BCPT Basic & Clinical Pharmacology & Toxicology

Basic & Clinical Pharmacology & Toxicology, 2014, **114**, 97–102 Doi: 10.1111/bcpt.12109

MiniReview

Adiponectin and Leptin: New Targets in Inflammation

Morena Scotece[1], Javier Conde[1], Verónica López[1], Francisca Lago[2], Jesús Pino[3], Juan Jesús Gómez-Reino[1] and Oreste Gualillo[1]

[1]NEIRID Lab (NeuroEndocrine Interaction in Rheumatology and Inflammatory Diseases), SERGAS, Santiago University Clinical Hospital, Institute of Medical Research (IDIS), Santiago de Compostela, Spain, [2]Research Laboratory 7 (Molecular and Cellular Cardiology), SERGAS, Santiago University Clinical Hospital, Institute of Medical Research (IDIS), Santiago de Compostela, Spain and [3]Division of Orthopaedics Surgery and Traumatology, SERGAS, Santiago University Clinical Hospital, Santiago de Compostela, Spain

(Received 20 May 2013; Accepted 28 June 2013)

Abstract: Inflammation is a complex mechanism of cell/tissue responses to injuries triggered by multiple causes, including trauma, pathogens or autoimmune abnormal responses. In the last years, a novel line of thought is emerging by giving a more holistic vision of chronic arthropathies through a recently identified group of molecules, called adipokines. Actually, most of these recently identified factors, produced prevalently by white adipose tissue but also by cells of the joints (chondrocytes and synovial fibroblasts) and immune cells, play a significant role in chronic inflammation. Adipokines dysregulation has emerged as a common characteristic of chronic inflammation in rheumatic diseases in particular when obesity or, more precisely, adipose tissue dysfunction is associated with common rheumatic diseases, such as osteoarthritis and rheumatoid arthritis. In this MiniReview, we discuss the role of adipokines in osteoarthritis and rheumatoid arthritis providing an updated overview of their pathophysiological role and potential use as therapeutic targets.

With the discovery of leptin in 1994 [1], white adipose tissue (WAT) has been recognized to be a true endocrine organ, which is able to secrete a wide variety of factors termed adipokines [2,3]. In spite of their metabolic activities, adipokines represent a new family of compounds that could participate in several processes, including inflammation and immunity [4–6], and are also involved in the pathophysiology of rheumatic diseases.

Adipokines include a variety of pro-inflammatory factors most of them being increased in obesity and appearing to contribute to the so-called 'low-grade inflammatory state' in obese individuals.

Obesity, the condition that spurred the research on adipokines, has been considered a risk factor for developing osteoarthritis (OA) [7,8]. It has been reported that obesity increases the incidence of OA, particularly in weight-bearing joints such as knees [9], but the fact that obese individuals have an increased risk of OA also in non-weight-bearing joints such as hands, wrists and shoulder [10,11], which reveals that soluble factors, adipokines indeed, are at play in the onset and progression of this rheumatic disease.

The aim of this MiniReview is to present the data concerning the role of two important adipokines: leptin and adiponectin. We analyse the role of these adipokines in inflammation focusing our attention on their involvement in rheumatic diseases, particularly in osteoarthritis (OA) and rheumatoid arthritis (RA).

Author for correspondence: Oreste Gualillo, NEIRID Lab (NeuroEndocrine Interaction in Rheumatology and Inflammatory Diseases), SERGAS, Santiago University Clinical Hospital, Institute of Medical Research (IDIS), Santiago de Compostela, Spain (fax +34981950905, e-mail oreste.gualillo@sergas.es).

Leptin

Leptin, the protein product of the *ob* gene, the murine homologue of human LEP gene [1] exerts its biological actions through the activation of its OB-Rb long-form receptor isoform that is encoded by the gene diabetes (db) and belongs to the class 1 cytokine receptor superfamily. This hormone decreases food intake increasing anorexigenic factors as cocaine- and amphetamine-related transcript (CART) and increases energy consumption by suppressing orexigenic neuropeptides such as neuropeptide Y (NPY) [12]. Leptin levels are mostly dependent on the amount of body fat, but its synthesis is also regulated by inflammatory mediators [13].

