosis, are key drivers of OA onset and progression.[9–11]

Mechanistic Link Between Obesity and OA

Emerging evidence suggests a bidirectional relationship between obesity and aging. Obesity contributes to aging-related processes such as cellular senescence and chronic inflammation, while aging exacerbates obesity-associated metabolic dysfunction and joint degeneration.[9,11–13] Both obesity and aging contribute to a systemic inflammatory state and the accumulation of senescent cells, which secrete pro-inflammatory factors and matrix-degrading enzymes, exacerbating joint degeneration. Understanding the central role of chronic inflammation and senescence in the obesity-aging-OA axis is critical for developing targeted therapies to slow OA progression.

Role of Epigenetic Regulation in OA

Recent studies have demonstrated that epigenetic regulators in healthy cartilage promote anabolic gene expression and suppress catabolic pathways through interactions with transcription factors and non-coding RNAs. In OA, factors such as obesity and aging disrupt the integrity of the cartilage epigenome.[14–17] Aberrant DNA methylation, histone modifications, and dysregulation of non-coding RNAs (eg, miR-140, miR-146a) in chondrocytes have been implicated in OA pathogenesis.[15,18] These epigenetic alterations lead to metabolic dysregulation, cartilage degradation, and joint dysfunction (Figure 1). A deeper understanding of obesity- and aging-induced epigenetic alterations may improve strategies for OA prevention and treatment, although the precise molecular mechanisms remain to be fully clarified.[17]

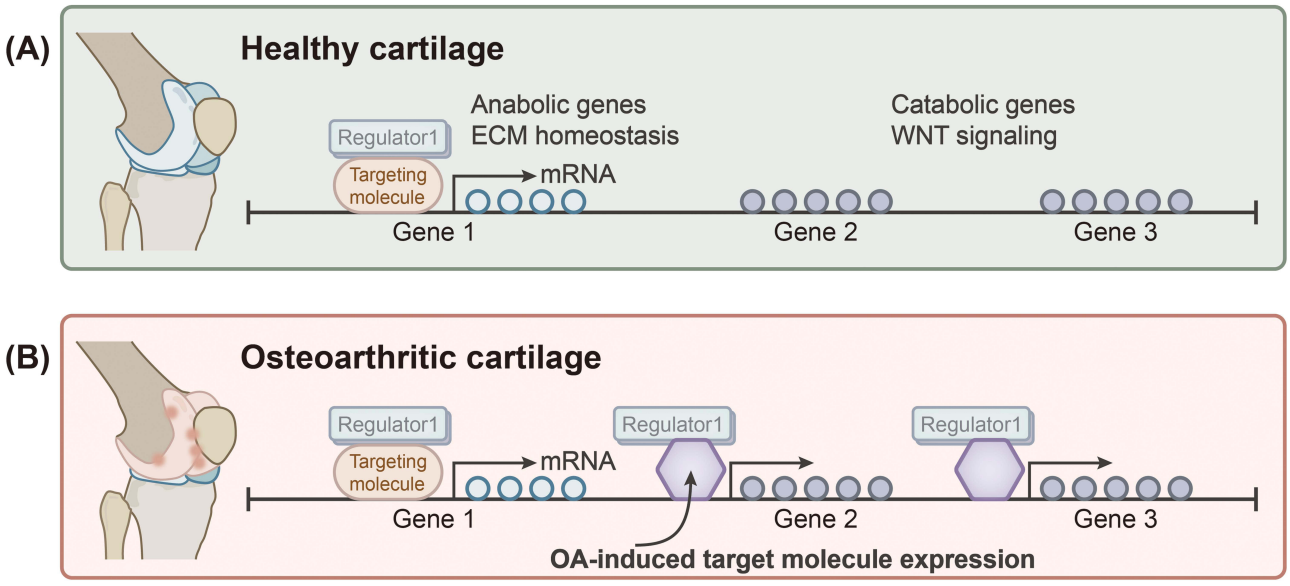

Figure 1 Epigenetic regulation model of OA.
Notes: Epigenetic regulatory patterns in normal (**A**) and osteoarthritic (**B**) cartilage tissues. "Regulator1" represents an epigenetic or transcriptional regulatory factor, which may include transcription factors, epigenetic modifiers (eg, DNA methyltransferases, histone-modifying enzymes), or miRNAs. "Targeting molecule" indicates the specific target influenced by the regulatory factor, typically a gene, protein, or RNA molecule. Created in BioRender. T, J. (2025) https://BioRender.com/nonzokl.

Current Therapeutic Strategies and Limitations

Current treatment strategies for OA include non-pharmacological interventions, pharmacological therapies, intra-articular injections (eg, hyaluronic acid, corticosteroids, stem cells), and emerging molecular therapies such as gene editing and exosome-based treatments. Advances in the understanding of OA pathogenesis have facilitated the development of various disease-modifying osteoarthritis drugs (DMOADs), including small-molecule inhibitors targeting inflammatory and catabolic pathways, protein analogs promoting anabolic processes, and regenerative drugs modulating Wnt signaling to delay cartilage degeneration.[19,20] Although several compounds have demonstrated therapeutic potential in preclinical and early-phase clinical trials, none have received regulatory approval for clinical use.[20,21] Current therapies largely focus on symptom management without addressing the underlying molecular pathology. Epigenetic therapies offer a novel approach for reversing cartilage degradation and inflammation, potentially altering the disease trajectory.[22,23]

Objective of This Review

This review aims to summarize and analyze recent advances in understanding the bidirectional relationship between obesity and aging in the pathogenesis of OA, focusing on the associated molecular mechanisms and epigenetic regulation. The review further explores the potential implications of these findings for OA prevention and treatment, providing new perspectives and references for future research and clinical applications. A systematic methodology was adopted for literature collection and analysis. First, a structured search of PubMed, Embase, and Web of Science was conducted using keywords such as "osteoarthritis" "obesity" and "epigenetics" to ensure the inclusion of high-quality studies. Second, only peer-reviewed journal articles published between 2013 and 2023 were included, while studies with poor design or limited relevance were excluded. Third, data were extracted from eligible studies, including OA pathogenesis, the association between obesity and OA, and relevant epigenetic regulatory mechanisms. Lastly, the extracted data were analyzed to summarize the molecular mechanisms of OA and the epigenetic effects of obesity on OA progression, while identifying critical gaps and future research directions.

Mechanistic Exploration of the Bidirectional Relationship Between Obesity and Aging

With global economic development and an increasingly aging population, obesity and aging have emerged as two critical public health challenges worldwide.[24–26] A recent study analyzing nine hallmarks of aging reported that individuals with obesity are significantly more susceptible to developing age-associated diseases, such as cardiovascular disease, diabetes, cancer, and OA, compared to individuals with healthy body weight.[27,28]

Dysfunctional Adipose Tissue and Inflammatory Response

Obesity and aging share significant biological mechanisms, particularly in relation to changes in adipose tissue function and inflammatory responses. Recent studies have shown that obesity promotes cellular senescence through multiple pathways, including increased oxidative stress, dysregulated inflammatory signaling, and impaired cellular metabolism.[29] In obese individuals, adipocytes undergo senescence and exhibit the senescence-associated secretory phenotype (SASP), characterized by the release of pro-inflammatory mediators that promote inflammatory signaling in surrounding healthy cells.[30]

These pathological changes are not confined to adipose tissue alone but extend to multiple organs and systems.[31] Obesity-induced systemic metabolic dysregulation and inflammation can impair the function of organs such as the heart and liver and lead to premature cellular aging.[32,33] In particular, models combining high-fat diet (HFD)-induced obesity and D-galactose-induced aging demonstrate increased susceptibility to myocardial injury, exacerbated mitochondrial dysfunction, and disrupted mitochondrial dynamic remodeling in cardiac tissue.[34] As illustrated in Figure 2, dysfunctional adipose tissue plays a central role in linking obesity and aging, primarily through inflammation-driven signaling pathways that promote the expression of aging-associated biomarkers. Aging further exacerbates the detrimental health effects of obesity, establishing a self-perpetuating vicious cycle.

Clinical advances in recent decades have shown promising responses to interventions targeting adipose tissue inflammation and cellular composition. Given the similarities between obesity-associated and age-related adipose tissue

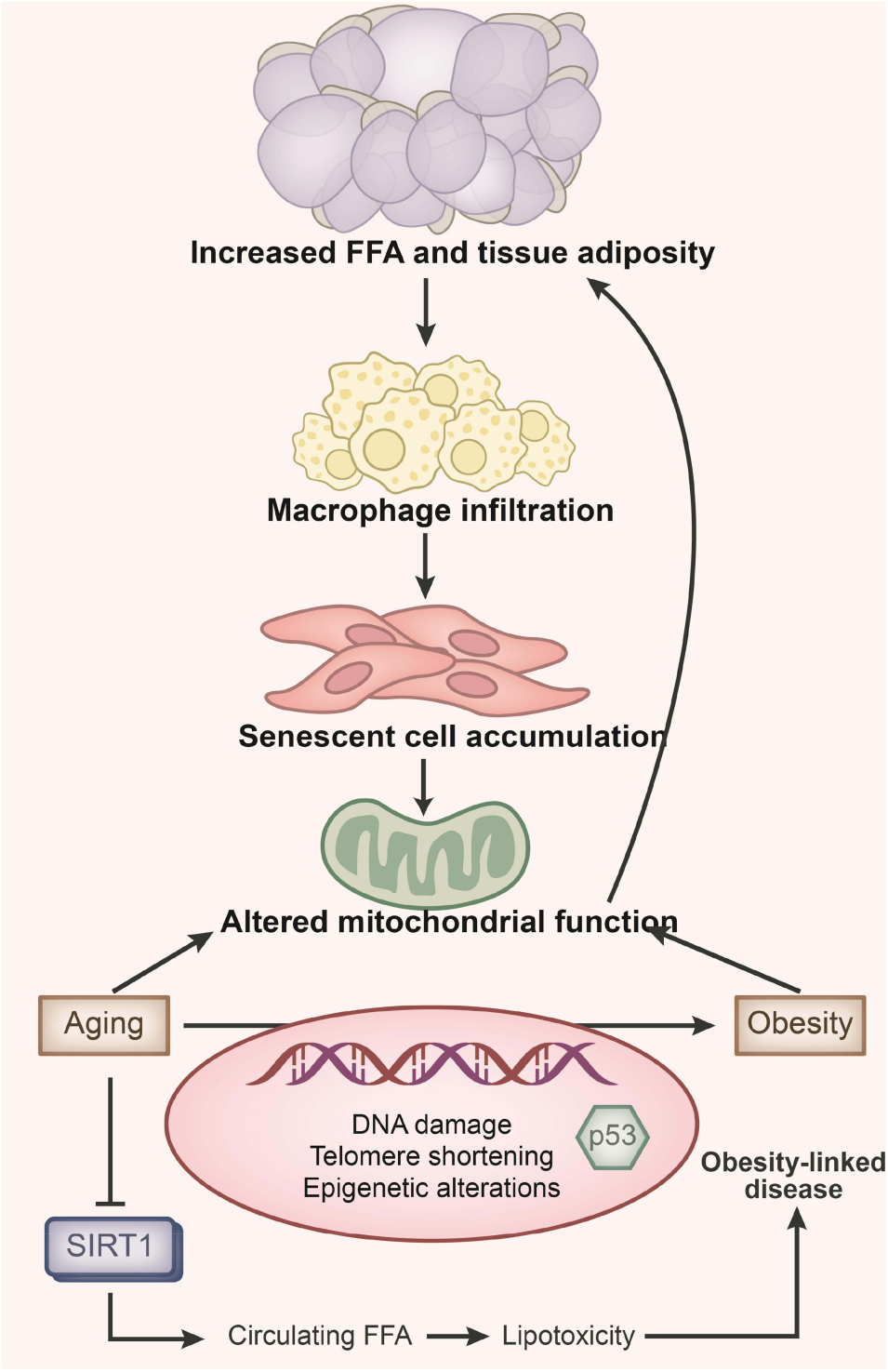

Figure 2 Mechanisms linking obesity and aging.
Notes: Created in BioRender. T, J. (2025) https://BioRender.com/9hdyuc6.
Abbreviation: FFA, Free Fatty Acids.

dysfunction, including changes in cell number, insulin responsiveness, secretory profiles, and inflammatory status,[29] a shared set of underlying mechanisms can be inferred. Therefore, similar interventions may be applicable for addressing both obesity-related dysfunctions and age-associated pathologies.[31]

The accumulation of senescent cells within adipose tissue is closely linked to the metabolic dysfunction observed in obesity. Increased adiposity leads to a higher burden of senescent cells,[35] amplifying local and systemic inflammation through the secretion of pro-inflammatory cytokines and other bioactive molecules.[33] Studies have also demonstrated that adipose tissue dysfunction associated with both obesity and aging shares common features, such as reduced cell number, diminished insulin sensitivity, altered secretory characteristics, and increased inflammatory states, collectively elevating the risk of various chronic diseases.[36]

Key Roles of Non-Coding RNA and Epigenetic Modifications in Obesity and Aging

Although the relationship between obesity and aging has been extensively studied, many molecular mechanisms remain insufficiently explored. Unexplored regulatory pathways, including the involvement of non-coding RNAs, epigenetic modifications, and changes in the microbiome, may play critical roles in the development and progression of both conditions. Research has shown that non-coding RNAs play pivotal roles in the pathology of obesity and aging. For instance, the expression of the long non-coding RNA (lncRNA) MALAT1 is significantly altered in obesity and metabolic syndrome, influencing adipocyte differentiation and function by regulating gene expression.[37] Epigenetic modifications are also essential in obesity and aging. Studies have demonstrated that changes in DNA methylation and histone modifications are closely associated with metabolic disorders related to both conditions. In obese individuals, DNA methylation levels at certain gene loci, such as *ELOVL2*, increase with age and may contribute to metabolic dysregulation.[38] DNA methylation involves the addition of a methyl group to the 5′ position of cytosine residues, catalyzed by DNA methyltransferases (DNMTs) using S-adenosylmethionine (SAM) as the methyl donor, resulting in the formation of 5-methylcytosine.

Epigenetic regulation of gene expression also plays a crucial role in normal development, aging, and the pathogenesis of OA. In healthy articular chondrocytes, the expression of most catabolic proteases remains silenced or minimally active, likely due to transcriptional repression mediated by epigenetic mechanisms such as DNA methylation and microRNAs.[39] However, in OA cartilage, various matrix-degrading enzymes, including MMP-3, MMP-9, and ADAMTS-4, are markedly elevated and are associated with promoter demethylation events. Future research should investigate these molecular mechanisms to develop novel therapeutic strategies targeting health conditions associated with obesity and aging.

In-depth studies on obesity and aging have revealed complex and multilayered interactions. First, obesity contributes to the development of age-related chronic diseases by promoting cellular senescence through oxidative stress, inflammatory responses, and metabolic disturbances, thereby advancing the aging process in adipocytes and organs such as the heart and liver. Second, obesity and aging share common features of adipose tissue dysfunction, characterized by the accumulation of senescent cells and increased secretion of inflammatory factors, ultimately exacerbating systemic inflammation. These interconnected mechanisms collectively impair metabolic health. Moreover, recent findings underscore the critical roles of non-coding RNAs and epigenetic modifications in the pathophysiological processes of obesity and aging, indicating their potential as targets for future therapeutic strategies.

