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The emerging role of adipokines in osteoarthritis: a narrative review

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Abstract Osteoarthritis (OA) is a most common multifactorial degenerative joint disease in elderly individuals. OA is affecting severely the quality of life of patients, while the causes of OA are not completely understood. Age, obesity, the female sex, and previous injury are considered as significant risk factors. Recently, increased levels of adipokines which are mainly produced by adipocytes have been detected in patients with osteoarthritis. Moreover, studies on different adipokines all reveal that they have played proinflammatory and catabolic/anabolic roles during the pathophysiology of OA. In the present review, we summarize current data on the effect of the adipose tissue-derived hormones leptin, adiponectin, resistin and visfatin on initiation and progression of OA.

Keywords Adipokines · Osteoarthritis · Leptin · Adiponectin · Resistin · Visfatin

Introduction

Osteoarthritis (OA), a degenerative joint disorder, is characterized by degeneration of articular cartilage, changes in subchondral bone, osteophyte formation, and synovial inflammation. It is the most common arthritis and may lead to severe symptoms like pain, malformation of the joint and disability [1], while the causes of which are poorly understood. Present studies have proven the age, obesity, female sex and previous injury may play an important role in the process of OA [2].

Obesity is a strong risk factor for incident of OA. The obesity-induced OA may be due to high mechanical stresses applied on the tissues. So some weight-bearing joints, particularly the knee and hip, are easily suffering from OA as a result of increased joint loading [3, 4]. And patients with knee OA would experience the symptomatic relief after weight loss [5]. However, various cohort studies have demonstrated that obesity is also a risk factor for non-weight bearing joints OA, such as hands [6]. Since the mechanical factor can't explain this phenomenon, more and more teams are paying their attention to an obesity-related systemic factor on the pathogenesis of OA. Nowadays, obesity was commonly considered as a low grade inflammatory state. Adipose tissue was a real endocrine organ that releases cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α), as well as adipokines, such as leptin, adiponectin, resistin, visfatin and so on [7]. The novel adipokine family exhibited pleiotropic functions through endocrine, paracrine, autocrine in a wide variety of physiological or physiopathological processes, including food take, energy expenditure, lipid and glucose metabolism, inflammation, insulin resistant, bone formation and so on [8, 9]. Adipokine was also viewed as a potential systemic factor which links obesity to arthritis [10]. This review addresses recent studies concerning the involvement of adipokines in OA, concentrating on the roles of adipokines played in the pathophysiology of OA.

Leptin

Leptin, a 16 kDa non-glycosylated protein secreted by adipose tissue, was encoded by the obese (ob) gene localized on

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7 and 6 chromosomes in human and mouse. The levels of serum leptin were directly correlated with white adipose tissue (WAT) mass [11]. Leptin receptor (Ob-R) was a member in class I cytokine receptor superfamily and mediated various biological activity of leptin [12]. Structurally, both leptin and its receptor shared common structural and functional properties with IL-6, so this adipose-derived protein has been classified as an adipocytokine or adipokine [13]. By binding to Ob-R leptin triggered a signal cascade involving the JAK (janus kinase)/STAT (signal transducers and activators of transcription) family, as well as/PI3K/Akt/NF-κB and p300 signaling pathway [14, 15].

Leptin played a key role in the regulation of body weight by decreasing food intake and stimulating energy consumption [16]. The other function of leptin system has been widely studied and implicated as a regulatory molecule in various physiologic processes, such as infection, inflammation, autoimmune diseases, rheumatoid arthritis (RA) and so on [17–19].