Leptin and Rheumatic Diseases

It is increasingly evident that this hormone plays a key role in the rheumatic diseases, particularly osteoarthritis (OA) and rheumatoid arthritis (RA). Serum leptin levels are increased in patients with OA [14], and although some initial findings have suggested an anabolic role of this hormone in the cartilage [15], most studies reveal a catabolic role of leptin at cartilage level. For instance, our group has demonstrated that, in cultured human and murine chondrocytes, type 2 nitric oxide synthase (NOS2) is synergistically activated by the combination of leptin plus interferon-γ or IL-1β via a mechanism involving JAK2, PI3K and mitogen-activated kinases (MEK1 and p38) [4,16]. Nitric oxide (NO), which is induced by a wide range of pro-inflammatory cytokines, is a well-known pro-inflammatory mediator on joint cartilage, where it triggers chondrocyte phenotype loss, apoptosis and metalloproteinases (MMPs) activatiozn.

Recently, it has been demonstrated that leptin is able to induce also the expression of MMPs involved in OA cartilage damage, such as MMP-9 and MMP-13 [17]. In fact, conditioned media from osteoarthritic infrapatellar fat pad, containing leptin, induce the synthesis of certain MMPs [18], demonstrating that the local production of leptin participate in the degradation processes occurred in the joints. More evidence suggested that leptin, alone and in combination with IL-1β, up-regulates MMP-1 and MMP-3 production in human OA cartilage through the transcription factor NF-κB, protein kinase C and MAP kinase pathways. This adipokine is also correlated positively with MMP-1 and MMP-3 in synovial fluid from patients with OA [19]. Noteworthy, very recently, leptin has been demonstrated to increase IL-8 production in human chondrocytes [20]. Additionally, the gene expression of ADAMTS-4 and ADAMTS-5 was markedly increased, and a depletion of proteoglycan in articular cartilage was observed after treatment with leptin [21].

Very recently, our group demonstrated that leptin is also able to increase the expression of vascular cell adhesion molecule-1 (VCAM-1), a relevant adhesion molecule involved in the recruitment and extravasation of leucocytes from circulating blood to inflamed joints [22].

Leptin and leptin's receptor expression levels were significantly increased in advanced OA cartilage and in synovial fluid [23]. Moreover, a very recent study showed that leptin bioactive levels are increased in synovial fluid from obese patients with OA, and SOCS-3 (a typically leptin-induced signalling suppressor) expression in cartilage is decreased in these patients compared with non-obese patients with OA [23].

These results suggested that leptin might act as a pro-inflammatory factor on cartilage metabolism, suggesting a prominent catabolic effect in OA joints.

Leptin was also implicated in autoimmune diseases such as RA, but the role of this adipokine in this disease is still unclear. In patients with RA, circulating leptin levels have been described as either higher or unmodified in comparison with healthy controls [17,24]. Experimental antigen-induced arthritis is less severe in leptin-deficient *ob/ob* mice than in wild-type mice, whereas leptin-deficient mice and leptin-receptor-deficient mice exhibited a delayed resolution of the inflammatory process in zymosan-induced experimental arthritis. Notably, leptin decreased the severity of septic arthritis in wild-type mice. So, in the light of the present results, it seems difficult to make an unambiguous conclusion about a potential role of leptin in RA [25]. Several studies have also demonstrated that there may exist a close dependence between the risk of aggressive course of RA and leptin levels [26,27]. In addition, a correlation between serum leptin, synovial fluid/serum leptin ratio, disease duration and parameters of RA activity has been also reported [28].

It is relevant to mention that current biological treatments for RA, such as anti-TNF (tumour necrosis factor) therapies, do not directly modulate leptin levels [29–31].

Many studies have demonstrated the effect of this adipokine in different joint cell types. Apart from the prominent activity of leptin in chondrocytes, which was shown by our group and others [4,16,22,32], leptin has more recently been shown to exert a pro-inflammatory effect in synovial fibroblasts. Leptin induced IL-8 production in these cells via a mechanism involving a canonical activation of the leptin receptor and nuclear factor κB (NFκB) [33]. To note, this effect was also demonstrated by our group in human chondrocytes [20].

The action of leptin in RA is not only targeted to articular tissue; this adipokine also exerts direct modulatory effects on activation, proliferation, maturation and production of inflammatory mediators in a variety of immune cells [34].

In particular, it is known that leptin is able to modulate T regulatory cells (Treg) that are potent suppressors of autoimmunity. Matarese *et al.* have recently demonstrated that leptin secreted by adipocytes sustains Th1 immunity by promoting effector T cell proliferation and by constraining Treg cells expansion [35]. Weight loss, with concomitant reduction in leptin levels, induces a reduction in effector T cells proliferation and an increased expansion of Treg cells leading to a down-regulation of Th1 immunity and cell-mediated autoimmune diseases associated with increased susceptibility to infections. On the contrary, an increase in adipocyte mass leads to high leptin secretion, which results in expansion of effector T cells and reduction in Treg cells. This fact determines an overall enhancement of the pro-inflammatory immunity and of T cell-mediated autoimmune disorders.