Molecular Mechanisms of Obesity-Induced Aging

Research has shown that excessive nutrient and energy intake associated with obesity leads to an increase in stem cell numbers, followed by telomere shortening, cellular senescence, and accelerated aging.[40] Obesity also triggers inflammatory responses, increased DNA damage, and protein instability, all closely linked to changes in DNA methylation levels. Increased DNA methylation in obesity may contribute to the acceleration of biological aging and promote the development of age-related diseases.[41]

Mitochondrial Dysfunction and ROS

Furthermore, obesity induces mitochondrial dysfunction closely associated with the aging process. Studies have identified significant hypomethylation of the *TFAM* gene in obese individuals, which may reduce TFAM expression and impair its function. Additionally, increased methylation at the CpG site cg14926485 within the *PIEZO1* gene has been reported in obese children, potentially leading to elevated *PIEZO1* expression.[42]

ROS-induced oxidative damage plays a crucial role in age-related physiological dysfunction and loss of cellular homeostasis, leading to disease progression and mortality.[43]

The growth hormone (GH)/Insulin-like Growth Factor 1 (IGF-1) signaling pathway undergoes significant changes in obesity and contributes to cellular senescence.[44] GH, IGF-1, and IGF Binding Protein 5 (IGFBP5) have been shown to induce cellular aging in vitro.[45,46] Animal studies have indicated that GH-deficient or GH-resistant mice accumulated fewer senescent cells in adipose tissue compared to controls. However, the role of GH signaling in obesity-associated aging requires further investigation.

In obese individuals, the mTOR signaling pathway is notably activated and plays a critical role in adipocyte differentiation and insulin resistance.[47] The activation of mTOR in cellular senescence may be associated with the induction of eIF-4E expression.[48] Studies have demonstrated that overexpression of eIF-4E in mouse fibroblasts and B cells can induce cellular senescence, with mTOR significantly upregulated during the formation of senescent cells. Additionally, mTOR may influence the SASP through the induction of IL-1α expression.[49]

Psychological and Environmental Factors in Obesity

Obesity is a metabolic disorder characterized by an imbalance between energy intake and expenditure, leading to excessive energy storage in adipose tissue. Its etiology involves a combination of genetic predisposition and environmental factors. Emerging evidence indicates that psychological stress and emotional states influence dietary behaviors and metabolic responses, thereby modulating the risk of obesity.[50] Studies have demonstrated that psychological interventions, including emotion regulation, stress coping strategies, mindful eating, cognitive behavioral therapy (CBT), social support, and mind-body therapies like yoga and meditation, effectively support the regulation of eating behavior, reduction of emotional eating, and improvement of mental health.[51,52] These interventions promote healthy lifestyle changes by modulating emotions, enhancing self-control, and providing a supportive environment, thereby contributing to effective obesity management.

Telomeres and Aging

In elderly individuals, aging cardiac stem cells exhibit a pronounced SASP and diminished differentiation capacity.[53] Myocardial cells from young individuals with obesity show shorter telomeres and elevated ROS levels, closely resembling those in aged individuals.[54] These findings suggest a strong association between obesity and premature cardiac aging.

In obese mouse models, elimination of senescent cells improves cardiac diastolic function. However, whether this benefit arises from the clearance of senescent cells within cardiac tissue or from systemic effects remains unclear.[55] Obesity induces aging-like characteristics in cardiac tissue, including mitochondrial dysfunction, increased oxidative stress, and enhanced inflammatory responses.[56] Further research is needed to determine whether obesity independently induces senescence in cardiac cells.

In HFD-induced obese mice, obvious telomere-associated foci (TAF) and Aging Lipid-Induced Senescence (ALISE) have been identified in neuroglial cells, findings absent in mice fed a normal diet.[57] Additionally, significant lipid droplet accumulation in the brain has been noted in aged mice and Alzheimer's disease (AD) mouse models, indicating a potential link between brain aging and lipid metabolism.[33] Clinical observations in AD patients further support this association. These findings imply that obesity may promote brain aging by accelerating senescence and inducing pathological changes in neural tissues.[58,59]

Cellular senescence represents a response to stress-induced proliferative arrest.[60,61] Research has shown that oncogenic signals, DNA damage, and metabolic disturbances, can induce senescence. Cellular senescence leads to the upregulation of the p53/p21 and p16/RB signaling pathways and increased expression of enzymes such as beta-galactosidase.[62] These cells also produce elevated levels of metabolic byproducts, including pro-inflammatory factors, chemokines, non-coding nucleotides, and ROS.[63] Through paracrine signaling, senescent cells influence neighboring cells and reshape the local immune microenvironment,[64,65] thereby amplifying inflammatory responses, promoting immune cell recruitment, and inducing secondary senescence in adjacent cells.

Adipokines and Obesity-Induced Inflammation

Obese individuals exhibit elevated levels of inflammatory proteins, largely due to increased secretion of pro-inflammatory cytokines by excess adipose tissue. Studies have reported that the circulating levels of inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C-reactive protein, are altered in overweight and obese adults.[66–68] The predominant cellular components of adipose tissue are adipocytes, or fat cells.

Adipose tissue is a significant source of pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α, Intercellular Adhesion Molecule 1 (ICAM1), Monocyte Chemoattractant Protein-1 (MCP-1), and adipokines like LEP and adiponectin. These factors play key roles in regulating glucose metabolism, appetite, and systemic inflammation.[69] Adipose tissue is recognized as an endocrine organ comprised of adipocytes, nerve tissue, and immune cells.[70,71] It is now widely acknowledged that obesity can be classified as a state of low-grade chronic inflammation.[72]

Immune Cells and Adipose Tissue Inflammation

Various immune cells, including macrophages, T cells, B cells, and neutrophils, participate in adipose-related inflammation.[73,74] In lean individuals, adipose tissue is dominated by alternatively activated macrophages (M2), which exert anti-inflammatory effects.[75] In contrast, obesity induces a shift toward classically activated macrophages (M1), which secrete pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α. M2 macrophages typically produce IL-10, IGF-1, and TGF-β, supporting tissue repair and immune regulation.[75–79]

Obesity also alters T cell subpopulations within adipose tissue. CD8+ effector T cells and CD4+ Th1 cells are more abundant in obese individuals, contributing to macrophage recruitment and activation through Th1-associated cytokines, thereby sustaining inflammation and promoting insulin resistance.[80–82] An imbalance in Th1 and Th2 signaling influences macrophage polarization, affecting either inflammatory progression or tissue homeostasis. Additionally, B cells contribute to inflammation by promoting the activation of T cells and macrophages.[83]

Macrophages can produce MCP-1, an effective chemokine for monocytes.[84] Elevated MCP-1 levels in white adipose tissue and plasma of obese mice suggest its role as an upregulated adipokine in obesity.[85,86] Macrophages also form "crown-like structures" around necrotic adipocytes in obese adipose tissue, further amplifying the local pro-inflammatory state.[87–89]

Mechanisms of Adipokines Leptin and Adiponectin in OA

In obese individuals, adipose tissue undergoes a phenotypic shift from anti-inflammatory M2 macrophages to pro-inflammatory M1 macrophages, establishing a pro-inflammatory microenvironment.[75] Additionally, adipose tissue in obese patients secretes adipokines such as leptin and adiponectin, which are associated with the pathological changes observed in OA[90] (Figure 3). As illustrated in Figure 3, pro-inflammatory cytokines, including TNF-α, IL-1, and IL-6, promote OA progression by activating signaling intermediates such as p38 and ERK1/2, leading to upregulation of matrix metalloproteinases (MMPs) and degradation of cartilage structure. Leptin levels in OA patients are elevated compared to healthy individuals, with increased leptin content and activity observed in both articular cartilage and synovium. Notably, leptin concentrations are significantly higher in the body fluids of patients with advanced-stage OA.[91] Evidence also suggests that adipokines play a critical role in the progression of OA. LEP increases the expression of MMP-2, MMP-9, cathepsin D, and type II collagen, while reducing basic fibroblast growth factor (bFGF) in joint cartilage.[92] It also promotes expression of aggrecanases ADAMTS-4 and ADAMTS-5, with histological assessments confirming proteoglycan loss following LEP treatment.[93] LEP enhances IL-1β-induced production of MMP-1, MMP-3, and MMP-13 in human OA cartilage,[94] indicating its role as a catabolic regulator of cartilage metabolism.[95]

Adiponectin exerts complex, concentration-dependent effects on cartilage and joint homeostasis. In synovial fluid, adiponectin correlates with proteoglycan degradation and induces catabolic responses via AMPK and JNK signaling pathways, upregulating MMPs and iNOS.[96,97] However, at lower concentrations, adiponectin may promote chondrocyte proliferation and matrix synthesis, enhancing expression of type II collagen, aggrecan, Runx2, type X collagen, and alkaline phosphatase activity.[98,99] These dual effects suggest a regulatory role that varies with concentration and disease stage.[100]

Regulation of Immune Activity by Adipokines

LEP and adiponectin modulate obesity-induced inflammation by regulating immune activity. LEP modulates immune responses at various levels by stimulating monocyte proliferation and differentiation into macrophages, enhancing the

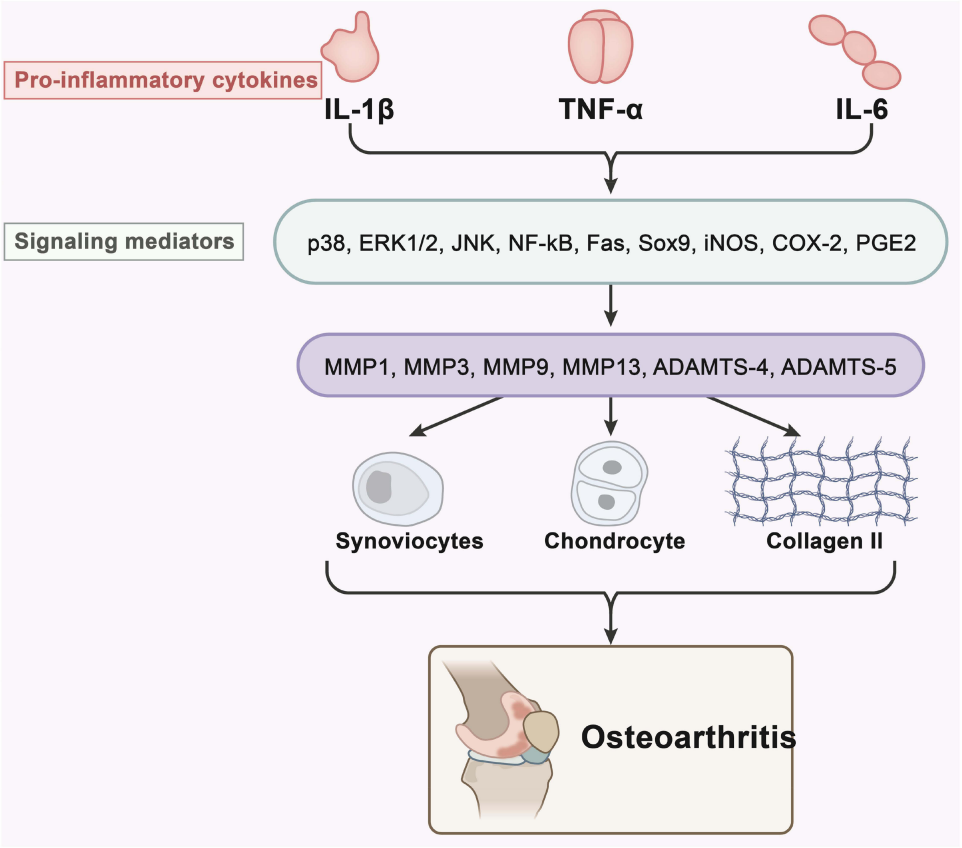

Figure 3 Effects of TNF-α, IL-1, and IL-6 on joint cartilage in OA.
Notes: Created in BioRender. T, J. (2025) https://BioRender.com/31v7ojz.
Abbreviations: IL-1, Interleukin-1; TNF-α, Tumor Necrosis Factor-alpha; MMPs, Matrix Metalloproteinases; p38, p38 mitogen-activated protein kinases (p38 MAPK); ERK1/2, Extracellular Signal-Regulated Kinase 1/2; JNK, c-Jun N-terminal Kinases; NF-kB, Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells; Fas, Fas Receptor (also known as TNFRSF6 or CD95); Sox9, SRY-Box Transcription Factor 9; iNOS, Inducible Nitric Oxide Synthase; COX-2, Cyclooxygenase-2; PGE2, Prostaglandin E2; MMP1, Matrix Metalloproteinase 1; MMP3, Matrix Metalloproteinase 3; MMP9, Matrix Metalloproteinase 9; MMP13, Matrix Metalloproteinase 13; ADAMTS-4, A Disintegrin And Metalloproteinase with Thrombospondin Motifs 4; ADAMTS-5, A Disintegrin And Metalloproteinase with Thrombospondin Motifs 5.

activation of natural killer (NK) lymphocytes and inducing pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1.[92] In LEP-deficient (ob/ob) mice, reductions in thymic mass, lymphocyte and NK cell counts, and pro-inflammatory cytokine expression highlight the immunomodulatory role of LEP. LEP receptor-deficient (db/db) rats exhibit reduced lymphocyte counts and phagocytic capability.[92] Macrophages exposed to LEP upregulate M2 surface markers while producing M1 typical cytokines (TNF-α, IL-6, IL-1), indicating that LEP regulates adipose tissue macrophage phenotype.[93] In contrast, adiponectin exerts opposing effects on the LEP system, inhibiting macrophage phagocytosis, TNF-α production, monocyte precursor differentiation, endothelial adhesion molecule synthesis, and foam cell formation.[101] Adiponectin suppresses M1 macrophage differentiation and classical activation while promoting M2 macrophage proliferation and the expression of anti-inflammatory M2 markers by reducing pro-inflammatory factors (TNF-α, IL-6).[102] Unlike LEP, adiponectin levels are inversely correlated with body weight.