Increasing evidence suggested that leptin was a novel proinflammatory adipocyte-derived factor in the pathophysiology of OA. Figenschau et al. demonstrated that both serially cultured human articular chondrocytes and native human cartilage expressed the Ob-R. And chondrocytes stimulated with leptin exhibited an increased proliferation and an enhanced synthesis of proteoglycans and collagen [20]. Another study by Dummond et al. found that leptin played a key role in the pathogenesis of OA. Their study was the first one to show the presence of leptin in synovial fluid (SF) obtained from OA patients and the significant correlation between leptin levels and BMI. Intra-articular injection of leptin strongly stimulated the synthesis of insulin-like growth factor-1 (IGF-1) and transforming growth factor-β (TGF-β) at both the messenger RNA (mRNA) and protein levels which might exert anabolic activity in cartilage metabolism [21]. Moreover, exogenous leptin could enhance chondrocytes proliferation and subsequent cell differentiation [22]. Actually, up-regulation the number of chondrocytes by leptin was a considerably effective way in the treatment of OA-affect articular cartilage. The process which increases the amount of chondrocytes in damaged cartilage by autologous chondrocyte transplantation could repair the chondral defects [23, 24]. It seemed that they all regarded leptin as an anabolic role in cartilage.

On the contrary, not all evidence supported the view above. Simopoulou and Ku et al. showed that SF leptin level significantly increased in advanced OA cartilage compared to minimal. The evidence that leptin induced IL-1β production and matrix metalloproteinases-9 (MMP-9), MMP-13 protein expression, indicated that leptin may act as a proinflammatory role on cartilage metabolism [25, 26]. Vuolteenaho et al. also found that leptin could mediate the cartilage metabolism by enhancing the production of NO, Prostaglandin E2 (PGE2), IL-6, and IL-8 in OA cartilage [27]. Using small interference RNA to induce leptin down-regulation could directly inhibit MMP-13 expression in chondrocytes [28]. Furthermore, treatment of ATDC5 chondrocytes and human primary chondrocytes with leptin pointed out that leptin played a proinflammatory role by inducing NO production and increasing the expression of nitric oxide synthase (NOS) type II in synergy with IL-1 [29]. All of these work focused on the proinflammatory effect in vitro and leptin seemed to a foe of cartilage homeostasis. Interesting, by comparing incidence of knee OA between leptin-deficient (ob/ob) and leptin receptor-deficient (db/db) female obese mice and controls, researcher failed to detect any significant between them. This novel-designed experiment suggested that leptin was a necessary role in the pathophysiology of the OA associated with obesity. Obesity alone was insufficient to induce systemic inflammation and knee OA [30].

Recently, our team has studied the role of leptin on normal articular cartilage in vivo. By injecting into the knee joints of rats with recombinant rat leptin, we found that proteolytic enzymes, including MMPs, and cysteine proteases, were markedly increased at both gene and protein levels, while anabolic factor, likes basic fibroblast growth factor (bFGF), was decreased. In addition, the gene expression of ADAMT-4 (a disintegrin and metalloproteinase with thrombospondin motifs) and ADAMT-5, which were considered as the most efficient aggrecanases in the pathogenesis of OA, were markedly increased after leptin treatment in our study [31–33]. These evidences clearly indicated that leptin may act as a catabolic factor involved in the progression of osteoarthritis [34].

Besides, it was now evident that leptin was also expressed in osteoblasts, stromal cells, and disc cell in the musculoskeleton system and could modulate bone growth [35–39]. Mutabaruka et al. showed that subchondral osteoblasts in OA exhibited high levels of leptin compared to normal and this local leptin production could respond for abnormal osteoblast function [40]. Osteophytes, synovium and infrapatellar fat pad could also secrete generous leptin to synovial fluid in OA [41]. These observations collectively demonstrated that leptin was also partly involved in or responded for the pathological change of other joint tissues in the pathophysiology of OA.

In a word, leptin was a double-edged sword, inducing both synthesis and degradation of articular cartilage. To date, the mechanism of leptin in the development of arthritis was still unclear and should be further investigated.