Very recently, it has been demonstrated that leptin can activate mammalian target of rapamycin (mTOR) and regulate the proliferative capacity of regulatory T cells. This study suggests that the leptin-mTOR signalling pathway is an important link between host energy status and Treg cell activity. Authors conclude that oscillating mTOR activity is necessary for Treg cell activation and suggest that this might explain why Treg cells are unresponsive to TCR stimulation *in vitro* when high levels of leptin and nutrients may sustain mTOR activation [35,36]. However, leptin can be considered as a link among immune tolerance, metabolic function and autoimmunity, and future strategies aimed at interfering with leptin signalling may represent innovative therapeutic tools for autoimmune disorders.

Adiponectin

Adiponectin, also known as GBP28, apM1, Acrp30 or AdipoQ, is a 244-residue protein produced mainly by WAT. This hormone has structural homology with collagens VIII and X and complement factor C1q, and it circulates in the blood in relatively large amounts in different molecular forms [37,38].

It increases fatty acid oxidation and reduces the synthesis of glucose in the liver.

Adiponectin acts via two receptors, one (AdipoR1) found predominantly in skeletal muscle and the other (AdipoR2) in liver. Transduction of the adiponectin signal by AdipoR1 and AdipoR2 involves the activation of AMPK, PPAR-α, PPAR-γ and other signalling molecules [37].

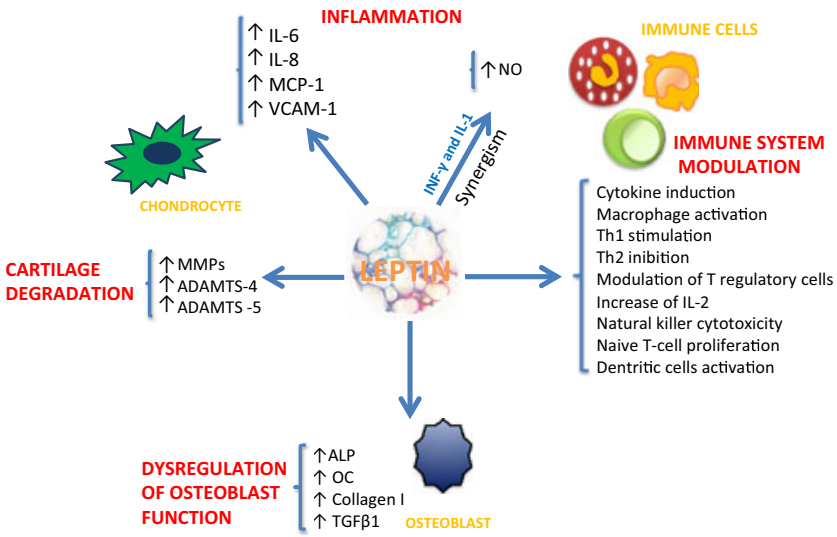

Fig. 1. Schematic representation of the main activities of leptin in inflammatory response and interactions with the immune system.

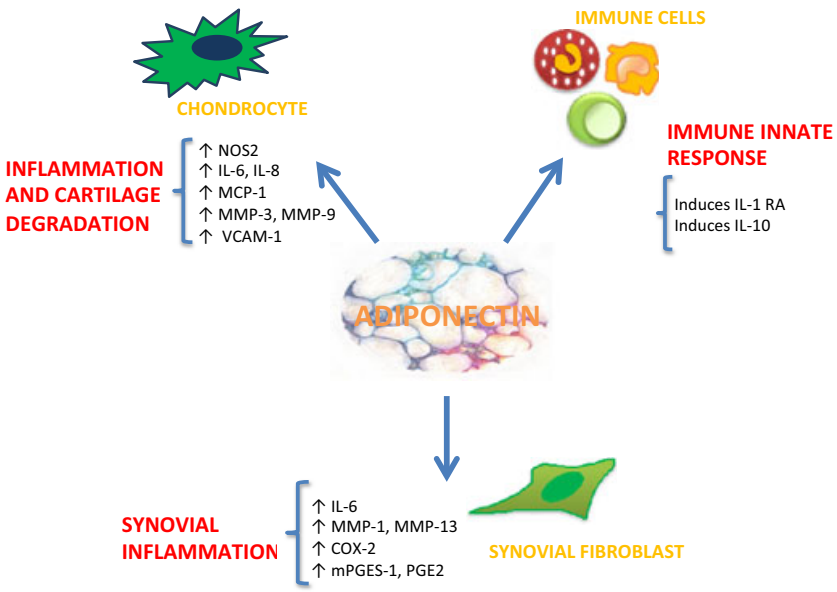

Fig. 2. Schematic representation of the main activities of adiponectin in inflammatory response and interactions with the immune system.