Impact of Obesity on Joint Cartilage Metabolism: Accelerated Degradation and Damage

Hormones play a crucial role in the pathogenesis of OA and obesity, particularly in postmenopausal women. Estrogen decline following menopause is associated with increased incidence and severity of OA.[103,104] Estrogen has anti-inflammatory and chondroprotective effects, and its deficiency contributes to cartilage degeneration and increased joint inflammation.[105] Estrogen is also essential in regulating fat distribution and metabolism, with declining levels contributing to abdominal fat accumulation and metabolic disorders, thereby increasing OA risk.[106] Mechanisms linking obesity

and OA extend beyond mechanical load to include pro-inflammatory factors secreted by adipose tissue, such as leptin and TNF-α, which promote OA progression by activating immune responses.[107,108] Studies have shown that estrogen modulates gene expression and signaling pathways, including inhibition of the NF-κB pathway, thereby preserving cartilage integrity.[109,110] Hormone replacement therapy (HRT) may alleviate postmenopausal OA symptoms by supplementing estrogen to improve cartilage metabolism and reduce inflammation. However, its long-term use requires balancing potential risks, such as cardiovascular disease and breast cancer.[111,112]

Feedback Role and Mechanisms of Cellular Senescence in Obesity Development

Aging affects the onset of OA by influencing joint stiffness and lubrication, while also promoting early obesity through a decline in metabolic rate.[113,114]

Role of Aged Adipocyte Progenitor Cells and Insulin Resistance

Aged adipocyte progenitor cells exhibit reduced differentiation potential and influence surrounding cells through the SASP. The activins they secrete can reduce the differentiation capacity of adjacent cells, impair their insulin sensitivity, and attract immune cells, further promoting insulin resistance.[115] Through these mechanisms, senescent cells are implicated in the development of type II diabetes and obesity. The senescence response functions as an important anticancer mechanism[113] and also plays essential roles during embryonic development.[114] However, excessive accumulation of senescent cells is closely associated with various chronic diseases, such as diabetes and cardiovascular dysfunction.[116] As a result, targeting cellular senescence has emerged as a promising therapeutic strategy for age-related diseases.

Threshold Theory of Aging and the Accelerating Effect of Obesity

The threshold theory of aging proposes that senescent cells are routinely cleared by the immune system under physiological conditions. However, when the rate of senescent cell formation exceeds a certain threshold, immune clearance becomes insufficient, thereby inducing and accelerating systemic aging.[117,118] Animal studies support this hypothesis, indicating that obesity facilitates the accumulation of senescent cells to threshold levels. Transplantation of senescent cells into young mice has been shown to reduce lifespan and increase frailty, with more severe effects observed in obese models compared to normal mice.[119] These findings indicate that obesity contributes to the attainment of the senescent cell burden threshold, potentially contributing to the progression of various chronic diseases associated with aging and obesity.[120]

Inflammatory Response of Obesity-Induced Senescent Cells

Obesity induces cellular senescence, while aging further exacerbates obesity-related complications. Senescent cells influence inflammatory progression by secreting aging-associated phenotypic factors. Approximately 30% to 70% of senescent cells express pro-inflammatory factors such as TNF-α, IL-1α, IL-6, and IL-8.[121,122] Chronic low-grade inflammation driven by these factors is a key contributor to insulin resistance in obesity. Moreover, senescent cells can also secrete chemokines that attract macrophages and neutrophils to sites of senescence within adipose tissue.[123,124] Studies have shown that macrophages are more likely to accumulate in visceral adipose tissue, further enhancing insulin resistance.

Bone Marrow Factors and Adipose Tissue Inflammation

Functional changes in adipose-derived stem cells (ASCs), rather than numerical changes, play a crucial role in the progression of obesity.[125] Obesity promotes immune cell accumulation in the bone marrow and the release of Grancalcin (GCA) into circulation. GCA interacts with the Prohibitin-2 (PHB2) receptor on adipocytes, activating the PAK1-NF-κB signaling pathway and inducing innate and adaptive immune responses. This mechanism highlights the critical role of the bone marrow-derived factor GCA in inflammation and insulin resistance induced by obesity.[126]

During aging, senescent cells impact tissue function by secreting SASP factors. For instance, aging skeletal muscle fiber-associated progenitor cells (FAPs) show high expression of the cyclin-dependent kinase inhibitor p16 and genes related to chemokine signaling and cytokine-receptor interactions.[127] In obesity, single-cell RNA

sequencing has identified a pro-inflammatory phenotype in ASCs. In the early stages of obesity, ASCs recruit T cells into adipose tissue through CCL5. TNF-α stimulates obese ASCs to secrete CCL5 via the NF-κB pathway. Bone marrow transplantation studies confirm that ASC-derived CCL5 is essential for T cell accumulation in obese adipose tissue. In obese individuals, the chemotactic effect of ASCs depends on CCL5 upregulation, highlighting their key role in mediating adipose inflammation.[128]

Impact of Epigenetic Modifications

ASCs in obese individuals exhibit aging characteristics that impair adipogenesis, contributing to hypertrophic obesity and the progression of metabolic disorders. The related signaling pathways (Wnt, Hedgehog (Hh), and Notch) are overactivated in obesity, inhibiting the process of fat formation and promoting adipocyte hypertrophy and aging.[129] Obesity also exacerbates tissue degeneration and impairs the integrity and regenerative potential of mesenchymal stem/stromal cells (MSCs). Recent studies have shown that obesity mediates dysfunction in human adipose-derived MSCs through epigenetic alterations in 5-hydroxymethylcytosine (5hmC), particularly affecting genes involved in mitochondrial function.[130]

Cellular senescence impairs the function of adipose-derived stem cells through paracrine signaling. Recent studies have revealed distinct patterns of whole-genome DNA methylation in senescent cells.[131,132] In OA patients, similar changes have been confirmed in chondrocytes, partially attributed to variations in the expression of Dnmts (methylation) and Tet (demethylation) enzymes involved in methylation and demethylation processes, respectively.[133–137] Senescent cell accumulation in adipose tissue is more pronounced in females, with β-galactosidase activity positively correlating with pro-inflammatory cytokine expression.[138] Animal studies show increased senescent cells primarily in visceral, rather than subcutaneous, fat of obese mice.[139] Intraperitoneal injection of senescent cells leads to their localization in visceral adipose tissue, indicating a high susceptibility of adipose progenitor cells to senescence under obese conditions.[140] MSCs derived from obese individuals show reduced proliferation and upregulated aging markers.[141] The burden of senescent cells in adipose tissue correlates with fat mass and is associated with metabolic dysfunction.[35] Potential inducers of cellular senescence in obesity include oxidative stress, hyperinsulinemia, hyperglycemia, fatty acids, and telomere shortening.[142] HFD-fed mice exhibit substantial accumulations of senescent CD4+ T cells in visceral adipose tissue, contributing to local inflammation via elevated pro-inflammatory factor expression.[143,144] Transplanted immune cells migrate to the visceral fat of normal lean mice and induce insulin resistance, similar to adipocyte transplantation effects.[145] These findings suggest a mutually reinforcing relationship between immune cell senescence and obesity. In elderly individuals, satellite cells in muscle tissue are prone to senescence, and their removal can prevent age-related sarcopenia.[146] Obesity-induced fat accumulation around muscle further elevates muscle aging markers.[147] Further research is required to clarify the relationship between obesity and muscle senescence and its impact on muscle metabolic activity.

In summary, senescent cells play a crucial role in the development and progression of obesity. Understanding the feedback effects of aging on obesity may help in developing targeted treatment strategies to alleviate the burden of chronic diseases triggered by obesity.

Potential Applications of Obesity Intervention in Treating Age-Related Diseases

A direct correlation between obesity and cellular senescence suggests that targeting obesity may serve as a novel approach to treating age-related diseases. Obesity induces various cellular stress responses, leading to cellular senescence and the accumulation of senescent cells in adipose tissue and other organs (Figure 4). As depicted in Figure 4, obesity-associated cellular senescence accumulates in the liver, adipose tissue, and pancreatic β-cells, impairing lipid storage, metabolic function, and cellular proliferation. The resulting dysfunction contributes to insulin resistance and glucose intolerance, two key features of obesity-associated metabolic disorders. This section explores potential strategies, including exercise and dietary restriction, pharmacological approaches for clearing senescent cells, the effects of caloric restriction, and the application of new technologies.

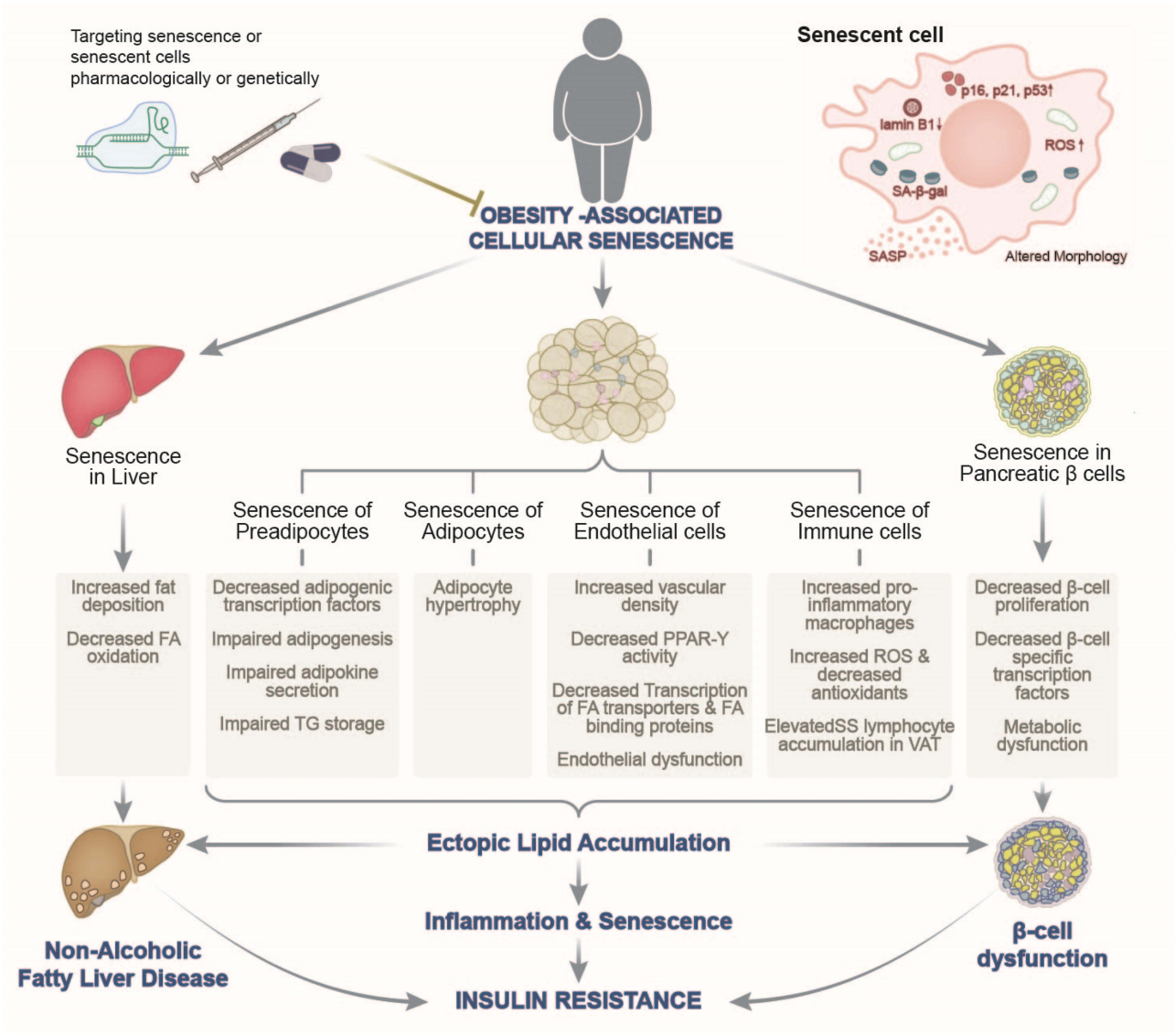

Figure 4 Obesity-related cellular senescence responses.
Notes: Characteristics of senescent cells such as increased expression of $p16^{INK4a}$, $p21^{CIP1}$, p53 proteins, elevated lysosomal senescence-associated β-galactosidase activity, altered cell morphology, increased ROS levels, and enhanced SASP. Accumulation of senescent cells in organs such as the liver, adipose tissue, and pancreatic β-cells play a critical role in the complications associated with obesity. Impacts of cellular senescence in adipose tissue impair lipid storage capabilities, increase pro-inflammatory macrophages, and disrupt adipogenesis; in hepatocytes, it leads to reduced capacity to oxidize and metabolize fatty acids, resulting in excessive lipid accumulation; in pancreatic β-cells, it causes reduced proliferative ability and metabolic dysfunction, making obesity-related cellular senescence a primary cause of insulin resistance and impaired glucose tolerance. Created in BioRender. T, J. (2025) https://BioRender.com/nayo8s4.

Effects of Exercise and Dietary Restriction on Aging

Studies have shown that exercise effectively inhibits the accumulation of senescent cells in HFD-fed mouse models[148] and can mitigate obesity-induced telomere shortening.[149] However, the impact of exercise on existing senescent cells requires further investigation. Both dietary restriction and exercise-induced caloric restriction can significantly reduce the accumulation of senescent cells in organs such as the kidneys, ovaries, and heart.[150] Notably, the elimination of senescent cells using CAR T cells targeting urokinase-type plasminogen activator receptor (uPAR) significantly enhanced glucose tolerance and exercise capacity in aged mice.[151] Additional studies have shown that the effects of high-intensity interval exercise (HIIE) on cellular senescence are linked to acute inflammatory responses. Exercise-induced muscle inflammation recruits immune cells to clear senescent cells and promote tissue regeneration, suggesting that inflammation plays a crucial role in exercise-induced cellular senescence.[152] In summary, exercise and dietary adjustments not only inhibit

the accumulation of senescent cells but also improve obesity- and age-related metabolic dysfunctions through various mechanisms. These findings provide essential scientific evidence for future intervention strategies.