Adiponectin

Adiponectin, also called acrp30 (adipocyte complement-related protein of 30 kDa), was a newly discovered

hormone secreted by adipocytes [42]. It shared sequence homology with collagen VIII, X and complement factor C1q [42, 43] and presented in three molecular forms: trimer, hexamer, and a high molecular weight (HMW) species [44]. In human beings, the circulating levels of adiponectin were decreased in obese and diabetic states. The biological activity of adiponectin was mediated by specific receptors, AdipoR1 and AdipoR2. AdipoR1 was abundantly expressed in skeletal muscle, whereas AdipoR2 was most abundantly in the liver [45]. Previously, it has been reported that 5′-AMP-activated protein kinase (AMPK)/p38/IKK$\alpha\beta$, NF-κB and c-Jun N-terminal kinases (JNKs) signaling pathway were involved in the adiponectin-mediated pathological processes [46, 47].

There was emerging evidence that adiponectin may have wide range of effects in cardiovascular disease, type 2 diabetes, and metabolic syndrome [48–50]. Previous reports have demonstrated that adiponectin was particularly important for inflammation. In vitro study, cytokines such as IL-6 and TNF-α could inhibit adiponectin secretion in cultured adipocytes [51, 52]. However, a negatively correlation between plasma adiponectin level and plasma C-reactive protein (CRP) level indicated that adiponectin may exert an anti-inflammatory role by regulating CRP expression in adipose tissue [53]. So sometimes adiponectin could exert anti-inflammatory rather than proinflammatory activities.

A growing number of investigations have consistently demonstrated that adiponectin played a dual role in arthritis. Adiponectin has been described as a potent mechanistic link between obesity and RA since its plasma level was higher in RA patients compares to healthy controls [54]. And another study about synovial fibroblasts in vitro revealed that adiponectin could stimulate the production of IL-6 and pro-MMP-1, which were regarded as key mediators of destructive arthritis [55]. So, the intracellular regulation of adiponectin might contribute to proinflammatory and matrix-degrading. As to OA, a present study revealed that OA plasma exhibited significantly 100-fold increase of adiponectin (5.3 ± 1.3 μg/ml) as compared with OA SF (44 ± 17 ng/ml) [56]. Synovium and infrapatellar fat pad have been shown to be the main sources of adiponectin in the OA-affect joint [41]. These findings provided evidence for a specific local dysregulation of adiponectin in the arthritis joint space. They also suggested adiponectin may act as a protective role against OA by up-regulating tissue inhibitor of metalloproteinase-2 (TIMP-2) and down-regulating IL-1β-induced MMP-13 at both mRNA and proteins levels [56]. In STR/Ort mice, a spontaneous primary osteoarthritis model, the serum adiponectin concentration was significantly low than in the control group [57]. All of these above puzzled us: did adiponectin play a protective role during the pathophysiology of OA?

Unfortunately, the role of adiponectin played in OA was controversial. Lago's study demonstrated that adiponectin may have proinflammatory effects on chondrocytes by inducing the expression of NOS2 and stimulating proinflammatory cytokines release, such as IL-6, MMP-3, MMP-9 and monocyte chemattractant protein-1 (MCP-1) [58]. Surprisingly, Filkova et al. reported that increased serum levels of adiponectin in erosive OA was found compared with non-erosive OA, suggesting that adiponectin may play a role in matrix degradations [59]. Also, by stimulating the syntheses of vascular endothelial growth factor (VEGF) and MMPs, adiponectin facilitated joint inflammation and destruction [60]. All of the above reveal the close relationship between adiponectin and OA, no matter by protecting the joints or facilitating the osteoarthritis.