Adiponectin and Rheumatic Diseases

Adiponectin has a wide range of effects in pathologies with inflammatory component, such as cardiovascular disease, endothelial dysfunction, type 2 diabetes, metabolic syndrome and rheumatic diseases [39]. In contrast to its previously described protective role in vascular diseases, there are some evidence that show that adiponectin might act as a pro-inflammatory factor in joints, and it could be involved in matrix degradation.

Adiponectin in chondrocytes leads to the induction of NOS2 via a signalling pathway that involves PI3 kinase. Similarly, this adipokine increases IL-6, MMP-3, MMP-9 and MCP-1 production in the same cell type [40]. Kang *et al.* have reported that collagenase-cleaved type II collagen neoepitope, a product of collagen type II degradation, was increased in supernatants of adiponectin-treated OA cartilage explants [41]. Furthermore, it has been reported that adiponectin is able to induce the expression of IL-6 in human synovial fibroblasts [42].

Adiponectin, in a similar manner to that of leptin, was recently described as a potent inductor of VCAM-1 in chondrocytes, even more powerful than the classic pro-inflammatory cytokine IL-1β [22]. So, it is reasonable to describe a scenario in which this adipokine is able to perpetuate cartilage-degrading processes by inducing molecules responsible of monocyte and leucocyte infiltration to the joint.

The implication of adiponectin in OA pathogenesis is supported also by clinical observations. It has been reported that plasma adiponectin levels were significantly higher in patients

with OA than in healthy controls [43], and this adipokine has been detected in OA synovial fluids correlating with aggrecan degradation [44].

Actually, Filkova *et al.* found higher adiponectin serum levels in patients with erosive OA compared with patients with non-erosive OA [45]. In the same way, Koskinen and colleagues reported that serum adiponectin and adiponectin synthesis from OA cartilage are higher in patients with the radiologically most severe disease [46]. Furthermore, these authors and others observed an association between adiponectin serum levels, OA biomarkers and local synovial inflammation [14,46]. Intriguingly, adiponectin/leptin ratio was proposed as predictor of pain in patients with OA [47]. An increase in IL-6 and adiponectin production in the infrapatellar fat pad (IFP) of osteoarthritic knees has been observed [48–50]. This suggests that IFP might contribute to the local production of cytokines and adipokines. Taken together, these results suggest that adiponectin may be considered a potential molecule involved in joint disorders and matrix degradation.

The potential role of adiponectin has also been actively investigated in rheumatoid arthritis. Generally, low adiponectin levels have been associated with obesity, type 2-diabetes, atherosclerosis and vessel inflammation. So, in metabolic syndrome, the role of adiponectin is clearly anti-inflammatory. On the other side, multiple studies described high adiponectin levels in patients with RA, and these levels correlate with severity of RA [24,51,52]. Several authors identified an association between serum adiponectin levels and radiographic damage in patients with RA [48,53], suggesting that this adipokine may be a mediator of the paradoxical relationship between increasing adiposity and protection from radiographic damage in RA, due to adiponectin circulating levels decrease as adiposity increases and considering that adiponectin may have negative effects on joints. In addition, other studies reveal that adiponectin is also related to erosive joint destruction in RA [54], and recently, it has been described that this adipokine is associated with the pro-inflammatory cytokine IL-6 [55,56].

In contrast to its 'protective' role against obesity and vascular diseases at joint levels, adiponectin might be pro-inflammatory. In synovial fibroblasts, adiponectin induces IL-6 production and MMP-1 via a p38 MAPK pathway [57]. Similarly, IL-8 is induced by adiponectin through an intracellular pathway involving NF-κB [20,58]. In addition, adiponectin, in association with IL-1β, synergizes in the induction of IL-6, IL-8 and prostaglandin E_2 (PGE_2) in RA synovial cells [26], suggesting that adiponectin and IL-1β may act synergistically in the induction of pro-inflammatory factors during RA progression.