Senescent cells have emerged as therapeutic targets for obesity and diabetes.[35] In obese animal models, the removal of senescent cells significantly improved metabolic conditions. Although animal models can partially mimic OA-related pathological changes, they fail to fully replicate human cartilage structure and responses, potentially leading to discrepancies in therapeutic efficacy. More physiologically relevant models, such as tissue-engineered constructs and organoids, are needed to better simulate OA pathogenesis in humans. Based on this principle, pharmaceutical strategies targeting senescent cells are being explored and developed. These therapies primarily target the senescent cell anti-apoptotic pathways (SCAPs), promoting selective apoptosis and clearance of senescent cells. In obese mice, the genetic removal of cells expressing high levels of $p16^{Ink4a}$ (a marker of senescent cells) significantly improved insulin resistance and reduced fat accumulation. Additionally, the combination of dasatinib and quercetin demonstrated efficacy in eliminating senescent cells.[153] In vitro studies demonstrated that treating human adipose tissue cells with dasatinib and quercetin reduced the burden of senescent cells and decreased the secretion of inflammatory markers, including IL-6, IL-8, GM-CSF, and MCP-1.[154]

Among lifestyle-based interventions, caloric restriction and protein supplementation remain practical and effective strategies for obesity management.[155] Caloric restriction typically involves a daily reduction of 500–1000 kcal, with a goal of losing approximately 0.5 kg per week. Over six months, this approach results in an average weight loss of 8–10%, equivalent to 8–10 kg for most patients.[156] High-protein diets represent another effective approach, as they prolong satiety, help regulate portion size, and suppress hormones involved in lipogenesis. Excess dietary protein is not readily stored as fat but is instead metabolized for energy or excreted. Beyond its metabolic benefits, dietary protein also enhances the plasticity of white adipose tissue and improves obesity-related symptoms induced by an HFD.[157,158]

Effects of Pharmacotherapy on Aging

Advancements in molecular biology and obesity research have facilitated the development of novel targeted pharmacological therapies. Imcivree, a peptide-like melanocortin-4 receptor (MC4R) agonist, promotes fat consumption by activating the MC4R signaling pathway, thereby reducing patient body mass index (BMI). The emergence of nanomaterials has enabled precise targeting of adipose depots. For example, the use of Polyamidoamine Generation 3 (P-G3) nanomaterial has been shown to reduce the body weight by about 20% during the experimental period, suggesting significant potential clinical applications for P-G3.[159] Deletion of the protein kinase cAMP-dependent type II regulatory subunit alpha (Prkar2a) gene in experimental subjects has shown a marked decrease in appetite and an increase in physical activity.[160] Furthermore, CRISPR-based activation of enhancers or promoters of the Sim1 and MC4R genes has effectively treated obesity caused by haploinsufficiency in mouse models.[161]

Bariatric surgery remains the most effective treatment for obesity. Bariatric procedures such as gastric banding, sleeve gastrectomy, intragastric balloon placement, and gastric bypass result in substantial weight loss and rapid metabolic improvements.[162,163]

In summary, obesity induces various cellular stress responses, leading to cellular senescence and the accumulation of senescent cells in adipose tissue and other organs. Although senescent cells constitute only a small proportion of any tissue, their secretion of SASP factors significantly contributes to tissue dysfunction. Caloric restriction and other weight loss strategies the aging process, while senescent cell clearance mitigates obesity-induced tissue damage. Therefore, targeting senescent cells represents a promising therapeutic approach to delay, prevent, or treat the adverse consequences of obesity.

The Role of Aging in the Pathogenesis of OA and Its Epigenetic Regulation

Effects of Aging on Chondrocytes and Joint Tissues

Key Role of Chondrocyte Aging in OA

OA is an age-related joint disease characterized by cartilage degeneration, bone sclerosis, and chronic low-grade inflammation within the joint.[164] Chondrocyte aging is a primary factor contributing to the structural and functional deterioration of cartilage, driven by oxidative stress, inflammatory signaling, epigenetic alterations, and diminished

proliferative capacity. Oxidative stress leads to mitochondrial dysfunction, increased ROS levels, and mitochondrial DNA (mtDNA) damage, further amplifying ROS production and promoting chondrocyte aging.[165]

In aging chondrocytes induced by TBHP and in mouse OA cartilage, Sirt4 expression is significantly reduced, accelerating chondrocyte aging and degradation, while overexpression of Sirt4 protects these cells.[166] Additionally, ECM stiffness promotes chondrocyte senescence by suppressing HDAC3 expression, enhancing Parkin acetylation, and triggering excessive mitophagy through dysregulated mitochondrial quality control, thereby accelerating OA progression.[167]

Epigenetic mechanisms, including DNA methylation and histone modification, contribute to chondrocyte senescence and are exacerbated by mechanical and oxidative stress.[168]

In osteoarthritic cartilage, DPP-4 positive chondrocytes exhibit typical aging and OA phenotypes, characterized by reduced expression of anabolic genes and increased expression of hypertrophic markers and matrix-degrading enzymes.[169]

In summary, cartilage cellular senescence is influenced by telomere shortening, genomic damage, oxidative stress, and epigenetic changes, and is aggravated by biomechanical loading and adverse microenvironmental conditions such as hypoxia, low pH, and high osmotic pressure. Once aged, chondrocytes exhibit increased expression of beta-galactosidase, shortened telomeres, and inflammaging characteristics.

Effects of Telomere Shortening and DNA Damage

Telomere shortening is a primary hallmark of aging and a contributing factor to cellular senescence. In response to telomere erosion, two major pathways are activated: the DDR-dependent pathway P53-$P21^{CIP1}$-retinoblastoma protein (pRB) and the DDR-independent pathway $P16^{INK4A}$-pRB.[170] In OA research, Martin et al confirmed that age-related SAf-Gal activity increases with age, while mitotic activity and average telomere length decrease in chondrocytes, indicating replicative senescence in vivo.[171]

Effects of ROS Generation and Mitochondrial Dysfunction on Chondrocytes

Chondrocytes reside in a low-oxygen environment but can generate ROS, which abnormally increases under pathological conditions, thereby accelerating the degradation of cartilage tissue. Elevated ROS levels upregulate MMPs and induce the expression of inflammatory factors such as NO synthase, IL-6, IL-1, and TNF-α, exacerbating the inflammatory pathology of OA. TNF-α and IL-1, pivotal in OA progression, degrade the ECM components and suppress their repair, further promoting joint degeneration. Thus, ROS serve as key drivers disrupting the balance between catabolic and anabolic signaling in cartilage, leading to progressive matrix degradation.[172]

Joint degeneration affects the majority of individuals over 65 years of age.[173–177] Beyond cartilage, aging affects other joint tissues, including the synovium, subchondral bone, and muscles, contributing to alterations in joint loading. Studies of joint chondrocytes and other cells have shown that aging cells enhances oxidative stress, which promotes cellular senescence and mitochondrial dysfunction. Mitochondrial damage and cell death are closely associated with OA progression. A reduced reparative capacity in aging chondrocytes has been linked to altered expression of cell surface receptors.[178–180]

A shift toward ALK1 signaling increases Smad1/5/8 phosphorylation, enhancing chondrocyte hypertrophy, terminal differentiation, and matrix degradation, such as MMP-13.[181]

Roles of Autophagy and Oxidative Stress in OA

The progression of OA is associated with increased senescent cells in joint tissues. The SASP has been linked to cartilage degradation and OA development. A key feature of SASP is the enhanced secretion of bioactive molecules such as chemokines, cytokines, proteases, and growth factors by aging cells. These molecules induce a range of pathological responses in the surrounding microenvironment, including inflammation, growth arrest, and tumorigenesis.[182] Mechanistically, mTOR regulates SASP factor expression by modulating the translation of MAPKAPK2 and IL-1α. Inhibition of mTOR by rapamycin has been shown to reduce SASP-related factor production.[153,183] SASP factors, including IL-6, IL-17, IL-1β, oncostatin M, and TNF, further contribute to inflammation, osteophyte formation, and ECM degradation.[63]

In aged individuals, common inflammatory mediators such as IL-1β and TNF-α, along with chemokines, contribute to systemic inflammation, activating the NF-κB signaling pathway in synovial and cartilage cells.[184] Innate inflammatory signals also play a role in OA pathogenesis, involving damage-associated molecular patterns (DAMPs), alarmins

(S100A8 and S100A9), and complement components.[185–187] According to the literature, DAMPs and alarmins regulate the expression of MMPs and ADAMTS through TLR or NF-κB signaling pathways. Furthermore, complement activation can be triggered by DAMPs, ECM fragments, and apoptotic cell debris.[188,189] Recent studies have further elucidated that systemic inflammation can reprogram cartilage cells through the NF-κB pathway, the ZIP8/Zn+/MTF1 axis, and autophagy mechanisms, leading to hypertrophic differentiation and catabolic activity.[190–198] Pathway analyses using the Kyoto Encyclopedia of Genes and Genomes (KEGG) have identified key inflammatory signaling, including cytokine-induced mitogen-activated protein (MAP) kinases, NF-κB activation, and oxidative phosphorylation, as central contributors to OA pathogenesis.[199]

Studies have shown that chondrocytes facilitate intercellular communication through the production of EVs. Compared to healthy individuals, the levels of EVs are significantly elevated in OA patients and induce a senescent state in neighboring cells.[200] Cytokines can upregulate the expression of MMPs family members. Similar to cytokines, MMPs such as MMP-13 (also known as collagenase-3) and ADAMTS, like ADAMTS-5, are secreted into the ECM. The degradative activity of MMPs and ADAMTS can degrade ECM proteins in cartilage, including proteoglycans, collagen, and fibronectin. The loss of the cartilage ECM is a key early feature of OA, further suggesting that the senescence of chondrocytes and other synovial joint cells is a driving factor in the pathogenesis of OA.

Autophagy is one of the regulatory mechanisms of cellular senescence and is closely associated with the development of OA. Both clinical and experimental studies have demonstrated a marked decline in autophagy in OA cartilage.[201] Most evidence suggests that autophagy exerts protective effects by preventing chondrocyte apoptosis. However, other studies have reported that reduced autophagy is accompanied by increased cell death.[202,203] Additionally, upregulation of autophagy inhibits glucocorticoid-stimulated apoptosis in chondrocytes, paradoxically representing another form of cell death commonly observed in various pathological conditions. These findings indicate that the role of autophagy is context-dependent and influenced by donor age, OA stage, and the nature of autophagic activation.

During aging, trauma, or stress, autophagy is suppressed while oxidative stress increases, leading to chondrocyte senescence and enhanced SASP secretion. Through paracrine signaling, senescence-associated factors propagate inflammation and aging to adjacent cells, promoting OA progression. Additionally, DAMPs in cartilage amplify oxidative stress via ROS, further intensifying inflammatory responses and cellular aging[204] (Figure 5).

Epigenetic regulation plays a crucial role in OA. Obesity is a significant risk factor affecting the onset and progression of OA.[205] In obese individuals, excessive joint load, especially on the knees, can lead to cartilage damage and promote chondrocyte apoptosis. Both acute mechanical injury and chronic matrix degradation can trigger OA in obese patients. Furthermore, adipokines such as LEP, adiponectin, TNF-α, and IL-6 alter the metabolic activity of cartilage cells, promoting degeneration and OA development. OA driven by such metabolic disturbances is commonly referred to as metabolic OA OA.[206]

With the aging of the baby boomer generation, OA prevalence in the United States is projected to rise from 30 million to 67 million cases by 2030, with over half of patients aged 65 or older.[207] OA not only causes pain and limited mobility but also imposes an annual economic burden of $27 billion on the US healthcare system and results in substantial productivity losses.[208] Globally, significant regional differences exist in OA research. The European League Against Rheumatism (EULAR) prioritizes multicenter clinical trials to investigate disease mechanisms and therapeutic strategies. In contrast, research in Asia, particularly in China and Japan, emphasizes lifestyle, diet, and weight management, with growing attention to population-specific approaches. Understanding the role of aging in the development and progression of OA is critical for disease management and the development of new therapies. As illustrated in Figure 6, a hallmark of the SASP is the secretion of pro-inflammatory cytokines such as IL-6, IL-17, IL-1β, oncostatin M, and TNF-19,24. Several SASP factors induce OA-related changes, including inflammation, bone growth, and ECM degradation.[172] Age-related stress increases the accumulation of senescent cells, which in turn promote OA development by triggering inflammatory responses and damaging the cartilage matrix. The pathogenesis of OA involves coordinated activity among multiple pathways, including mTOR, IL-6-STAT3, and EVs, which collectively promote cartilage degeneration and inflammatory responses. Epigenetic modifications influence gene expression and chondrocyte fate, further shaping disease initiation and progression.

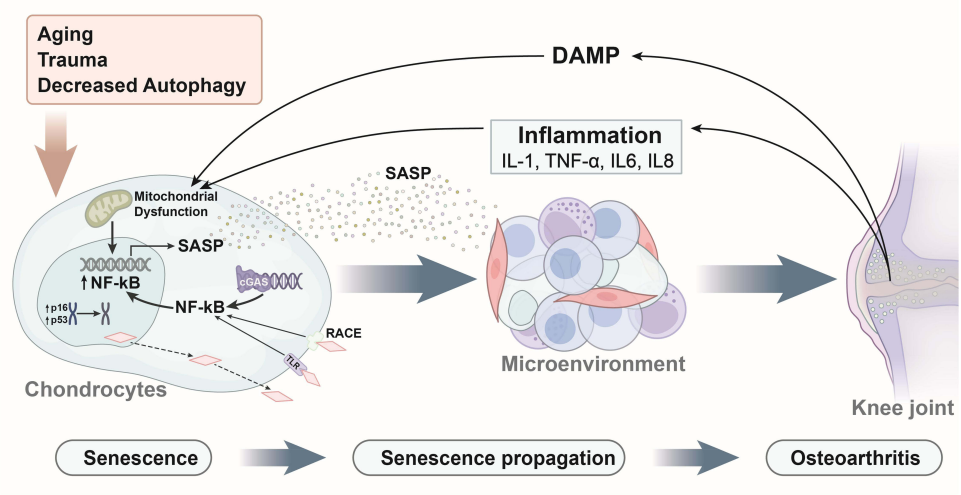

Figure 5 Interrelationships between autophagy, aging, and inflammation in OA onset.
Notes: Created in BioRender. T, J. (2025) https://BioRender.com/8ztygh2.
Abbreviations: SASP, Senescence-Associated Secretory Phenotype; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; DAMP, Damage-Associated Molecular Pattern; IL1, Interleukin-1; TNFα, Tumor Necrosis Factor αlpha; IL6, Interleukin-6; IL8, Interleukin-8.

