



Adipokines: New Therapeutic Target for Osteoarthritis?

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Abstract

Purpose of the Review Osteoarthritis (OA) is an aging-associated and injury-induced joint disease characterized by cartilage degradation, bone sclerosis, and persistent low-grade inflammation in the joint. Aging and injury are triggers of joint pathological changes mediated by pro-inflammatory factors, some of which are secreted by white adipose tissue. Adipokines including adiponectin, leptin, resistin, chemerin, IL-6, and TNF- α are major players not only during inflammation but also in metabolic regulation of joint cells including chondrocytes, osteoblasts, osteoclasts as well as mesenchymal stem cells. The purpose of this review is to summarize the signal transduction pathways of adipokines in the articular joint to provide new information on potential targets for intervention of OA.

Recent Findings The risk of knee osteoarthritis is associated with adipokine gene polymorphism. While the infrapatellar fat pad is a major source of adipokines in knee synovial fluid, adipocytes also accumulate in the bone marrow during aging and obesity. Adipokines can act as SASPs (senescence associated secretory phenotype factors) that participate in cellular senescence of chondrocytes, but they also regulate energy metabolism impacting bone remodeling. Thus, adipokines are closely related to the metabolic syndrome and degenerative pathological changes in cartilage and bone during OA.

Summary Modulating the effects of adipokines on different cell types in the intra-articular joint will be a promising new option for OA intervention.

Keywords Adipokine · Osteoarthritis · SASPs · Chondrocytes · Bone cells

Introduction

Osteoarthritis (OA) is a chronic disease leading to cartilage degradation, synovial inflammation, subchondral bone remodeling, and the formation of osteophytes. Obesity is a common metabolic syndrome caused by excess fat accumulation in the body due to disorders of fat metabolism. Previous research has demonstrated a strong association between knee OA and obesity [1–5]. Obesity not only causes increased weight bearing by the joint but also enhances adipokine production by the adipose tissue, thereby contributing to inflammatory or autoimmune diseases [6, 7].

Adipocytes, the major cellular component of adipose tissue, have the ability to synthesize and release physiologically active molecules such as adiponectin, leptin, resistin, and chemerin, as well as inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor (TNF- α) [8]. These secretory products of adipocytes are named adipokines. While the infrapatellar fat pad (IFP) is a major source of adipokines in knee synovial fluid, adipocytes also accumulate in other joint fat pads and the bone marrow during aging and obesity (Fig. 1). IFP is also in close contact with the synovium, into which blood vessels and immune cells can infiltrate (Fig. 1). Thus, IFP can be viewed not only as a structural cushion to absorb shock in the knee joint but also an endocrine or paracrine tissue to regulate inflammation in the joint. Although adipocytes are major sources of adipokines, some adipokines are also synthesized by other resident joint cells, including chondrocytes, synoviocytes, osteoblasts, stromal cells, macrophages, and immune cells (Table 1). Furthermore, adipokine receptors are present in many types of joint cells, thus

This article is part of the Topical Collection on *Osteoarthritis*

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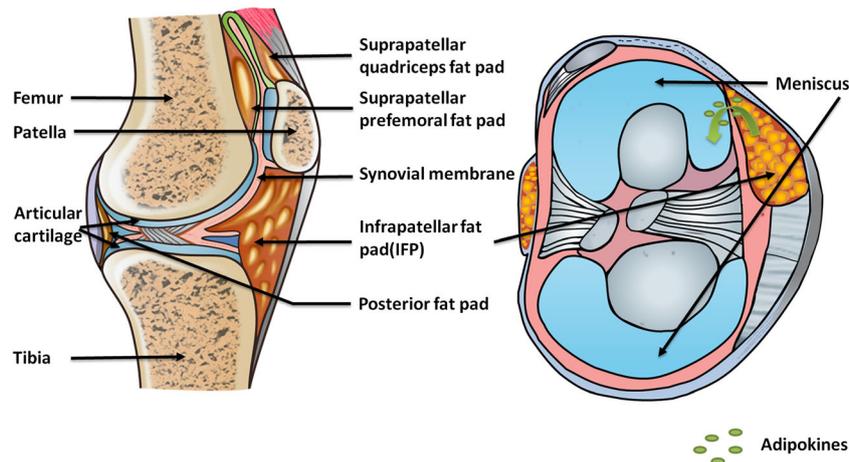