Recent studies showed that adiponectin might also contribute to synovitis and joint destruction in RA by stimulating MMP-1, MMP-13 and vascular endothelial growth factor (VEGF) expression in synovial cells, surprisingly, more than conventional pro-inflammatory mediators (i.e. IL-1β) [59]. A recent study performed in RA synovial fibroblasts (RASFs) showed that adiponectin increases both cyclooxygenase-2 (COX-2) and membrane-associated PGE synthase-1 (mPGES-1) mRNA and protein expression, resulting in an increase in PGE_2 production in a time- and concentration-dependent manner [60]. This increase was inhibited by siRNA against adiponectin receptor (AdipoR1 and AdipoR2) or using inhibitors of specific proteins involved in adiponectin signal transduction [60]. Frommer *et al.* have confirmed the pro-inflammatory role of adiponectin in RA by demonstrating that this adipokine promotes inflammation through cytokine synthesis by the different cells present in the joint. Also, it participates in the attraction of inflammatory cells to the synovium via chemokines synthesis and promoting matrix destruction due to the increased release of matrix metalloproteinases by chondrocytes [61]. Moreover, these authors described that the different isoforms of adiponectin can induce the expression of different genes involved in the pathogenesis of RA [62], supporting the concept that adiponectin has detrimental effects in joint inflammatory diseases like RA.

Conclusions

Several clinical and experimental lines of evidence showed that adipokines could contribute to inflammatory/immune and rheumatic diseases (Figs 1 and 2). The relationship between obesity and rheumatic diseases, such as OA, has been considered a mere stress for decades. However, the discovery of these adipose-derived factors introduced a novel idea of a close metabolic relationship. The recent knowledge about adipokines activities in rheumatic and inflammatory diseases opens up new potential therapeutic strategies. For instance, the use of specific antibodies in a similar way to anti-TNF-α therapy might be an interesting approach. Also, some data suggest that adipokines might serve as biomarkers of the severity of certain rheumatic diseases.

However, only further insights into the deep mechanisms by which adipokines are regulated, and the elucidation of the potential role of adipokines in the pathogenesis of rheumatic diseases might propose new pharmacological approaches.

Acknowledgements

The work of OG and FL is funded by Instituto de Salud Carlos III and Xunta de Galicia (SERGAS) through a research-staff stabilization contract. OG is supported by Instituto de Salud Carlos III and Xunta de Galicia (grants PI11/01073 and 10CSA918029PR). FL is supported by Instituto de Salud Carlos III [grants PI11/00497 and REDINSCOR (RD06/0003/0016)]. This work was also partially supported by the RETICS Programme, RD08/0075 (RIER) via Instituto de Salud Carlos III (ISCIII), within the VI NP of R+D+I 2008-2011 (OG). Morena Scotece is a recipient of the "FPU" program of the Spanish Ministry of Education. Javier Conde is a recipient of a fellowship from the Foundation IDIS-Ramón Dominguez. Veronica Lopez is a recipient of a grant from Xunta de Galicia.

Conflict of Interest Statement

All authors declare that there is no conflict of interest with any financial organization regarding the content discussed in the manuscript.

References

1 Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature 1994;**372**:425–32.

2 Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 1993;**259**:87–91.

3 Fantuzzi G. Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol 2005;**115**:911–19; quiz 920.

4 Otero M, Lago R, Lago F, Reino JJ, Gualillo O. Signalling pathway involved in nitric oxide synthase type II activation in chondrocytes: synergistic effect of leptin with interleukin-1. Arthritis Res Ther 2005;**7**:R581–91.

5 Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 2006;**6**:772–83.

6 Lago F, Dieguez C, Gomez-Reino J, Gualillo O. Adipokines as emerging mediators of immune response and inflammation. Nat Clin Pract Rheumatol 2007;**3**:716–24.

7 Edwards C, Rogers A, Lynch S, Pylawka T, Silvis M, Chinchilli V *et al.* The effects of bariatric surgery weight loss on knee pain in patients with osteoarthritis of the knee. Arthritis 2012;**2012**:504189.

8 Vincent HK, Heywood K, Connelly J, Hurley RW. Obesity and weight loss in the treatment and prevention of osteoarthritis. PM R 2012;**4**:S59–67.

9 Wluka AE, Lombard CB, Cicuttini FM. Tackling obesity in knee osteoarthritis. Nat Rev Rheumatol 2012;**9**:225–35.

10 Yusuf E, Nelissen RG, Ioan-Facsinay A, Stojanovic-Susulic V, DeGroot J, van Osch G *et al.* Association between weight or body mass index and hand osteoarthritis: a systematic review. Ann Rheum Dis 2010;**69**:761–5.