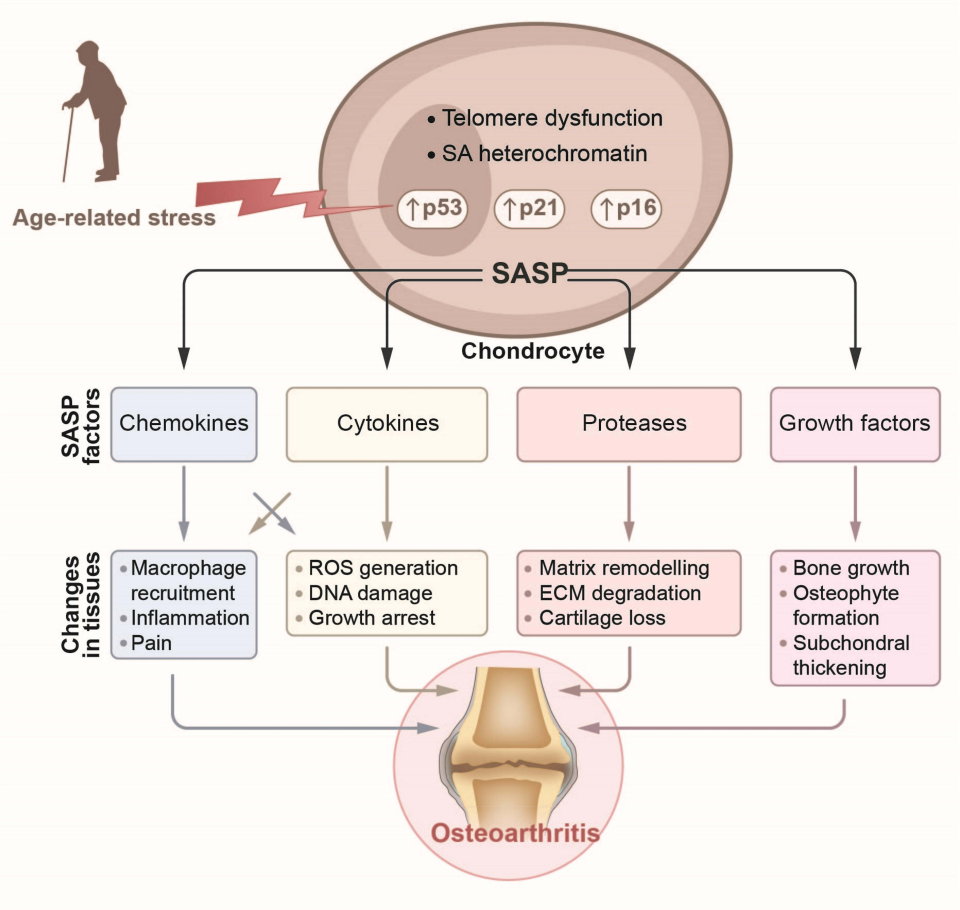

Figure 6 Relationships among age-related stress, senescence, and OA.
Notes: Age-related stress including DNA damage, Oxidative stress, Replicative senescence, Excessive mechanical loading, Mitochondrial dysfunction; Chemokines including CCL2, CCL4, GROα; Cytokines including IL-1, IL-6, IL-7, IL-8, OSM, GM-CSF, TNF; Proteases including MMP1, MMP3, MMP10, MMP13, ADAMTS5, ADAMTS7; Growth factors including TGFβ, IGFBP. Created in BioRender. T, J. (2025) https://BioRender.com/8w1yvb9.

https://doi.org/10.2147/JIR.S514521

Role of Epigenetic Mechanisms in OA Pathogenesis

Research has shown that certain lncRNAs can influence cartilage cell expression by regulating the changes in MMPs and ADAMTS.[209] For instance, Liu et al found that lncRNA-CIR can inhibit the expression of MMP-13 and ADAMTS-5, while promoting the synthesis of type I and II collagen and proteoglycans, ultimately mitigating cartilage degradation in OA.[209] MMPs are involved in the degradation of various matrix components in cartilage tissue, such as glycosaminoglycans and laminins, contributing to the progression of OA. HOTAIR (HOX transcript antisense intergenic RNA), has been implicated in promoting cartilage degradation. Knockdown of HOTAIR reverses matrix breakdown and reduces ECM loss, potentially by modulating the Wnt/β-catenin signaling pathway.[210] Similarly, the lncRNA Nespas has been shown to decrease the expression of type II collagen and increase the expression of MMP2 and MMP13 in OA, suggesting its potential as a prognostic marker for OA progression.[211]

Research on circRNAs has revealed their emerging importance in OA pathophysiology. CircANKRD36 has been shown to protect chondrocytes from IL-1β-induced apoptosis and inflammation.[212] Acting as a molecular sponge, circANKRD36 sequesters miR-599, thereby enhancing the expression of CASZ1, a transcription factor that suppresses chondrocyte apoptosis and inflammation. Conversely, circNFKB promotes OA development by activating the NF-κB pathway through its interaction with the ENO1 protein.[213]

Employing specific strategies to reduce the expression or inhibit the activity of specific proteases is one of the important therapeutic approaches to delay or inhibit the progression of OA. Epigenetic changes enable cells to rapidly respond to environmental variations. While recent advances in epigenomic technologies have resolved many technical and analytical challenges, substantial obstacles remain, particularly in distinguishing the causal relationships between specific epigenetic modifications and changes in gene expression patterns. Given the reversible nature of epigenetic modifications, further elucidation of their roles in OA pathogenesis could facilitate the development of targeted therapeutics aimed at preventing or slowing disease progression.

Altered levels of numerous epigenetic markers have been observed in OA tissues. Recent evidence suggests that OA-associated genetic variants may exert their effects through epigenetic regulatory elements, influencing the disease onset and progression. Future research should expand in both scale (increased sample sizes) and depth (multi-dimensional metrics). Analyses should extend beyond adult samples to include developmental tissues, such as fetal specimens, to capture early-stage regulatory changes relevant to OA. Furthermore, linking these epigenetic data with OA genetic risk loci is essential to elucidate the foundations of epigenetic influence and identify potential therapeutic targets. Lastly, integrating machine learning and artificial intelligence technologies with genomic, epigenetic, metabolomic, proteomic, and imaging data offers a comprehensive framework for elucidating OA pathogenesis and enables patient stratification and individualized treatment strategies.

As shown in Figure 7, OA is a multifactorial disorder influenced by aging-related inflammation and cellular dysfunction. In older individuals, classical inflammatory mediators such as IL-1β and TNF-α, along with chemokines, contribute to systemic inflammation, activating the NF-κB signaling pathway in synovial and cartilage cells. Innate inflammatory signals, including DAMPs, alarmins (S100A8 and S100A9), and complement, further contribute to OA pathogenesis. As shown in Figure 7, aging promotes the molecular mechanisms and progression of OA through inflammatory activation and cellular dysfunction. Inflammation is a well-recognized driver of OA progression, with pro-inflammatory cytokines such as TNF and IL-1 acting through the stimulation of proteases, NO, and prostaglandin synthesis. However, therapies targeting TNF or IL-1 have shown only moderate effectiveness in OA, suggesting the involvement of additional inflammatory pathways. Alarmins, a group of endogenous molecules released into the extracellular space following trauma or cell activation, represent one such alternative mechanism. These extracellular alarmins initiate innate and adaptive immune responses, thus triggering inflammation.

In summary, chondrocyte senescence, angiogenesis, and oxidative stress are potential mechanisms through which aging contributes to OA. Autophagy and epigenetic regulation further highlight the multifactorial nature of OA pathogenesis. These mechanisms interact and collectively drive the onset and progression of OA. A deeper understanding of these mechanisms is essential for identifying effective therapeutic targets. Future research should expand in scope and depth, integrating machine learning and artificial intelligence technologies to more comprehensively understand the pathogenesis of OA and to develop personalized treatment approaches.

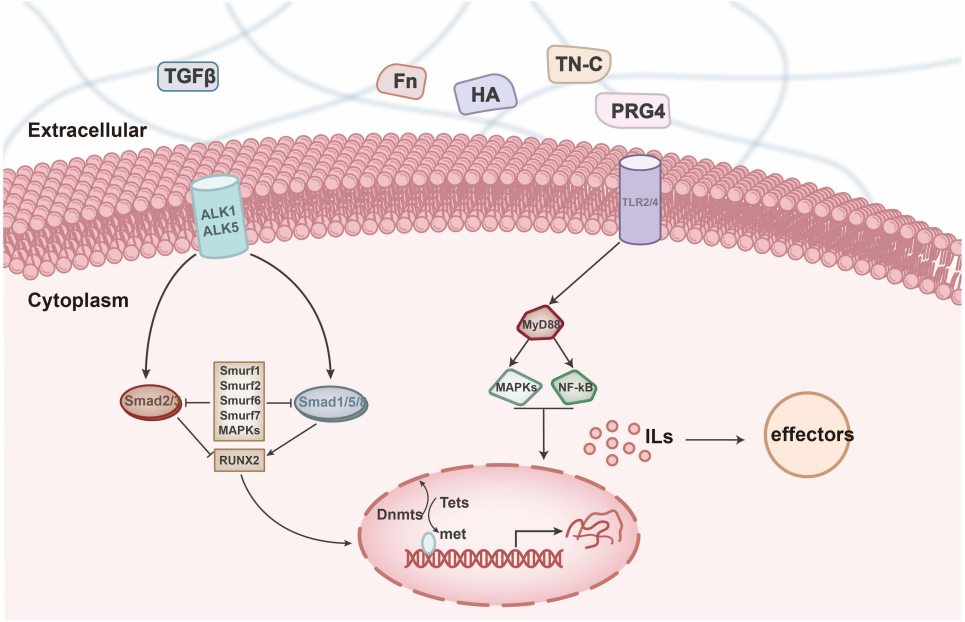

Figure 7 Molecular mechanisms of OA mediated by aging.
Notes: Created in BioRender. T, J. (2025) https://BioRender.com/4dan27d.

Obesity-Mediated Epigenetic Regulation and the Pathogenesis of OA

Previous research has identified OA as a systemic metabolic disorder. Both epidemiological and biological research support the concept of metabolic OA, a subtype associated with metabolic syndrome or cumulative metabolic dysfunction.[214] Obesity induces the formation and accumulation of senescent cells in various organs, including adipose tissue,[215,216] indicating a potential mechanistic link between aging and obesity. Obesity leads to multiple changes in adipose tissue, including increased release of pro-inflammatory factors.[217] In obese individuals, adipose tissue may become the largest organ in the body,[218] serving not only as an energy reservoir but also as an active endocrine organ.[219]

Different adipose tissue depots exert varying effects on obesity and aging. In the early stages of obesity, fat primarily accumulates in subcutaneous tissue, with subcutaneous expansion closely associated with insulin resistance. In contrast, increased visceral adiposity has been identified as a critical risk factor for chronic metabolic diseases.[220] Studies have confirmed that visceral fat accumulation leads to a higher incidence of type 2 diabetes and increased mortality rates.[221] Compared to subcutaneous fat, visceral fat exhibits a significantly greater capacity to secrete pro-inflammatory cytokines and chemokines.[222]

Recent studies have increasingly emphasized the critical role of adipokines in the initiation and progression of OA. Obesity has emerged as a major and potentially preventable risk factor for OA. Previous studies have demonstrated a strong association between knee OA and obesity.[223] The relationship between obesity and OA has been well established: each 5-unit increase in BMI corresponds to a 35% higher risk of developing OA. Conversely, a 2-unit reduction in BMI lowers OA risk in women by up to 50%, and losing 10% or more of body weight significantly improves clinical symptoms.[224,225]

Role of Adipokines in OA Pathogenesis

OA is a joint disease associated with degenerative changes, inflammation, and aging. Mechanical stress and synovial inflammation jointly promote the degradation of the ECM in cartilage, ultimately compromising cartilage integrity. Obese individuals may suffer from OA due to excessive mechanical stress on weight-bearing joints such as the hips and knees, leading to total joint replacement.[223] However, clinical studies have shown that not all obese individuals exhibit OA progression, and high OA prevalence is also observed in non-weight-bearing joints such as the hands and shoulders. These findings suggest that obesity influences OA pathogenesis not only through mechanical overload but also via systemic inflammation and immune dysregulation mediated by adipokines.[226]

Adipokines could serve as therapeutic targets for OA, particularly in obese patients.[227] Recent studies have suggested that intrajoint adipokine signaling pathways may become potential targets for OA treatment. LEP levels are significantly elevated in obese individuals and may be linked to obesity-induced OA.[95] Visfatin mediates OA pain in a dose-dependent manner by stimulating the expression and release of nerve growth factor (NGF) in chondrocytes.[228] Adiponectin levels are higher in OA patients than in healthy individuals.[229] Resistin, an adipocyte-specific hormone, forms a critical link between inflammation, obesity, and OA.[230] OA patients exhibited significantly higher serum resistin levels compared to controls.[231]

Obesity increases the secretion of pro-inflammatory mediators from adipose tissue, including adiponectin, LEP, resistin, IL-6, and TNF-α. Adiponectin, LEP, and resistin play key roles in the inflammatory process and also significantly influence the metabolic regulation of chondrocytes, osteoblasts, osteoclasts, and MSCs, collectively impacting the development and progression of OA.[232] The IL-6-STAT3 signaling pathway can induce premature senescence in normal human fibroblasts, potentially triggering a bystander effect that promotes secondary senescence and SASP expression in neighboring cells.[233] A hallmark of SASP is the increased secretion of bioactive molecules such as chemokines, cytokines, proteases, and growth factors by senescent cells, which can induce inflammation, growth arrest, and tumorigenesis in the surrounding microenvironment.[182]

Obese individuals and animals exhibit elevated levels of TNF-α, IL-1β, and IL-6, primarily produced by macrophages in adipose tissue. These cytokines regulate adipocyte proliferation and apoptosis through autocrine and paracrine mechanisms, promote fat breakdown, inhibit lipid synthesis, and reduce blood lipid levels.[227]

In OA patients, elevated levels of TNF-α, IL-1, and IL-6 have been observed in the synovial fluid, synovium, subchondral bone, and cartilage, underscoring their significant roles in the pathogenesis of OA.[234] These cytokines directly regulate the degradation of cartilage matrix and bone resorption and can induce the production of other cytokines, indirectly causing OA through the modulation of adiponectin and LEP release.[107] Studies have shown that IL-6 levels increase with age and are closely associated with the progression of OA.[235]

Chemerin is expressed in adipocytes and chondrocytes. Although research on its role in OA is limited, it is hypothesized that its regulation of pro-inflammatory functions plays a critical role in the initiation and progression of OA.[236] Vaspin, primarily derived from visceral adipose tissue and also expressed in joint tissues, exhibits anti-catabolic and anti-inflammatory properties, acting as a potential protective adipokine in OA.[237] Visfatin-1, found in synovium and cartilage, shows significantly elevated serum levels in OA patients.[238] As shown in Figure 8, levels of pro- and anti-inflammatory mediators vary with age. In lean individuals, immune cell infiltration is limited, whereas overweight or obese individuals with OA display increased immune cell presence, aggravating inflammation and accelerating disease progression.

Pathological changes induced by aging stem cells play a significant role. Under steady-state conditions, joint cartilage relies on the self-repair mechanisms of chondrocytes and the autonomous and non-autonomous functions of MSCs. Compared to embryonic stem cells and induced pluripotent stem cells, MSCs display more limited differentiation potential.[239] MSCs possess self-renewal capabilities and are recognized for their high osteogenic and adipogenic potential. Basic research has shown that MSC-derived exosomes enhance cartilage protection by upregulating type II collagen and proteoglycans, suppressing MMP-13, ADAMTS5, and iNOS expression, preventing chondrocyte apoptosis, and reducing macrophage activation.[240] Clinical trials have shown that MSC treatment can alleviate inflammatory states and reduce pain symptoms in OA patients with minimal adverse reactions.[241]

The ECM of chondrocytes functions as a mechanical barrier and mitigates environmental damage, thereby preserving cartilage integrity.[242] During inflammation or cartilage injury, fibronectin (Fn) in the cartilage ECM undergoes proteolytic cleavage, releasing fibronectin fragments (Fn-fs) into the joint microenvironment. These fragments interact with receptors (integrins and TLRs) and activate various signaling pathways, increasing the expression of proteases (uPA, MMPs, and ADAMTS). The resulting enzymatic activity contributes to ECM degradation, establishing a self-perpetuating cycle of inflammation and cartilage breakdown.