Fig. 1 The relative position of fat pads in the knee joint. There are multiple fat pads in the knee joint, including infrapatellar, posterior, suprapatellar prefemoral, and suprapatellar quadriceps. All of them

contain adipose tissues, which may serve both structural and regulatory roles. The regulatory roles are mainly achieved by signaling of adipokines that are secreted by adipocytes

forming a complex regulatory network of cellular “adipo-interaction” [8]. Thus, adipokines may contribute to synovial inflammation, matrix metalloproteinase (MMP) production, cartilage degeneration, and bone remodeling during OA pathogenesis (Fig. 2).

Osteoarthritis and Adipokines

The association between adipokines and OA is multi-factorial. Genetically, a SNP rs182052 in the ADIPOQ gene that encodes adiponectin may potentially modify individual susceptibility to knee OA in the Chinese population [9]. Thus, a polymorphism in the adiponectin gene has been linked to OA. Biochemically, adiponectin is at higher levels in the circulation and in joint

tissues of patients with rheumatoid arthritis (RA) and OA, and thus it is considered as a biomarker of arthritis [6, 7, 10]. Functionally, adipokines play a regulatory role affecting the metabolic balance in the joints through regulation of cytokine, chemokines, matrix-degrading enzymes, and cell growth and differentiation factors [11]. Chronologically, OA is associated with aging. The total amount of fat in the IFP is increased in aged people, compared with younger people, leading to the increase of adipokines during aging [12, 13]. In addition, joint cells undergo senescence induced by replicative exhaustion, telomere shortening, oxidative stress, and chromatin damage during OA [14]. One prominent feature of senescent cells is that they express senescence-associated secretory phenotype factors (SASPs), which include pro-inflammatory cytokines [15]. Adipokines, including some of the cytokines defined as

Table 1 Summary of adipokine properties

	Cell source	Receptor	Form	Signaling pathway	Regulatory function
Adiponectin	Adipocyte	AdipoR1 AdipoR2 T-cadherin	Full-length adiponectin, globular adiponectin	PPAR α , AMPK/m-TOR	Glucose and lipid metabolism
Leptin	Adipocyte, Chondrocyte	OB-R	Free form, Inactive form associated with receptor (OB-Re)	JAK/STAT ERK1/2, p38, JNK, PKC, SHP2/GRB2, PI3K/Akt	Food intake, energy consumption
Resistin	Adipocyte, osteoblast, osteoclast, chondrocyte, macrophage	TLR4		Soc-3, STAT3, NF-KB, C/EBP β	Insulin resistance, glucose homeostasis
Chemerin	Adipocyte, immune cell	CMKLR1, ChemR23	Precursor form, activation form	ERK1/2, Akt	Adipocyte differentiation, lipolysis, insulin resistance
IL-6	Adipocyte, myocyte, osteoblast, macrophage	Membrane bound IL-6R, soluble IL-6R, gp130		Trans-signaling, classic signaling	Liver regeneration, anti-inflammatory, pro-inflammatory
TNF-alpha	Adipocyte, immune cell	TNF-R1, TNF-R2	mTNF- α , sTNF- α	P38MAPK, NF- κ B, NOTCH	Bone formation, induce inflammation process