11 Grotle M, Hagen KB, Natvig B, Dahl FA, Kvien TK. Obesity and osteoarthritis in knee, hip and/or hand: an epidemiological study in the general population with 10 years follow-up BMC. Musculoskelet Disord 2008;**9**:132.

12 Ahima RS, Prabakaran D, Mantzoros C, Qu D, Lowell B, Maratos-Flier E *et al.* Role of leptin in the neuroendocrine response to fasting. Nature 1996;**382**:250–2.

13 Gualillo O, Eiras S, Lago F, Dieguez C, Casanueva FF. Elevated serum leptin concentrations induced by experimental acute inflammation. Life Sci 2000;**67**:2433–41.

14 de Boer TN, van Spil WE, Huisman AM, Polak AA, Bijlsma JW, Lafeber FP *et al.* Serum adipokines in osteoarthritis; comparison with controls and relationship with local parameters of synovial inflammation and cartilage damage. Osteoarthritis Cartilage 2012;**20**:846–53.

15 Dumond H, Presle N, Terlain B, Mainard D, Loeuille D, Netter P *et al.* Evidence for a key role of leptin in osteoarthritis. Arthritis Rheum 2003;**48**:3118–29.

16 Otero M. Gomez Reino JJ, Gualillo O. Synergistic induction of nitric oxide synthase type II: *in vitro* effect of leptin and interferon-gamma in human chondrocytes and ATDC5 chondrogenic cells. Arthritis Rheum 2003;**48**:404–9.

17 Toussirot E, Streit G, Wendling D. The contribution of adipose tissue and adipokines to inflammation in joint diseases. Curr Med Chem 2007;**14**:1095–100.

18 Hui W, Litherland GJ, Elias MS, Kitson GI, Cawston TE, Rowan AD *et al.* Leptin produced by joint white adipose tissue induces cartilage degradation via upregulation and activation of matrix metalloproteinases. Ann Rheum Dis 2012;**71**:455–62.

19 Koskinen A, Vuolteenaho K, Nieminen R, Moilanen T, Moilanen E. Leptin enhances MMP-1, MMP-3 and MMP-13 production in human osteoarthritic cartilage and correlates with MMP-1 and MMP-3 in synovial fluid from OA patients. Clin Exp Rheumatol 2011;**29**:57–64.

20 Gomez R, Scotece M, Conde J, Gomez-Reino JJ, Lago F, Gualillo O. Adiponectin and leptin increase IL-8 production in human chondrocytes. Ann Rheum Dis 2011;**70**:2052–4.

21 Bao JP, Chen WP, Feng J, Hu PF, Shi ZL, Wu LD. Leptin plays a catabolic role on articular cartilage. Mol Biol Rep 2010;**37**:3265–72.

22 Conde J, Scotece M, Lopez V, Gomez R, Lago F, Pino J *et al.* Adiponectin and leptin induce VCAM-1 expression in human and murine chondrocytes. PLoS ONE 2012;**7**:e52533.

23 Vuolteenaho K, Koskinen A, Moilanen T, Moilanen E. Leptin levels are increased and its negative regulators, SOCS-3 and sOb-R are decreased in obese patients with osteoarthritis: a link between obesity and osteoarthritis. Ann Rheum Dis 2012;**71**:1912–13.

24 Otero M, Lago R, Gomez R, Lago F, Dieguez C, Gomez-Reino JJ *et al.* Changes in plasma levels of fat-derived hormones adiponectin, leptin, resistin and visfatin in patients with rheumatoid arthritis. Ann Rheum Dis 2006;**65**:1198–201.

25 Bernotiene E, Palmer G, Gabay C. The role of leptin in innate and adaptive immune responses. Arthritis Res Ther 2006;**8**:217.

26 Lee YA, Choi HM, Lee SH, Yang HI, Yoo MC, Hong SJ *et al.* Synergy between adiponectin and interleukin-1beta on the expression of interleukin-6, interleukin-8, and cyclooxygenase-2 in fibroblast-like synoviocytes. Exp Mol Med 2012;**44**:440–7.

27 Targonska-Stepniak B, Majdan M, Dryglewska M. Leptin serum levels in rheumatoid arthritis patients: relation to disease duration and activity. Rheumatol Int 2008;**28**:585–91.

28 Olama SM, Senna MK, Elarman M. Synovial/serum leptin ratio in rheumatoid arthritis: the association with activity and erosion. Rheumatol Int 2012;**32**:683–90.