Low-grade inflammation has emerged as a central mechanism linking obesity, aging, and metabolic syndrome, all of which are established risk factors for OA development and progression.[243]

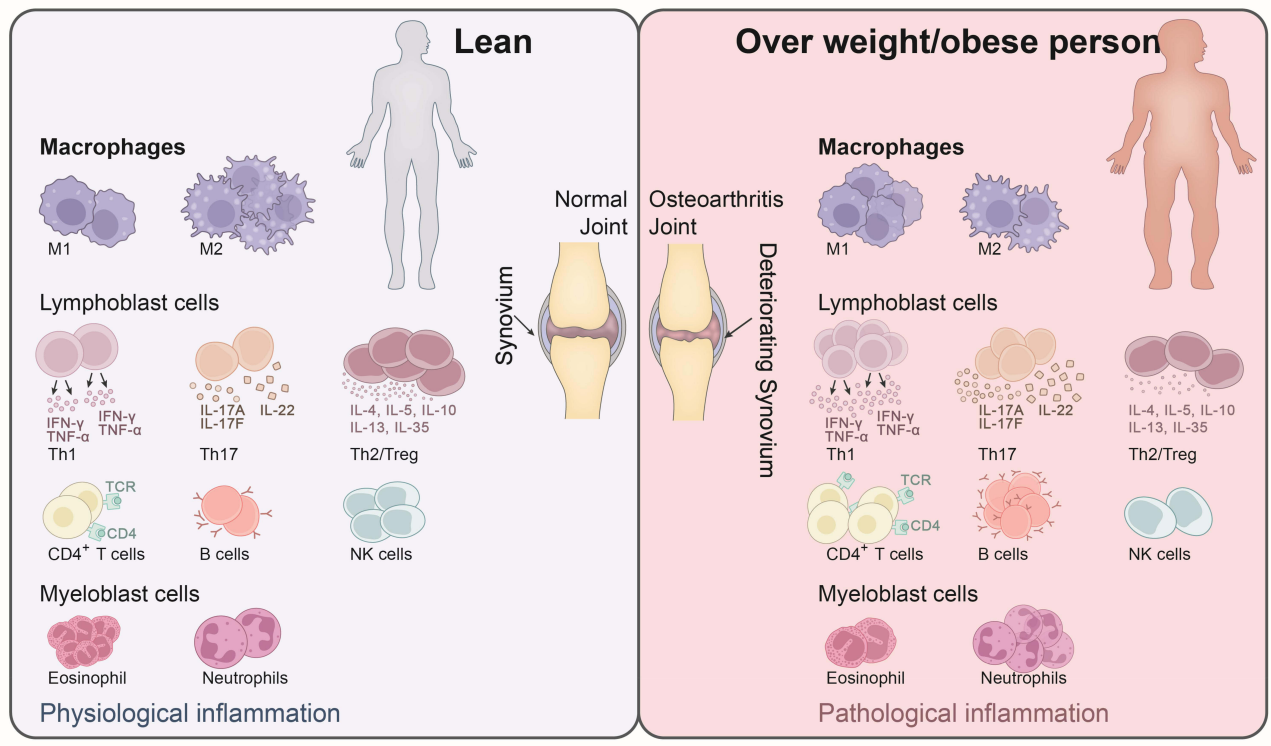

Figure 8 Changes in immune cells in lean and overweight/obese individuals with OA.
Notes: Created in BioRender. T, J. (2025) https://BioRender.com/g5eqnze.
Abbreviations: SASP, Senescence-Associated Secretory Phenotype; uPAR, Urokinase Plasminogen Activator Receptor; IFN-γ, Interferon-gamma; TNFα, Tumor Necrosis Factor αlpha; IL-17A, Interleukin-17A; IL-17F, Interleukin-17F; IL-22, Interleukin-22; IL-4, Interleukin-4; IL-5, Interleukin-5; IL-10, Interleukin-10; IL-13, Interleukin-13; IL-35, Interleukin-35.

Epigenetic Regulation of OA

Recent methylome studies have revealed distinct DNA methylation profiles in OA patients, indicating that epigenetic modifications to DNA may play a key role in disease initiation and progression.[244] The dynamic DNA methylation process is mediated by DNMTs and demethylation enzymes, including the TET methylcytosine dioxygenases (TETs) in mammals—TET1, TET2, and TET3. Three DNMTs (DNMT1, DNMT3A, DNMT3B) have been reported. These enzymes catalyze the transfer of a methyl group to the cytosine of CpG dinucleotides, producing 5-methylcytosine (5mC). DNA methylation occurring in promoters, enhancers, or gene bodies can significantly affect gene expression patterns. DNMT3A and DNMT3B primarily act as de novo methyltransferases that establish DNA methylation patterns during development, while DNMT1 maintains these patterns during cell division.[245–248] The absence of these enzymes in mice leads to embryonic (Dnmt1, Dnmt3b) or postnatal (Dnmt3a) lethality, confirming their crucial roles in development.[249,250]

Role of DNA Methylation in OA

Numerous studies have shown that DNA methylation is closely linked to the pathogenesis of OA. Genome-wide association studies have revealed[251] that hypomethylation in the promoter regions of ECM genes such as COL2A1 and ACAN, as well as transcription factors including SOX9 and RUNX2, is associated with altered gene expression during OA progression. Abnormal DNA methylation patterns can be inherited by daughter cells, resulting in persistent dysregulation of gene expression.

During the chondrogenic differentiation of MSCs, two CpG sites in the COL10A1 promoter are demethylated.[252] In OA cartilage, reduced methylation at specific CpG sites is associated with increased expression of key catabolic genes, including MMP-3, MMP-9, MMP-13, ADAMTS-4, IL-1β, and LEP.[253] Early embryonic studies suggest that methylation regulates chondrocyte differentiation through modulation of type I and II collagen genes.[254] Both normal and OA chondrocytes exhibit low methylation levels at the promoters of COL2A1 and ACAN,[255] while SOX9 and RUNX2 remain hypomethylated during in vitro cartilage formation.[256] In joint tissues, the C allele of GDF5 forms CpG

dinucleotides that can undergo methylation, leading to allelic expression imbalance and contributing to musculoskeletal disorders. LEP expression in OA chondrocytes is regulated by DNA methylation, and silencing LEP via RNA interference downregulates MMP-13 expression.[257] These findings demonstrate that these mechanisms can directly or indirectly regulate the expression of metalloproteinases. Given the reversibility of DNA methylation, targeting these epigenetic mechanisms may offer novel therapeutic opportunities for OA.

Current research on DNA methylation in OA primarily focuses on articular cartilage, the main tissue affected during disease progression and readily accessible from joint replacement surgeries. Additionally, articular cartilage is composed of a single cell type, chondrocytes, which avoids the genetic heterogeneity present in tissues composed of multiple cell types. The main tissue affected during disease progression and readily accessible from joint replacement surgeries,[258] reported increased expression of MMP3, MMP9, MMP13, and ADAMTS4 in femoral head cartilage, correlating with demethylation at specific CpG sites in their promoters.[259] This study was among the first to propose a role for DNA methylation in OA pathogenesis. Subsequent investigations examined genes functionally linked to OA by assessing promoter methylation and mRNA expression in cartilage tissue, primary chondrocytes, and chondrocyte cell lines.[260] Whether DNA methylation changes causally influence gene regulation in OA cartilage remains unresolved. Further studies are needed to clarify whether these epigenetic modifications directly contribute to OA and how variables such as study design and tissue source may affect the observed outcomes.

Regulation of Gene Expression by Histone Modifications

Research by YEL et al identified histone demethylases KDM4B and KDM6B as key regulators of osteogenic differentiation in MSCs in a mouse model.[261] Studies have shown that in human chondrocytes, the knockdown of the deacetylase SIRT6 contributes to the progression of cellular senescence and increases the expression of matrix-degrading enzymes (MMP1 and MMP13).[262] Furthermore, studies have reported significantly elevated expression of HDAC1, HDAC2, and HDAC7 in cartilage from OA patients compared to healthy controls, with HDAC7 specifically promoting cartilage degradation by increasing MMP-13 expression.[263] In a rabbit OA model induced by anterior cruciate ligament transection, increased expression of MMP-1, MMP-3, MMP-13, and IL-1 was observed. Weekly intra-articular injections of the HDAC inhibitor TSA reduced the expression of these genes, suggesting that HDAC activity contributes to cartilage catabolism.[264] Additionally, experiments have shown that the ubiquitin-proteasome pathway, activated post-viral linkage, increases the incidence of OA when applied to joint cartilage.[265] Collectively, these findings indicate that histone deacetylation is essential for maintaining joint homeostasis and regeneration.

Histone lysine or arginine residues are methylated by histone methyltransferases and protein arginine methyltransferases, which introduce one or more methyl groups to regulate the transcription process.[266] However, these modifications can be reversed by the action of demethylases. Inhibition of the histone methyltransferase SET-1A can block IL-1-induced expression of COX-2 and iNOS.[267] Mouse model studies have shown that histone methyltransferases KDM4B and KDM6B play critical roles during the osteogenic differentiation of MSCs by removing methyl groups from H3K9me3 and H3K27me3.[268] The absence of KDM4B or KDM6B severely affects the osteogenic differentiation of MSCs and promotes adipogenic differentiation. In aged and ovariectomized mouse models, an increased presence of H3K27me3 and H3K9me3 was observed in bone marrow MSCs (BMSCs), correlating with enhanced adipogenic potential.[269]

Recent research has highlighted the significant function of WW domain-containing protein 2 (WWP2) in chondrocytes through cartilage-specific transcription factors.[270] Additionally, WWP2 subtypes have been shown to selectively target oncogenic signaling pathways, binding to the PTEN tumor suppressor and the TGF-β/Smad signaling pathway.[271] WWP2 subtypes act as central regulators and represent novel targets for disease intervention. Studies have demonstrated that various viruses can exploit the ubiquitin-proteasome pathway for pathogenesis. Research by Rollin et al found that 16.7% of OA patients tested positive for viral DNA/RNA, including two cases involving Epstein-Barr virus (EBV).[272] They confirmed that viral linkage followed by proteasome-mediated degradation in joint cartilage increased OA incidence and highlighted a risk of EBV transmission or reactivation in patients requiring tissue reconstruction. Runx2 and Runx3 are osteogenic transcription factors critical for the osteogenic differentiation of stem cells.[273] Parathyroid hormone-related protein (PTHrP) inhibits the expression of Runx2 and Runx3 in chondrocytes through cyclin D, suggesting that PTHrP may prevent premature hypertrophy of chondrocytes, at least partly by inducing the degradation of Runx2 and Runx3 through a cyclin D1-dependent pathway.

Regulation by Non-Coding RNAs in Obesity, Aging, and OA

Recent research has identified a crucial regulatory role for miRNAs in cartilage development. These miRNAs regulate the proliferation, differentiation, and apoptosis of chondrocytes, influence the synthesis of the ECM of cartilage, participate in cellular inflammatory responses, and play a significant role in the pathogenesis and progression of OA.[274] Among them, miR-140 is one of the most extensively studied OA-related miRNAs. It is within an intronic region of the E3 ubiquitin protein ligase gene WWP2 and exhibits high conservation across vertebrates. In healthy individuals, miR-140 expression increases during cartilage development but is markedly reduced in osteoarthritic cartilage.[275] In chondrocytes, miR-140 is primarily regulated by SOX9 and targets multiple genes involved in bone and cartilage development, differentiation, and proliferation. Overexpression of miR-140 can prevent cartilage damage. Studies have shown that aberrant expression of miR-214 can disrupt the regulation of bone and cartilage growth, leading to cartilage degeneration and subchondral bone remodeling.[276] Roberto et al demonstrated that miR-214 is highly expressed at the onset of cartilage differentiation and subsequently declines to maintain normal developmental trajectories. Sustained overexpression disrupts this balance and results in impaired cartilage formation. Articular chondrocytes generally maintain a stable and permanent phenotype throughout their lifetime to preserve joint function.

Body fluids containing miRNAs have emerged as biomarkers for OA. For instance, the levels of miR-16, miR-132, miR-146a, and miR-223 are significantly reduced in OA patients.[275] Evidence indicates that miR-34a regulates chondrocyte apoptosis.[277] Using microRNA expression profiling, Iliopoulos et al identified nine upregulated and seven downregulated miRNAs in OA cartilage compared to normal cartilage. Some of these microRNAs are involved in mediating inflammation and obesity, suggesting a regulatory connection between metabolic factors and OA onset.[278] Miyaki et al generated miR-140 knockout mice that exhibited age-related loss of proteoglycans and fibrosis of joint cartilage, typical pathological changes associated with OA.[279] In contrast, transgenic mice overexpressing miR-140 demonstrated resistance to OA induction, supporting the role of miR-140 in directly targeting ADAMTS-5 and mitigating cartilage matrix degradation. Akhtar et al reported that miR-27a expression in OA chondrocytes is significantly lower than in normal cartilage.[280] miR-27a directly targets MMP-13 mRNA to inhibit its translation, countering the increased expression of MMP-13 induced by IL-1β. Concurrently, IL-1β activates the NF-κB pathway, which further suppresses miR-27a expression. Additionally, Yamasaki et al reported that miR-146a is highly expressed in OA cartilage with low Mankin scores, and IL-1β can enhance its expression, indicating a potential role in OA-associated inflammatory responses.[281]

Extensive research has demonstrated that subchondral bone sclerosis accompanies OA development, indicating its significant role in disease progression. Gaur et al reported that the Dicer enzyme can increase bone mass during aging in mature osteoblasts expressing osteocalcin. Studies confirmed that miR-214 inhibits the activity of osteoblasts by directly targeting ATF4. Smith et al observed that miR-29 and miR-365 negatively regulate and inhibit osteoblast differentiation.[282] Bioinformatic analysis indicates that PPAR, Bambi, and Crim1 may serve as potential targets of miR-20a, all acting as inhibitors of the BMP signaling pathway.[283] In vitro experiments demonstrated that overexpression of miR-100 inhibits osteogenic differentiation, whereas its downregulation enhances it. Existing research suggests that miR-138 can suppress osteogenic differentiation. During MSC osteogenesis, miR-138 expression decreases, and its overexpression significantly inhibits differentiation.[284] In Sao2 and U2OS cells, enhanced expression of miR-214 reduces Osx protein levels, likely regulating osteogenic differentiation through Osx.[285] Overexpression of miR-196a down-regulates both mRNA and protein levels of HOXC8, a predicted target of miR-196a.[286] During osteogenic differentiation of human ASCs, the expression of HOXC8 decreases, correlating with an increase in miR-196a expression.

Multiple mechanisms mediate the pathogenesis and progression of OA, including ECM degradation, chondrocyte apoptosis, inflammatory responses, angiogenesis, and autophagy. Recent studies have shown a correlation between lncRNAs and joint cartilage disorders, suggesting that differential expression of these lncRNAs may provide novel mechanisms and therapeutic targets.[287] These emerging epigenetic insights offer new directions for OA diagnosis and treatment. Identifying epigenetic biomarkers linked to obesity and aging may support the development of more precise diagnostic tools and therapeutic strategies. However, clinical application of such technologies faces challenges, including the need for biomarker validation and management of inter-individual variability. Further studies are required to overcome these barriers and facilitate successful clinical translation of novel epigenetic approaches.