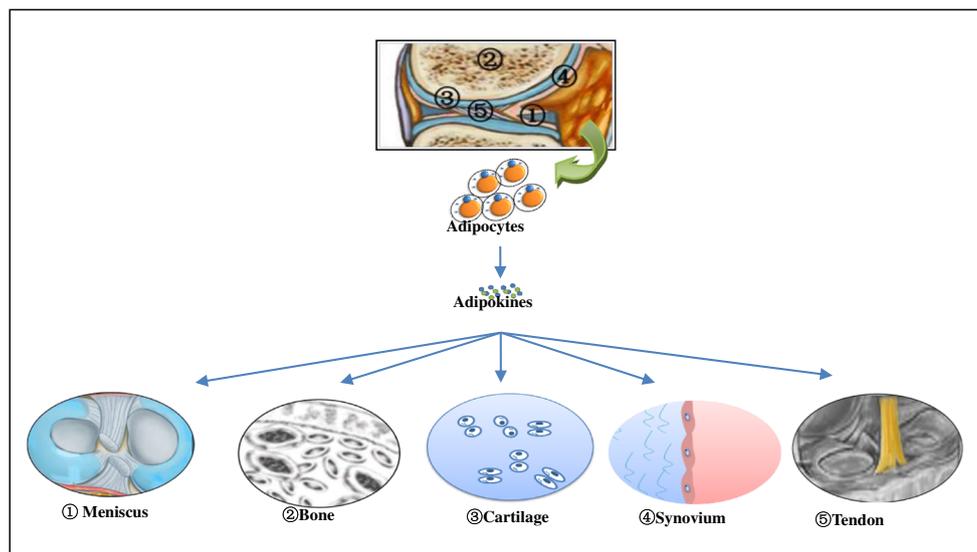


Fig. 2 Adipokine signaling in the joint. Within the joint capsule, fat pads are in close proximity with other joint tissues, such as meniscus, bone, cartilage, synovium, and tendon. The infrapatellar fat pad secretes adipokines thereby affecting neighboring tissues biochemically. Infiltrating through synovial membrane, adipokines also become part of

synovial fluid and affect cells at more distant sites in the joint. Since adipokine receptors are widely distributed in different types of cells, adipokine can regulate cellular functions of different joint tissues, including meniscus, bone, cartilage, synovium, and tendon

true SASPs such as IL-6 and TNF- α , are up-regulated in OA synovial fluid [16], readily infiltrate into cartilage, and activate the degenerative cascade [12, 13]. Different types of adipokines and their roles in OA are described as follows, with emphasis on adiponectin as a prototypical adipokine.

Adipokine

Adiponectin

Structure

Adiponectin (APN), also called Acrp30, AdipoQ, ApM1, and GBP28, is a hormone secreted exclusively by adipocytes [17, 18]. Human adiponectin gene spanned 17 kb on chromosome 3q27, consisting of three exons and two introns. Adiponectin protein is a 28–30 kDa collagen-like protein containing 244 amino acids. The basic structure of adiponectin is that of a trimer [19]. The heterotrimers consist of a full-length adiponectin (fAd) or a smaller globular adiponectin (gAd) generated by proteolytic cleavage [20]. Adiponectin can form a wide range of multimers from low molecular weight (trimers), medium molecular weight (hexamers) to high molecular weight (HMW) multimers connected by disulfide bonds at the amino terminus [19].

Adiponectin Receptors

Three adiponectin receptors have been identified: adiponectin receptors 1 and 2 (AdipoR1 and AdipoR2) and a small adiponectin receptor, T-cadherin [21, 22]. AdipoR1 is expressed

abundantly in liver, skeletal muscle, macrophages, and hypothalamus, while AdipoR2 is expressed in liver, white adipose tissue (WAT), and vasculature. AdipoR1 is a high-affinity receptor for globular adiponectin and a low-affinity receptor for full-length adiponectin, whereas AdipoR2 is an intermediate-affinity receptor for both full-length and globular adiponectin [21, 23–26]. T-cadherin is a unique cell adhesion molecule anchored to the cell surface membrane through a glycosylinositol (GPI) moiety. The extracellular portion of T-cadherin contains five ectodomains, having the ability to bind the physiological high-molecular weight (HWM) APN isoforms in vitro.

Adiponectin Signaling Pathways

AdipoR1 and AdipoR2 are receptors for globular and full-length adiponectin that mediate antidiabetic effects. Adiponectin binding to AdipoR1 activates peroxisome proliferation-activated receptor (PPAR α), AMPK and p38MAPK [27]. While PPAR α activation is involved in adiponectin-stimulated fatty-acid oxidation, AMPK and p38MAPK may be involved in adiponectin-stimulated fatty-acid oxidation and glucose uptake [22]. The signaling pathway activated by adiponectin binding to T-cadherin is still not clear.