29 Derdemezis CS, Filippatos TD, Voulgari PV, Tselepis AD, Drosos AA, Kiortsis DN. Effects of a 6-month infliximab treatment on plasma levels of leptin and adiponectin in patients with rheumatoid arthritis. Fundam Clin Pharmacol 2009;**23**:595–600.

30 Gonzalez-Gay MA, Garcia-Unzueta MT, Berja A, Gonzalez-Juanatey C, Miranda-Filloy JA, Vazquez-Rodriguez TR *et al.* Anti-TNF-alpha therapy does not modulate leptin in patients with severe rheumatoid arthritis. Clin Exp Rheumatol 2009;**27**:222–8.

31 Popa C, Netea MG, de Graaf J, van den Hoogen FH, Radstake TR, Toenhake-Dijkstra H *et al.* Circulating leptin and adiponectin concentrations during tumor necrosis factor blockade in patients with active rheumatoid arthritis. J Rheumatol 2009;**36**:724–30.

32 Otero M, Lago R, Gomez R, Lago F, Gomez-Reino JJ, Gualillo O. Phosphatidylinositol 3-kinase, MEK-1 and p38 mediate leptin/interferon-gamma synergistic NOS type II induction in chondrocytes. Life Sci 2007;**81**:1452–60.

33 Tong KM, Shieh DC, Chen CP, Tzeng CY, Wang SP, Huang KC *et al.* Leptin induces IL-8 expression via leptin receptor, IRS-1, PI3K, Akt cascade and promotion of NF-kappaB/p300 binding in human synovial fibroblasts. Cell Signal 2008;**20**:1478–88.

34 Lam QL, Lu L. Role of leptin in immunity. Cell Mol Immunol 2007;**4**:1–13.

35 De Rosa V, Procaccini C, Cali G, Pirozzi G, Fontana S, Zappacosta S *et al.* A key role of leptin in the control of regulatory T cell proliferation. Immunity 2007;**26**:241–55.

36 Procaccini C, De Rosa V, Galgani M, Abanni L, Cali G, Porcellini A *et al.* An oscillatory switch in mTOR kinase activity sets regulatory T cell responsiveness. Immunity 2010;**33**:929–41.

37 Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. Endocr Rev 2005;**26**:439–51.

38 Oh DK, Ciaraldi T, Henry RR. Adiponectin in health and disease. Diabetes Obes Metab 2007;**9**:282–9.

39 Matsuzawa Y. Therapy Insight: adipocytokines in metabolic syndrome and related cardiovascular disease. Nat Clin Pract Cardiovasc Med 2006;**3**:35–42.

40 Lago R, Gomez R, Otero M, Lago F, Gallego R, Dieguez C *et al.* A new player in cartilage homeostasis: adiponectin induces nitric