In summary, obesity mediates the onset and progression of OA through various mechanisms. Targeting specific proteases to reduce their expression or activity remains a key therapeutic strategy for delaying disease progression. Epigenetic changes allow cells to rapidly respond to environmental changes. Abnormal epigenetic regulation is associated with numerous pathological conditions and often reflects environmental or age-related influences. Given the reversibility of epigenetic changes, advancing the understanding of their role in OA pathogenesis may guide the development of targeted pharmacological interventions to slow or prevent disease progression.

Current Status and Emerging Explorations in OA Treatment Strategies

Ongoing advances in OA research have driven continuous refinement and expansion of treatment strategies. Current mainstream treatments for OA include non-pharmacological interventions, pharmacotherapy, intra-articular injections, and novel molecular biologic therapies.

Non-Pharmacological Treatments

Non-pharmacological treatment methods are the most accessible and cost-effective approaches for managing OA. These approaches are typically categorized into several key areas. One primary strategy involves reducing modifiable risk factors. For example, appropriate physical activity and weight loss can effectively relieve joint loading and alleviate OA symptoms. A recent large-scale randomized clinical trial demonstrated that participants receiving combined exercise and weight-loss interventions showed a 9.8-point reduction in the OA index compared to the control group, confirming the therapeutic value of lifestyle modification.[288]

Another key approach is physical therapy. Muscle-strengthening exercises, particularly targeting the quadriceps and hamstrings, can improve joint support, reduce friction and damage between joint surfaces, alleviate pain, and enhance functional activity. Such interventions are especially beneficial for individuals with knee OA, as strengthening thigh muscles reduces knee load and improves stability in walking and standing.[289,290]

Additionally, thermotherapy promotes blood circulation and relieves joint stiffness, while cryotherapy (such as cold packs and cold-water baths) reduces localized inflammation and relieves pain.[291] Alternating thermotherapy and cryotherapy often p yields enhanced analgesic and anti-inflammatory effects. As the preferred non-pharmacological intervention for OA management, physical therapy improves joint function and reduces pain through multi-level interventions, offering a safe, cost-effective, and clinically effective strategy.[292–294]

A systematic review by Minshull and Gleeson highlighted the lack of effective exercise prescriptions in OA management.[295] Low-impact aerobic exercise, resistance training, and flexibility training are the primary recommended types of exercise for OA patients.[296–299] Evidence suggests that weekly exercise duration exceeding 150 minutes significantly improves both pain and function in OA patients.[300] Moderate-intensity exercise has proven to be most effective in reducing pain and enhancing physical function.[301] In a recent randomized clinical trial with 206 OA patients, participants were divided into a control group (receiving only information about OA and exercise) and an intervention group (receiving a 24-week self-directed intensive exercise program, supported by automated SMS messages to enhance adherence). The intervention group showed significantly greater improvements in knee pain and function, indicating the effectiveness of structured, remotely supported exercise regimens.[302]

While exercise is effective for OA management, individual differences and adherence impact the implementation of exercise programs. Most studies are conducted under controlled conditions, which may not reflect real-life outcomes. A lack of standardized data across different stages of OA and limited healthcare resources further restrict broad implementation. Additional research is warranted to assess scalable, low-cost exercise-based interventions.

Pharmacological Treatments

Pharmacotherapy represents a core treatment modality for OA, supported by a substantial body of clinical and experimental evidence. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed due to their ability to inhibit cyclooxygenase (COX) enzymes involved in prostaglandin synthesis, thereby reducing pain and inflammation. Clinical studies confirm the effectiveness and relative safety of NSAIDs in OA management, with COX-2 selective NSAIDs such as diclofenac patches being among the most effective topical anti-inflammatory drugs.[303]

Recent studies have also shown that enflicoxib, another COX-2 selective NSAID, provides effective and safe treatment for canine OA when administered orally at an initial loading dose of 8 mg/kg followed by 4 mg/kg for six weeks.[304] Acetaminophen, a non-NSAID analgesic, is often utilized in early-stage OA. However, subsequent studies indicated limited efficacy in reducing OA symptoms.[305,306] Opioids, potent central nervous system analgesics, exhibit greater perceived effectiveness in patients with knee and hip OA compared to other treatments, as reported by Bruno R da Costa et al.[307] However, concerns over misuse and addiction have led to reduced clinical application and stricter regulatory oversight.

Certain orthobiologics modulate immune responses and reduce the release of inflammatory mediators, thereby slowing cartilage degeneration.[308,309] Sun et al developed a lipid nanoparticle, WG-PL14, for intra-articular injection to enhance the expression and enrichment of rhFGF18 mRNA, supporting OA treatment. Mouse model experiments demonstrated effective pain relief, enhanced cartilage regeneration, and improved subchondral bone homeostasis following treatment with the therapy.[310]

In clinical trials, orthobiologics such as tumor necrosis factor (TNF) inhibitors and interleukin-1 (IL-1) receptor antagonists have been investigated for the treatment of OA.[311] Inhibitors targeting TNF and IL-1, such as Adalimumab and Anakinra, have been evaluated in clinical trials for OA treatment.[312,313] However, these studies have demonstrated limited efficacy, suggesting the need for further research to clarify their therapeutic potential. These trials assessed the effects of orthobiologics on pain relief, improvement of joint function, and disease progression. Various growth factor/cytokine modulation therapies are currently under investigation, including Invossa (in Phase III), Kineret (in Phase I), and Sprifermin (in Phase II) for symptomatic OA.[314]

Overall, research on orthobiologics in OA treatment remains in the exploratory phase. Although preclinical findings are encouraging, clinical efficacy has not yet been conclusively established. Large-scale, randomized controlled trials are essential to confirm their efficacy and safety.

Intra-Articular Injection Therapy

Commonly administered agents for intra-articular injection in OA include viscosupplements such as hyaluronic acid to enhance joint lubrication, analgesics, and corticosteroids.[315] Nanomaterials used in intra-articular injections can restore joint lubrication, reduce inflammation, and promote cartilage repair.[316] Such therapies include polymer brushes, nanocomposite hydrogels, and nanoparticles. With advances in molecular biology, lipid nanoparticles (LNPs) encapsulating messenger RNA (mRNA) for intra-articular injection can precisely regulate protein expression at the molecular level in synovial or chondrocyte cells within the target joint, thereby significantly enhancing the therapeutic efficacy for OA.[317]

Novel Molecular Biological Therapies

With the growth of molecular biology and nanobiology, OA treatment strategies have increasingly advanced to the microscopic level, yielding impressive results. Recent developments, including the use of exosomes and gene-editing technologies, have expanded therapeutic options for OA, demonstrating efficacy across cellular, animal, and clinical models.

Research by Stella et al indicated that exosomes from different cellular sources exhibit comparable chondroprotective effects in vivo. Their study demonstrated that microparticles and exosomes isolated from adult mouse bone marrow mesenchymal stem cells (BMSCs) provide chondroprotective effects in a collagenase-induced OA model. Exosomes from BMSCs pretreated with TGF-β3 significantly upregulated anabolic marker genes and downregulated catabolic marker genes in OA chondrocytes.[318]

Intra-articular injection of BMSC-derived exosomes in collagenase-induced OA mice markedly reduced cartilage degradation and subchondral bone loss. These exosomes restored the expression of anabolic markers (eg, aggrecan and type II collagen), while inhibiting catabolic enzymes (eg, ADAMTS5 and MMP-13) and inflammatory markers (eg, inducible nitric oxide synthase) in OA-like chondrocytes. Additionally, BMSC-derived exosomes protected chondrocytes from apoptosis and suppressed macrophage activation.[319] Additionally, these exosomes may influence the biological phenotypes of other OA-related cells, such as synovial fibroblasts (SFB) and macrophages.

Gene editing technology is another promising, innovative approach for OA treatment. In animal experiments, CRISPR/Cas9-mediated deletion of the NGF gene alleviated OA-induced pain, and deletion of the MMP13 or

interleukin-1β (IL-1β) genes reduced structural damage in post-traumatic OA models. Targeted deletion of NGF, MMP13, and IL-1β contributed to both pain relief and preservation of joint architecture.[320,321]

In clinical studies, emerging therapies continue to show potential while presenting new challenges in OA treatment (Table 1). Muhammed Majeed et al conducted a study on 48 patients with knee OA using BSE treatment, which showed reduced pain, improved stiffness, and enhanced physical function.[322] Yang Song et al treated 18 OA patients with adipose-derived mesenchymal stem cells, observing pain relief and improved mobility.[323] Nicole Gerwin et al used LNA043 treatment in 28 knee OA patients and found reduced pain and improved cartilage health.[324] Yong-Beom Park et al applied a stem cell-based therapy (a combination of cultured allogeneic hUCB-MSCs and hyaluronic acid hydrogel [Cartistem]) in 7 patients with cartilage defects, resulting in ICRS cartilage repair and improvement in walking pain VAS scores.[325] Chun-Chieh Chen et al conducted HC-II and EC-HC-II injections in 160 knee OA patients, observing pain reduction, improved FFM, and enhanced grip strength.[326] Regenerative medicine therapies, such as stem cell therapy and tissue engineering, have demonstrated potential for repairing damaged cartilage.[327] Additionally, nerve-targeted therapy aims to relieve pain and improve joint function by targeting specific nerves.[328] These methods offer new avenues for OA treatment and may enhance therapeutic outcomes when combined with existing treatment strategies.

Translational Application of Clinical and Basic Research

Clinical research continues to explore how to translate findings from basic research into effective therapeutic strategies. Intra-articular injection therapies, particularly those involving lipid nanoparticles (LNPs) encapsulating mRNA, have garnered increasing attention for their ability to regulate gene expression precisely in OA-affected joints (Table 2). These therapies directly target diseased areas while minimizing systemic side effects, enhancing treatment safety and efficacy. In clinical research, intra-articular injection therapy has shown significant efficacy and safety in treating knee OA. Woo-Suk Lee et al conducted adipose-derived mesenchymal stem cell injections in 24 patients with knee OA, resulting in significant improvement in WOMAC scores and no adverse events observed.[329] Marcel Tschopp et al conducted a study on 95 patients with mild to moderate OA who received intra-articular injections of corticosteroids, hyaluronic acid (HA), platelet-rich plasma (PRP), or placebo. The results showed no significant changes in knee joint outcomes in either the short or long term.[330] Seyed Ahmad Raeissadat et al treated 238 elderly patients with chronic knee pain using HA, PRP, plasma rich in growth factors (PRGF), and ozone injections, and observed significant improvements in pain, stiffness, and function.[331] Liangjing Lun et al administered Re-Join® or HA injections to 53 patients with early-stage knee OA, resulting in significant improvements in joint function, pain, quality of life, and cartilage regeneration, with good tolerability.[332] Andrea Pintore et al treated 102 patients with advanced knee OA using BMAC and ADSC injections, which led to significant pain relief and functional improvement, although mild joint swelling was reported.[333]

In summary, AD-MSC injections and novel therapies have demonstrated promising outcomes in pain alleviation, functional recovery, and safety. Meanwhile, DMOAD research for OA is ongoing in various areas, including growth factors, gene therapy, exosome therapy, and gene editing technology. Although these strategies show therapeutic potential, further clinical trials are necessary to verify their safety and efficacy.

Multi-Targeted Therapeutic Strategies for Age-Related Degenerative Diseases and Their Potential Risks

Although aging is inevitable and irreversible, increasing evidence suggests that the process and rate of aging can be modified. Therefore, therapies targeting age-related degenerative diseases warrant further investigation. As shown in Figure 9, cellular senescence within joint tissues can be modeled using various experimental systems. Targeted interventions, including senolytic drugs and cell-based therapies, aim to eliminate senescent cells or suppress their deleterious effects, offering potential to delay OA progression. At present, three primary strategies have emerged for targeting senescent cells (Figure 9).

The first strategy involves therapeutic interventions through the immune system to enhance the immune response against senescent cells, facilitating their clearance from tissues. Senescent cells (SnCs) exhibit immunogenicity and are

Table 1 A Clinical Case Study of Novel Treatments for Arthritis

First Author	Publication Time	Sample Source	Sample Size	Age of Subject	Case Presentation	Diagnosis	Treatment	Outcome
Muhammed Majeed[322]	2019	VAS score > 4	48	35–75	Knee OA	Grade 1–3 OA	BSE	WOMAC used to assess improvements in pain, stiffness, and physical function
Yang Song[323]	2018	Moderate OA	18	40–70	Osteoarthritis	Grade 2–4 OA	Adipose-derived mesenchymal stem cells (AD-MSCs)	Pain reduction, improved mobility
Nicole Gerwin[324]	2022	Mild to moderate OA	28	50–80	Knee OA	Grade 1–3 OA	LNA043 (a derivative of angiopoietin-like 3 [ANGPTL3])	Pain reduction, improved cartilage health
Yong-Beom Park[325]	2016	K-L grade 3 with painful full-thickness cartilage defects (ICRS grade 4)	7	Mean 58.7	Cartilage defect patients	Grade 4 OA	Stem cell-based therapy (cultured allogeneic hUCB-MSCs combined with hyaluronic acid hydrogel [Cartistem])	ICRS cartilage repair evaluated via arthroscopy; improvement in walking pain VAS score
Chun-Chieh Chen[326]	2023	Mild to moderate knee OA	160	60–85	Knee osteoarthritis	Grade 1–3 OA	HC-II, EC-HC-II	Pain reduction, improved FFM and grip strength

Abbreviations: HC-II: Hematopoietic Cell Interferon-inducible Nucleotide-binding Protein 2; EC-HC-II: Endothelial Cell-Hematopoietic Cell Interferon-inducible Nucleotide-binding Protein 2; FFM: Fat-Free Mass; HA: Hyaluronic Acid. Boswellia serrata extract, BSE; WOMAC: Western Ontario McMaster Index.

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Table 2 A Clinical Case Study of Intra-Articular Injection for the Treatment of Knee Osteoarthritis

First Author	Publication Time	Sample Source	Sample Size	Age of Subject	Case Presentation	Diagnosis	Treatment	Outcome
Woo-Suk Lee[329]	2019	Patients with moderate knee osteoarthritis	24	18–75 years	Knee osteoarthritis	Clinical and radiologic examination	AD-MSC injection	Significant improvement in WOMAC score and pain relief; no adverse events observed
Marcel Tschopp[330]	2022	Patients with mild to moderate OA	95	54–68 years	Knee OA	Kellgren-Lawrence (KL) grade 1–3 mild to moderate OA	Corticosteroids, hyaluronic acid, PRP, or placebo injection	No changes in pain level or short-/long-term outcomes
Seyed Ahmad Raeissadat[331]	2021	Patients with mild to moderate knee pain	238	Mean age 56.9 ± 6.3 years	Chronic knee pain	Grade 2 or 3 OA	HA, PRP, PRGF, and ozone injections	Significant improvements in pain, stiffness, and function
Liangjing Lu[332]	2019	Patients with symptomatic knee OA	53	18–70 years	Early-stage knee OA	Grade 1–3 OA	Re-Join® or HA injection	Significant improvements in joint function, pain, quality of life, and cartilage regeneration; well tolerated
Andrea Pintore[333]	2023	Patients with advanced OA	102	Under 75 years	Advanced knee OA	Grade 2–4 OA	BMAC and ADSC injection	Significant pain relief and functional improvement; mild joint swelling observed

Abbreviations: AD-MSC: Adipose-Derived Mesenchymal Stem Cells; WOMAC: Western Ontario and McMaster Universities Arthritis Index.