Adiponectin Function

As an anti-diabetic and anti-atherogenic adipokine, adiponectin plays important roles in the regulation of glucose and lipid metabolism [8, 21, 22]. APN concentrations in the circulation of lean healthy individuals range between 5 and 30 $\mu\text{g/ml}$ and reduced in obese and insulin-resistant human subjects and in

animal models of metabolic syndrome [21, 22]. The reduction of plasma adiponectin levels by genetic or nutritional factors is one of the important causes of type 2 diabetes. Adiponectin reduces glucose content in tissues and up-regulates insulin signaling. This insulin-sensitizing effect of adiponectin seems to be mediated by increased fatty-acid oxidation through activation of AMP kinase and PPAR α [27].

Role of Adiponectin in OA Pathogenesis

In obese patients, OA is a comorbidity with diabetes, cardiovascular, and respiratory diseases [1]. Obesity may contribute to OA pathogenesis in two ways, by increasing joint load and mechanical wear of the joints, and by promoting systemic and local inflammation. Body composition studies demonstrated a direct association of obesity with the risk of knee OA, suggesting that weight loss strategies for knee OA should focus on reducing excess fat tissue [2, 3]. Partial or full IFP resection has been used to reduce knee pain resulting from IFP inflammation and impingement during total knee arthroplasty [28]. The clinical outcome of IFP resection in OA patients is controversial [28, 29]. For successful IFP resection, it is necessary to assess the pathology of the IFP before surgical intervention. Therefore, the development of pharmacological intervention to address IFP-derived inflammation and pain will require our understanding of the functions of adipokines such as adiponectin.

Adiponectin may have anti-inflammatory effects on chondrocytes, thereby protecting cartilage from degeneration. Adiponectin treatment of primary chondrocytes up-regulates tissue inhibitor of metalloproteinase-2 and down-regulates IL-1 β -mediated MMP13 gene expression. Treatment of rat articular chondrocytes with globular adiponectin (gAd) induces autophagy by AMPK/m-TOR activation and attenuates H₂O₂-induced apoptosis [30]. Decreased serum adiponectin is also associated with aseptic loosening 10 years after total hip replacement [31]. Thus, patients with high serum adiponectin have a longer durability of joint replacement than patients with low levels of adiponectin.

Adiponectin promotes osteogenic differentiation of human bone marrow stem cells via the Wnt/ β -catenin pathway [32]. Adiponectin increases the expression of osteogenic markers, including osteocalcin, alkaline phosphatase, and Runx2 and decreases PTEN, which suppresses osteoblast activity and bone mineral density [33]. Furthermore, adiponectin regulates bone metabolism by inhibiting osteoclastic differentiation and promoting osteoblastic commitment through APPL1/phosphoinositide 3-kinase (PI3K)/Akt signaling pathway *in vitro* and *in vivo* [34, 35].

However, during RA, adiponectin aggravates bone erosion by promoting the production of osteopontin which recruits osteoclasts in synovial tissue [36]. Adiponectin inhibits osterix and mineralization capacity in RA-derived-primary human osteoblasts and increases IL-8 secretion in osteoclasts and their bone

resorptive activity [37]. Although the pro-inflammatory effect of adiponectin in RA seems contrary to its anti-inflammatory property in OA, this could be due to the differences in concentrations of this adipokine occurring under these disease conditions. Alternatively, the differential effects of adiponectin on cells could be due to the different inflammatory environment. The mechanisms underlying the dichotomous effect of adiponectin on OA and RA remain to be elucidated.

Leptin

Leptin is the most extensively studied adipokine so far. Leptin, a 16-kDa adipokine secreted by adipose tissue, is associated with the regulation of food intake, energy assumption, and immunity. Leptin deficiency causes obesity in mouse models. However, humans exhibit leptin resistance. Increasing leptin concentration in the human body fails to reduce food intake, energy consumption, or body weight.

Leptin and its receptor (OB-R) are also detected in human chondrocytes [38]. Leptin can promote proliferation and differentiation of growth plate chondrocytes [39]. Leptin can stimulate *Coll10a1* in ATDC5 chondrocytes through the JAK/STAT and MAPK pathways [40]. Conversely, the growth plates of ob/ob mice show reduced type X collagen levels compared to the wild mice [41, 42]. Thus, leptin seems to be required for chondrocyte hypertrophy.