oxide synthase type II and pro-inflammatory cytokines in chondrocytes. Osteoarthritis Cartilage 2008;**16**:1101–9.
41 Kang EH, Lee YJ, Kim TK, Chang CB, Chung JH, Shin K *et al.* Adiponectin is a potential catabolic mediator in osteoarthritis cartilage. Arthritis Res Ther 2010;**12**:R231.
42 Tang CH, Chiu YC, Tan TW, Yang RS, Fu WM. Adiponectin enhances IL-6 production in human synovial fibroblast via an AdipoR1 receptor, AMPK, p38, and NF-kappa B pathway. J Immunol 2007;**179**:5483–92.
43 Laurberg TB, Frystyk J, Ellingsen T, Hansen IT, Jorgensen A, Tarp U *et al.* Plasma adiponectin in patients with active, early, and chronic rheumatoid arthritis who are steroid- and disease-modifying antirheumatic drug-naive compared with patients with osteoarthritis and controls. J Rheumatol 2009;**36**:1885–91.
44 Hao D, Li M, Wu Z, Duan Y, Li D, Qiu G. Synovial fluid level of adiponectin correlated with levels of aggrecan degradation markers in osteoarthritis. Rheumatol Int 2011;**31**:1433–7.
45 Filkova M, Liskova M, Hulejova H, Haluzik M, Gatterova J, Pavelkova A *et al.* Increased serum adiponectin levels in female patients with erosive compared with non-erosive osteoarthritis. Ann Rheum Dis 2009;**68**:295–6.
46 Koskinen A, Juslin S, Nieminen R, Moilanen T, Vuolteenaho K, Moilanen E. Adiponectin associates with markers of cartilage degradation in osteoarthritis and induces production of proinflammatory and catabolic factors through mitogen-activated protein kinase pathways. Arthritis Res Ther 2011;**13**:R184.
47 Gandhi R, Takahashi M, Syed K, Davey JR, Mahomed NN. Relationship between body habitus and joint leptin levels in a knee osteoarthritis population. J Orthop Res 2010;**28**:329–33.
48 Klein-Wieringa IR, Kloppenburg M, Bastiaansen-Jenniskens YM, Yusuf E, Kwekkeboom JC, El-Bannoudi H *et al.* The infrapatellar fat pad of patients with osteoarthritis has an inflammatory phenotype. Ann Rheum Dis 2011;**70**:851–7.
49 Ushiyama T, Chano T, Inoue K, Matsusue Y. Cytokine production in the infrapatellar fat pad: another source of cytokines in knee synovial fluids. Ann Rheum Dis 2003;**62**:108–12.
50 Distel E, Cadoudal T, Durant S, Poignard A, Chevalier X, Benelli C. The infrapatellar fat pad in knee osteoarthritis: an important source of interleukin-6 and its soluble receptor. Arthritis Rheum 2009;**60**:3374–7.
51 Alkady EA, Ahmed HM, Tag L. Abdou MA [Serum and synovial adiponectin, resistin, and visfatin levels in rheumatoid arthritis patients. Relation to disease activity]. Z Rheumatol 2011;**70**:602–8.
52 Ebina K, Fukuhara A, Ando W, Hirao M, Koga T, Oshima K *et al.* Serum adiponectin concentrations correlate with severity of rheumatoid arthritis evaluated by extent of joint destruction. Clin Rheumatol 2009;**28**:445–51.
53 Giles JT, Allison M, Bingham CO 3rd, Scott WM Jr, Bathon JM. Adiponectin is a mediator of the inverse association of adiposity with radiographic damage in rheumatoid arthritis. Arthritis Rheum 2009;**61**:1248–56.
54 Giles JT, van der Heijde DM, Bathon JM. Association of circulating adiponectin levels with progression of radiographic joint destruction in rheumatoid arthritis. Ann Rheum Dis 2009;**70**:1562–8.
55 Oranskiy SP, Yeliseyeva LN, Tsanaeva AV, Zaytseva NV. Body composition and serum levels of adiponectin, vascular endothelial growth factor, and interleukin-6 in patients with rheumatoid arthritis. Croat Med J 2012;**53**:350–6.
56 Ozgen M, Koca SS, Dagli N, Balin M, Ustundag B, Isik A. Serum adiponectin and vaspin levels in rheumatoid arthritis. Arch Med Res 2010;**41**:457–63.
57 Ehling A, Schaffler A, Herfarth H, Tarner IH, Anders S, Distler O *et al.* The potential of adiponectin in driving arthritis. J Immunol 2006;**176**:4468–78.
58 Katano M, Okamoto K, Arito M, Kawakami Y, Kurokawa MS, Suematsu N *et al.* Implication of granulocyte-macrophage colony-stimulating factor induced neutrophil gelatinase-associated lipocalin in pathogenesis of rheumatoid arthritis revealed by proteome analysis. Arthritis Res Ther 2009;**11**:R3.
59 Choi HM, Lee YA, Lee SH, Hong SJ, Hahm DH, Choi SY *et al.* Adiponectin may contribute to synovitis and joint destruction in rheumatoid arthritis by stimulating vascular endothelial growth factor, matrix metalloproteinase-1, and matrix metalloproteinase-13 expression in fibroblast-like synoviocytes more than proinflammatory mediators. Arthritis Res Ther 2009;**11**:R161.
60 Kusunoki N, Kitahara K, Kojima F, Tanaka N, Kaneko K, Endo H *et al.* Adiponectin stimulates prostaglandin E(2) production in rheumatoid arthritis synovial fibroblasts. Arthritis Rheum 2010;**62**:1641–9.
61 Frommer KW, Zimmermann B, Meier FM, Schroder D, Heil M, Schaffler A *et al.* Adiponectin-mediated changes in effector cells involved in the pathophysiology of rheumatoid arthritis. Arthritis Rheum 2010;**62**:2886–99.
62 Frommer KW, Schaffler A, Buchler C, Steinmeyer J, Rickert M, Rehart S *et al.* Adiponectin isoforms: a potential therapeutic target in rheumatoid arthritis? Ann Rheum Dis 2012;**71**:1724–32.