Resistin

Resistin, known as a macrophage/monocyte-derived proinflammatory mediator, belonged to the found in inflammatory zone (FIZZ) protein family and secreted mainly by peripheral-blood mononuclear cells [61–63]. Resistin received its name from its apparent induction of insulin resistance in mice [64]. It was secreted by adipose tissue, but also expressed in several other tissues such as neutrophils, lung, heart, and synovial tissue [62, 65]. In rodents, circulating levels of resistin were increased in obesity [66]. In recent years a growing number of studies proved that resistin has been implicated in inflammatory processes. It was reported that human resistin stimulated the synthesis and secretion of TNF-α and IL-12 and this involved the activation of NF-κB transcription factor in macrophages in vitro [67]. Moreover, proinflammatory cytokines including IL-1, IL-6, TNF-α, and lipopolysaccharides (LPS) could stimulate the up-expression of resistin mRNA [68].

Recent studies have shown that resistin made plenty of biological effects to arthritis. Resistin could be detected locally in the inflamed joints of patients with RA and OA and elevated in RA [41, 69]. It could induce arthritis when injected into healthy mouse joints and strongly up-regulated the release of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 [69]. Furthermore, markedly increased production of resistin was found at local sites of inflammation such as synovial tissue and synovial fluid in patients with rheumatoid arthritis [65]. To note, recombinant resistin stimulated proteoglycan degradation in mouse femoral head cultures and induction of inflammatory cytokine and PGE2 production, whereas it inhibited proteoglycan synthesis in human cartilage explants [70]. As noted above, it has been concluded that resistin may act as a novel proinflammatory mediator in chronic joint inflammatory diseases.

Visfatin

Visfatin was previously identified as a presumptive cytokine named pre-B cell colony-enhancing factor (PBEF) which synergized with IL-7 to promote the differentiation of B-cell precursors. It was coded by a novel gene which was isolated from a human peripheral blood lymphocyte cDNA library [71]. Several tissues expressed visfatin/PBEF, including skeletal muscle, liver, and bone marrow [71]. Visfatin was closely correlated with the regulation of insulin secretion, insulin receptor signaling as well as mRNA levels of diabetes-related genes in mouse [72, 73]. It was also up-regulated in acute lung injury, sepsis and atherosclerotic lesions [74, 75], while it was shown to induce the production of IL-1β, IL-6, IL-10, and TNF-α in human monocytes in vitro [76]. In turn, TNF-α, IL-1β, IL-6, LPS and dexamethasone could stimulate the synthesis of visfatin. All of above suggested that visfatin should be regarded as an inflammatory mediator in some circumstances.

There were indications that visfatin may also be involved in the pathogenesis of RA and OA. The expression of visfatin was detected in synovial tissue, serum, and synovial fluid and a marked higher level of serum visfatin was noted in patients with RA [54, 77]. Levels of visfatin in serum and synovial fluid were strong positive correlated with the severity of RA. Moreover, visfatin presented a proinflammatory and matrix-degrading role by inducing IL-6, IL-8, MMP-1, and MMP-3 production in RA synovial fibroblasts [77]. Nowell and colleagues demonstrated that visfatin was regulated via IL-6 trans-signaling and the IL-6-related cytokine oncostatin M [78]. Recently, a study focused on the role of visfatin in OA indicated that visfatin synthesis was increased by IL-1β treatment in vitro culture of human chondrocytes. Meanwhile, visfatin manifested a pro-degradative effect by increasing the synthesis and release of MMP-3, MMP-13, ADAMTS-4, and ADAMTS-5 and decreasing aggrecan production in chondrocyte, suggesting that visfatin had a catabolic function in cartilage and might have an important role in the pathophysiology of OA [79].

Adipokine, obesity and osteoarthritis: more complex than predicted

Given all this evidence, studies on different adipokines revealed that they have played proinflammatory and catabolic/anabolic role during the pathophysiology of OA. Recently, two newly discovered adipokines named vaspin and omentin, have been detected in synovial fluid obtained from RA and OA patients [80]. So the relationship between obesity and osteoarthritis was more complex than predicted!

In conclusion, adipokines exert lots of biological effects to joint and contribute to the progress of OA. Nevertheless, OA is a multifactorial disease and the exact mechanism of adipokines in obesity-induced OA is still unclear. Further investigations are needed to clarify their roles in OA.

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