The concentrations of leptin are increased in cartilage and synovial fluid of OA patients [40]. Higher leptin mRNA levels were detected in end-stage knee OA cartilage compared to healthy joints [41], although there is no evidence at present of an association between serum leptin and cartilage damage or synovial inflammation. Chondrocytes from obese OA patients (BMI > 30 kg/m²) respond more intensely to leptin, possibly due to the elevated leptin level in the joint or the disruption of a leptin resistance mechanism in cartilage tissue [43]. Leptin can synergize with other pro-inflammatory and catabolic factors during OA. Leptin induces the production of IL-8, MMP-1, MMP-13, MMP-9, and MMP-3 in primary cultures of human chondrocytes and its concentration correlates with MMP-1 and MMP-3 in synovial fluid from OA patients [44, 45].

Leptin regulates bone metabolism via both central and peripheral nerve pathways. In the central pathway, leptin binds to its hypothalamic receptors and signals to osteoblasts through β 2 adrenergic receptors [46]. It activates two molecular cascades, c-myc, which inhibits osteoblast proliferation, and the PKA/ATF4/RANKL pathway, which enhances bone resorption of osteoclasts [47]. In the peripheral pathway, leptin binds to Ob-Rb on human mesenchymal stem cells (MSCs), enhancing proliferation and differentiation into osteoblasts [48]. Thus, leptin may cause chondrocyte hypertrophy and degeneration and excessive ossification during OA.

Resistin

The gene of resistin, encoding a 12.5-kDa adipokine protein, is located on chromosome 19p13.2. While the major source of resistin is white adipose tissue, resistin is also expressed by macrophages in humans. Resistin is related to metabolic disease and inflammation, since reduction of the levels of resistin leads to enhanced insulin sensitivity and glucose homeostasis. The local concentration of resistin is increased during OA, which is probably due to the resident macrophage cells in synovium [49].

Resistin is also expressed by osteoblasts, osteoclasts, and chondrocytes. There is a synergistic regulation between resistin and several cytokines, as well as chemokines. Resistin induces the expression of cytokines and chemokines in chondrocytes. Treatment of mouse cartilage with resistin leads to increased IL-6 and IL-8 level. Resistin may stimulate bone remodeling by promoting osteoblast proliferation and osteoclast differentiation. Resistin stimulates proliferation of pre-osteoblastic MC3T3-E1 cells [50]. Transfection of RAW264.7 cells with resistin cDNA stimulates osteoclastogenesis by enhancing NF- κ B promoter activity [50]. Thus, resistin may promote OA pathogenesis by stimulating pro-inflammatory cytokines in cartilage and bone remodeling. However, the role of resistin in OA onset and progression in vivo remains to be determined.

Chemerin

Chemerin, a 14-kDa protein, is expressed mainly in white adipose tissue. The chemerin level in synovial fluid correlates with body mass index (BMI) and OA severity [51]. It is secreted as a 163 amino acid inactive form and then activated by cleavage in the C-terminus [52]. Chemerin is associated with energy metabolism that mediates glucose uptake, lipolysis, and adipocyte differentiation. Chemerin stimulates phosphorylation of ERK and MAPKs, signals that are involved in lipid synthesis in adipocytes, thereby promoting adipocyte maturation. In turn, adipocytes express higher levels of chemerin after differentiation.

Chemerin receptors contain CMKLR1 and ChemR23, which are expressed mainly in immune cells. Chemerin is a chemoattractant protein, which stimulates chemotaxis of dendritic cells and macrophages to the inflammatory site. For example, chemerin may recruit immune cells (including macrophages) in synovium as part of the inflammatory cascade in the pathogenesis of OA. Obesity patients have larger amount of chemerin in serum and the serum level of chemerin is correlated to OA severity [51].