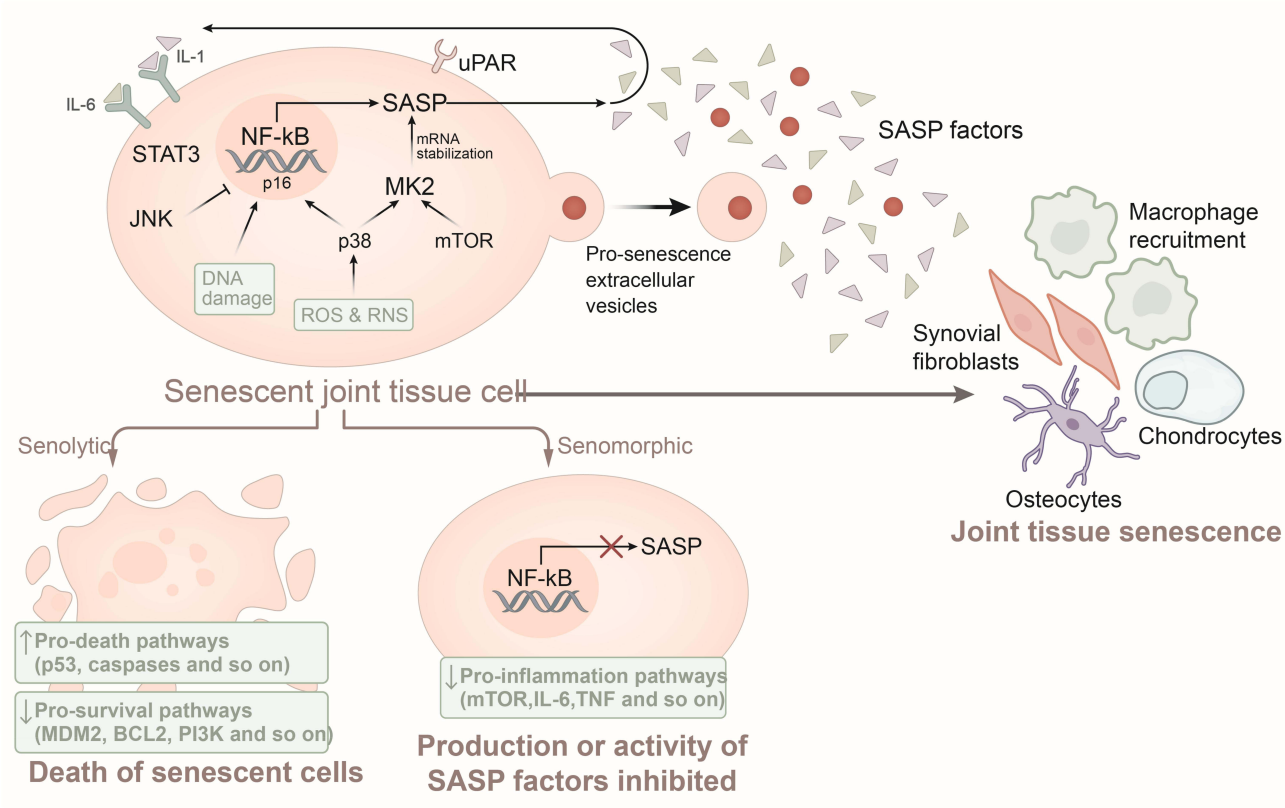

Figure 9 Models of cellular senescence in joint tissue and potential therapeutic approaches.
Notes: Created in BioRender. T, J. (2025) https://BioRender.com/xhv5o9p.
Abbreviations: IL-1β, Interleukin-1 beta; TNF-α, Tumor Necrosis Factor-alpha; CRP, C-reactive Protein; IL-1, Interleukin-1; IL-6, Interleukin-6; uPAR, Urokinase-type Plasminogen Activator Receptor; SASP, Senescence-Associated Secretory Phenotype; NF-KB, Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells; STAT3, Signal Transducer and Activator of Transcription 3; JNK, c-Jun N-terminal Kinase; MK2, MAP Kinase-Activated Protein Kinase 2; MDM2, Mouse Double Minute 2 Homolog; BCL2, B-Cell Lymphoma 2; PI3K, Phosphatidylinositol 3-Kinase.

subject to immune surveillance. Methods such as blocking the immune checkpoint protein programmed death receptor-1 (PD-1) and using chimeric antigen receptor (CAR) T-cell therapies are potential options for aging immune therapy.[334–336]

The second strategy involves inhibiting the SASP. (1) Administration of the JAK kinase inhibitor ruxolitinib has been shown to reduce key SASP factors, including IL-6, IL-8, and plasminogen activator inhibitor-1.[337] (2) Inhibition of the mTOR serine/threonine kinase pathway, a regulator of cartilage development and homeostasis, has been explored as a therapeutic strategy in OA. mTOR functions through two complexes: mTORC1 and mTORC2. While inhibition of mTORC1 confers anti-aging effects, inhibition of mTORC2 contributes to undesirable side effects. Thus, selective inhibition of mTORC1 may offer greater therapeutic benefit.[338] (3) SIRT6 activators have emerged as potential interventions. As a member of the sirtuin protein family known for longevity, SIRT6 exhibits various catalytic enzyme activities crucial for processes such as anti-aging, chromatin regulation, transcriptional control, lipid metabolism, and DNA damage repair.[339]

The third strategy involves the direct elimination of senescent cells. Therapeutic agents in this category include senolytics, SASP inhibitors, and regulators of nutrient signaling. Senolytics selectively induce apoptosis in senescent cells, while senomorphics suppress SASP factors associated with pro-inflammatory paracrine signaling and tissue damage. Among these, senolytics have demonstrated the most widespread application. Preclinical studies have shown that senolytics ameliorate age-related diseases in mouse models, such as idiopathic pulmonary fibrosis, atherosclerosis, and cancer.[172]

Obesity and OA represent two major public health challenges globally, with obesity identified as a key risk factor for OA development.[340] As depicted in Figure 10, obesity promotes OA development by stimulating adipocyte-derived inflammatory factors that induce cartilage damage and subchondral bone remodeling. Due to the close interaction between obesity and OA (Figure 10), some therapeutic strategies have been developed to target both conditions simultaneously, yielding promising results. Recent studies have shown that probiotics and prebiotics are safe and effective dietary substances that help construct

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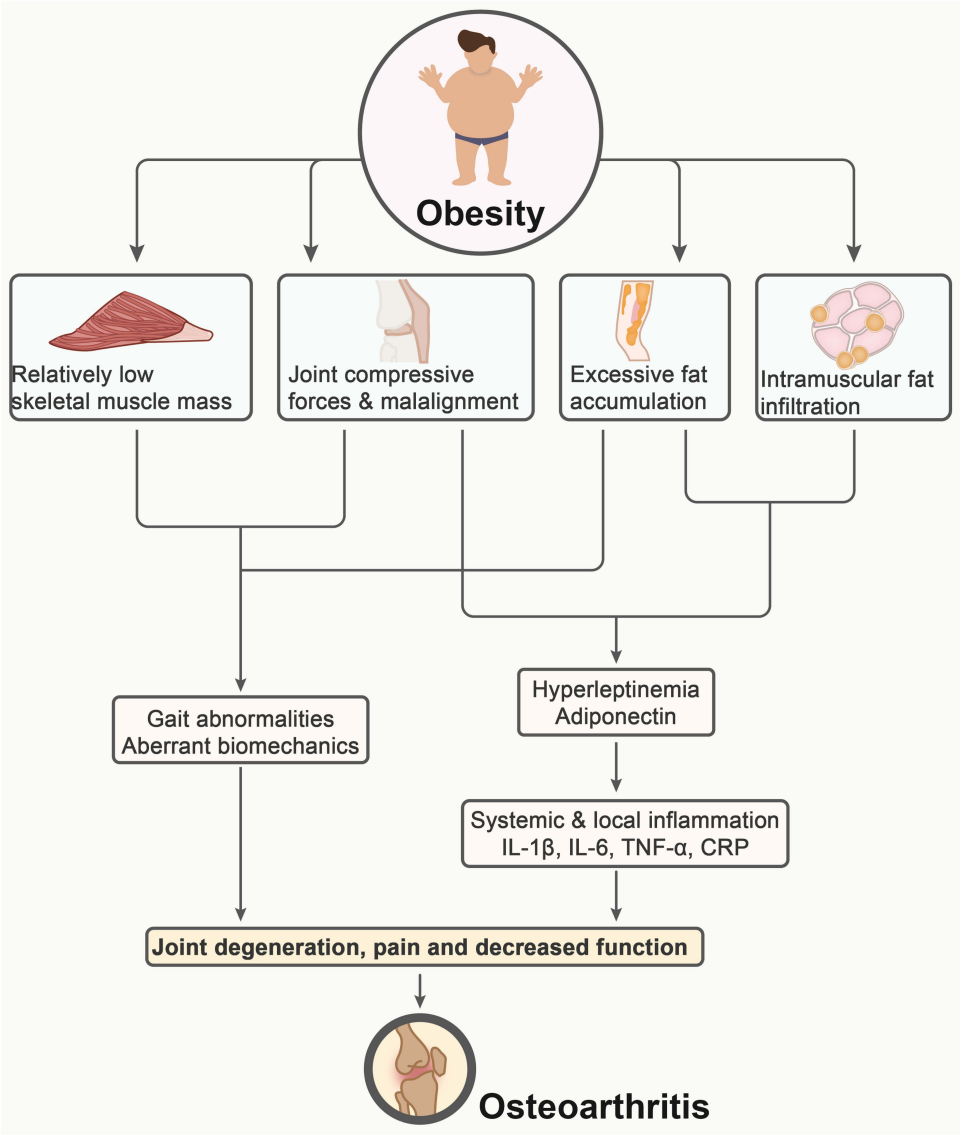

Figure 10 Potential molecular pathways of OA induced by obesity.
Notes: Created in BioRender. T, J. (2025) https://BioRender.com/mcx336r.

microbial communities, making them a viable treatment option for obesity-related OA.[341,342] Data from randomized double-blind clinical trials showed that the probiotic *L. casei Shirota* significantly benefits the treatment of OA in knee joints.[343] Additionally, prebiotic fibers such as oligofructose have been shown to counteract the adverse effects of an HFD by enhancing populations of beneficial Bifidobacteria and reducing pro-inflammatory microbes. These microbiota shifts reduce systemic inflammation and protect against cartilage degradation in OA models.[344] Furthermore, a large-scale, long-term, randomized double-blind trial has shown that additional supplementation with fish oil alleviates symptoms of both obesity and OA in older adults, significantly improving quality of life.[345] These findings suggest that targeted nutritional interventions may offer dual therapeutic benefits for managing obesity and OA.

Despite advances in emerging technologies and therapeutic strategies for OA, potential risks and adverse effects remain significant concerns. Gene-editing approaches such as CRISPR/Cas9 have demonstrated therapeutic potential but are associated with off-target effects, resulting in unintended gene mutations and potential health risks. Studies have shown that despite the optimization of sgRNA design using computer programs, off-target effects cannot be completely eliminated.[346] Furthermore, CRISPR-Cas interventions may induce unintended genomic alterations, including small insertions/deletions and structural variations such as translocations, inversions, and large deletions, posing risks to patients.[347]

Exosome therapy, although promising, requires optimization in its preparation and purification processes to ensure stability and targeting.[348] Exosomes, a subtype of EV, are chosen for targeted therapy of many diseases due to their low toxicity, high stability, and low immunogenicity.

Long-term use of NSAIDs is associated with the progression of knee OA (KOA). Compared to non-users, long-term NSAID users experience higher rates of symptom worsening, including pain, disability, and stiffness, and are more likely to undergo total knee replacement surgery.[349] Although structural deterioration may not differ significantly, extended NSAID use increases the risk of adverse effects on the gastrointestinal, renal, and cardiovascular systems.

To mitigate these risks, robust safety evaluation and management frameworks are essential. First, a comprehensive safety assessment must be conducted before the clinical application of new technologies and therapeutic methods to ensure their efficacy and safety. Second, a rigorous monitoring and follow-up system should be established to promptly identify and address potential side effects. For gene editing technologies, employing precision genome-editing tools and conducting long-term follow-up studies are necessary to minimize off-target effects. Exosome therapy requires optimized preparation and purification methods to ensure stability and targeting. NSAIDs and corticosteroids should be prescribed under professional supervision, with regular clinical evaluations to monitor adverse outcomes.[350] Additionally, enhancing public awareness of OA, its symptoms, and modifiable risk factors through targeted health education campaigns is also crucial.[351]

Conclusion and Future Outlook

This study systematically elucidates the bidirectional interaction between obesity and aging through the oxidative stress–inflammation–metabolism axis. Adipokines activate the NF-κB signaling pathway and cooperate with the SASP to induce epigenetic reprogramming of chondrocytes, including disruptions in DNA methylation, aberrant histone modifications, and dysregulation of non-coding RNA networks, ultimately accelerating OA progression through MMP-mediated extracellular matrix degradation. Based on these findings, future research should investigate these molecular mechanisms and explore emerging molecular biology technologies and epigenetic regulatory strategies to develop personalized therapeutic approaches for OA patients.

This review offers a novel perspective by innovatively framing its discussion within the obesity–aging–OA axis. In contrast to previous literature, the analysis not only provides a comprehensive overview of OA pathogenesis but also integrates recent advances in epigenetic regulation, thereby expanding the scope of OA research. The proposed framework enhances the systematic understanding of how obesity and aging jointly contribute to OA onset and progression, offering new directions for precision medicine in OA treatment.

Nevertheless, despite the growing body of research investigating the relationships among obesity, aging, and OA, several limitations remain in this field. First, most current studies are cross-sectional, which provide only static epidemiological data and are insufficient for elucidating the dynamics of disease progression. In contrast, longitudinal studies, although more demanding in terms of time and resources, are essential for establishing causal relationships by tracking disease progression and treatment response over time. Second, the specific roles of obesity and aging in OA pathogenesis remain incompletely defined and may vary across different populations, contributing to inconsistencies in current findings.

In summary, while significant progress has been made in understanding the epigenetic mechanisms of OA and the obesity–aging–OA axis, many uncertainties and debates remain. Future research should adopt more rigorous methodologies, including multicenter, cross-population analyses and long-term longitudinal studies, to clarify mechanistic pathways and enhance clinical relevance. Additionally, promoting healthy lifestyle interventions, such as balanced diets and regular physical activity, will be critical for preventing and mitigating both obesity and OA. In the short term, research should focus on accelerating the clinical translation of senolytic therapies and epigenetic editing tools. In the long term, the development of dynamic, microenvironment-targeted interventions will be essential for advancing precision medicine approaches in OA management.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request (Bo Wang, wb8788000@163.com).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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