Chemerin can be detected in cartilage and synovial fluid, while ChemR23 is also expressed in human chondrocytes [53]. In human chondrocytes, chemerin enhances the production of proinflammatory cytokines, as well as MMPs [53],

although chemerin usually reduces the production of pro-inflammatory cytokines in other types of cells. Chemerin regulates bone metabolism through mediating testosterone production and the balance between osteoblasts and osteoclasts differentiation [54]. Although inhibiting CMKLR1 stimulated expression of osteoblast markers in primary MSCs in vitro [55], its deficiency in vivo resulted in lower bone mass in male mice [54]. Thus, chemerin may stimulate inflammation, cartilage degeneration, and ossification. However, its role in OA pathogenesis remains to be determined in vivo.

IL-6

IL-6, a glycosylated protein of 21–28 kDa, has four- α -helix bundle structure in an up-up-down-down topology. The IL-6 family contains other members including IL-11, leukemia inhibitory factor (LIF), and oncostatin M (OSM). The IL-6 receptors include soluble IL-6 receptor (sIL-6R), membrane bounding receptor (mbIL-6R), and IL-6 family common receptor gp130, which exists as inactive dimers at the cell membrane [56, 57]. Two IL-6 signaling pathways exist. The classical signaling pathway involves IL-6 binding to mbIL-6R, which only a few cell types express, and activation of JAK/STAT, ERK, and PI3K in cells. The trans-signaling pathway involves binding of the IL-6/sIL-6R complexes to constitutively expressed receptor gp130, which then transduces IL-6 signals.

As one of the most prominent SASPs, IL-6 is expressed in adipose and muscle tissues especially during aging. It is involved in metabolic diseases such as obesity and other inflammatory diseases. IL-6^{-/-} mice develop late onset obesity [58]. Specific blockade of IL-6 trans-signals by spg130Fc affects insulin sensitivity and glucose tolerance [59]. High levels of IL-6 are associated with the increased risk of knee OA [60]. The patellar fat pad secretes adipokines, including IL-6, which infiltrates into cartilage via synovial fluid [12, 13]. IL-6 mediates suppression of aggrecan (Acan) and induction of Mmp13 gene expression by Notch in chondrocytes [61]. IL-6/sIL-6R trigger osteoclast formation and bone resorption by inducing RANKL expression via JAK/STAT signaling [62, 63]. Taken together, there is solid evidence that IL-6 regulates metabolism and OA progression. Thus, IL-6 or IL-6 receptor should be considered as a therapeutic target for obesity-related OA.

Tumor Necrosis Factor-Alpha (TNF- α)

TNF- α is a pro-inflammatory cytokine produced by macrophages, and also by adipocytes and vascular endothelial cells. TNF- α exists as two forms, membrane-bound (mTNF- α) and free soluble (sTNF- α) [64–66]. There are two TNF- α receptors, TNF-R1 (CD120a) and TNF-R2 (CD120b). While constitutively expressed TNF-R1 binds both sTNF- α and

mTNF- α , TNF-R2 is inducible and binds mTNF- α only. TNF-R1 contains a death domain, which is similar to the death region of Fas protein. This intracellular region is essential for TNF- α -initiated apoptosis by providing the binding sites for accessory signaling proteins, including Fas-associated death segment binding protein (FADD), TNFR-1 associated death segment binding protein (TRADD), and TNFR-related factor 2 (TRAF-2). TNF-R1 signaling initiates the inflammatory response pathway by recruiting two different signaling complexes that activate NF- κ B, ERK, and p38MAPK signaling pathways [67] and the FADD/pro-caspase-8 cell death pathway [68].

The critical role of TNF- α in OA pathogenesis is well established. TNF- α can be detected in synovial fluids of OA patients and the TNF- α level increases as the OA score increases [69, 70]. TNF- α induces the production of iNOS, COX-2, IL-6, and PGE₂ [71–73], and inhibits the synthesis of type II collagen, proteoglycans, and proteoglycan-binding proteins [73, 74]. TNF- α regulates the process of bone remodeling involving both osteoclasts and osteoblasts. While TNF- α induces osteoclastogenesis via RANKL, it suppresses bone formation by inhibiting MSC differentiation into osteoblasts via Notch activation [75].

Conclusion and Future Direction

Adipokines are a newly emerging class of signaling molecules, produced by adipocytes and involved in regulating inflammation, bone and cartilage metabolism, and homeostasis. In the past, attentions were focused on the cytokines and chemokines produced by synovium and immune cells in the joint. However, in recent years, research has shown that OA, which was considered as a local disease, can be related to systemic metabolism disease such as obesity [4, 5]. The close association between OA and obesity strongly suggests that OA can be a systemic disease involving multiple tissues and triggered by inflammation and metabolic imbalance. OA is also associated with aging and injury, both of which induce inflammation, cell senescence, and SASPs that hamper tissue repair.

In the joint, the roles of cartilage, bone, ligament, muscle, and synovium in OA pathogenesis have been well studied. In contrast, less is known about the roles of adipose tissues in the joint. Understanding the properties of adipose tissues and derived cells becomes even more critical when adipose-derived stem cells are touted as a good source of joint tissue repair. The sources of adipose tissues come from two sites in the joint, fat pads such as the IFP and bone marrow. During aging and obesity, the fat content in adipose tissues increases, which triggers increased secretion of adipokines in the joint. Furthermore, the yellow bone marrow is developed, which enriches adipocytes by activating adipocyte lineage expansion

[76•]. This is done at the expense of impairing osteogenic lineage in the long bone, resulting in bone dysfunction in the aged. An attractive hypothesis is that the metabolic syndrome in elderly people leads to increased body fat, inflammaging, and senescence of cells in articular tissues [77].

There are hundreds of adipokines and this review only cover several whose roles in bone and joint have been studied. These adipokines can be divided into two classes. The first class contains IL-6 and TNF- α , which are well-studied due to their synthesis by a variety of immune cells and are among the most important SASPs. Thus, the antagonists that neutralize their actions are some of the most successful drugs to treat arthritis. The second class contains adiponectin, leptin, resistin, and chemerin. In comparison to the first class of adipokines, these are more specifically synthesized by adipocytes although less well characterized for their roles in regulating joint health. For example, it is not known whether they can be classified as SASPs. However, their increased expression during aging and their synergistic effects in stimulating other SASPs such as IL-1, IL-6, and TNF- α make them excellent candidate SASPs.

These factors accumulate during aging and contribute to local inflammatory reactions in the joints. They can also cause changes the surrounding environment of the joint cells, thereby changing in the fate of the cells—inducing cell senescence. Therefore, attention to changes in the joint environment is important for the progress of OA research. It is important to note that chondrocytes are not the only cell type when studying the fate of cartilage-associated cells. There are also mesenchymal stem/progenitor cells in articular cartilage that undergo cell senescence [78•, 79••]. Studying the response of these cells to these new adipokines in the joint environment will be a new direction for the treatment of OA.

Injury-related OA induces the expansion of chondrocytes to repair cartilage lesion, which results in loss of quiescence of chondrocytes and increases the accumulation of cell cycle inhibitors (e.g., P16^{INK4A}), as well as reactive oxygen species (ROS), leading eventually to senescence. Local clearance of senescent cells attenuates the development of the injury-induced OA and creates a pro-regenerative environment [80••]. However, the source of senescent cells accumulating in joint tissues after ACLT (anterior cruciate ligament transection) has not been defined [80••]. Cells other than synoviocytes and chondrocytes may contribute to inflammation, SASP, and joint degeneration. We suggest that joint adipose tissues may contribute to synovial inflammation, cartilage degeneration, bone remodeling, and OA pathogenesis by producing two classes of adipokines, including SASPs.

If the first class of adipokines can be used as a good example, anti-arthritis pharmaceuticals may be developed using the second class of adipokines as targets. It will be necessary, therefore, to characterize the properties of these adipokines in more detail, especially in OA animal models in vivo.

Furthermore, while leptin, resistin, and chemerin seem to promote joint inflammation, adiponectin has dichotomous effects depending on its molecular forms and concentrations in the joint. Since adiponectin presents intriguing anti-inflammatory and pro-regenerative properties that are unique among adipokines, it warrants further investigation.

Funding Information Grant sponsor: NIGMS/NIH; Grant number: P30GM122732

Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors

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