

# Beyond Fat Mass: Exploring the Role of Adipokines in Rheumatic Diseases

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The cloning of leptin in 1994 by Zhang et al. introduced a novel concept about white adipose tissue (WAT) as a very dynamic organ that releases a plethora of immune and inflammatory mediators, such as adipokines and cytokines, which are involved in multiple diseases. Actually, adipokines exert potent modulatory actions on target tissues involved in rheumatic diseases including cartilage, synovial, bone and immune cells. The goal of this paper is to elucidate the recent findings concerning the involvement of adipokines in rheumatic diseases, such as rheumatoid arthritis (RA), osteoarthritis (OA), and systemic lupus erythematosus (SLE).

**KEYWORDS:** white adipose tissue (WAT), adipokines, cytokines, rheumatic diseases, immune response, immune tolerance, metabolism, energetic homeostasis

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## 1. INTRODUCTION

In addition to the central role of lipid storage, white adipose tissue (WAT) is now recognized to be a multifactorial organ. It has a major endocrine function secreting several hormones, most notably leptin and adiponectin, together with a diverse range of other protein signals and factors. These adipose-derived peptides have been termed collectively “adipokines.” It is important to underline that these factors might be also synthesized in other tissues, rather than WAT, and participate in other relevant functions correlated with energy homeostasis and metabolism [1].

Adipokines include a variety of proinflammatory peptides. These proinflammatory adipokines are increased in obesity and appear to contribute to the so-called “low-grade inflammatory state” of obese subjects creating a cluster of metabolic aberrations including cardiovascular complications and autoimmune inflammatory diseases.

Initially restricted to metabolic activities, adipokines represent a new family of compounds that can be currently considered as key players of the complex network of soluble mediators involved in the pathophysiology of rheumatic diseases. For instance, obesity has long been considered as a risk factor for osteoarthritis (OA). It has been reported that obesity increases the incidence of OA, particularly in weight-bearing joints such as knees, and weight reduction is correlated with decreased progression of OA. A prevailing hypothesis is that obesity increases mechanical loading across the articular cartilage that leads to its degeneration. However, obesity is also associated with OA in non-weight-bearing joints such as finger joints and wrists, which suggest that these metabolic factors contribute to the high prevalence of OA in obese subjects [2].

This paper addresses current data concerning the involvement of adipokines in the rheumatic diseases, focussing on the role of adipokines played in the pathophysiology of OA, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE).

## 2. LEPTIN AND ADIPONECTIN: A TALE OF TWO GIANTS

### 2.1. Leptin: A Short Overview

Leptin is the protein product of the *ob* gene, the murine homologue of the human gene LEP, cloned in 1994 [3]. White adipose tissue cells mainly produce this adipokine, and its plasma concentration is directly correlated with the body-fat stores. It has a central role in fat metabolism; in fact leptin is considered a major regulator of body weight by suppressing appetite and stimulating energy expenditure via hypothalamic receptors. This hormone decreases food intake by inducing anorexigenic factors as cocaine-amphetamine-related transcript (CART) and increases energy consumption by suppressing orexigenic neuropeptides such as neuropeptide Y (NPY). The biological activity of leptin is mediated by specific receptors (Ob-R), which belong to the class 1 cytokine receptor superfamily and are encoded by the gene diabetes (*db*). Alternative splicing of the *db* gene produces multiple isoforms, but only the long isoform Ob-Rb appears to be capable of transducing the leptin signal.

Leptin is a hormone with pleiotropic actions. In fact, in addition to regulation of food intake, it also affects a variety of other physiological functions, including fertility, bone metabolism, inflammation, infection, and immune responses.

In the last years, important advancements have been added to clarify the involvement of leptin in promoting autoimmune and rheumatic pathologies, particularly rheumatoid arthritis, osteoarthritis, and systemic lupus erythematosus (SLE).

### 2.2. Leptin and Osteoarthritis

It is increasingly evident that this hormone plays a key role in the OA pathophysiology. Leptin expression is much higher in osteoarthritic human cartilage than in normal cartilage, and there exists a strong correlation

of synovial fluid leptin levels with body mass index (BMI) in people with severe osteoarthritis [4]. The first findings have suggested that high circulating leptin levels in obese individuals may protect cartilage from osteoarthritic degeneration. Actually, Dumond et al. have demonstrated that the intra-articular injection of leptin can strongly stimulate the synthesis of insulin-like growth factor-1 (IGF-1) and transforming growth factor- $\beta$  (TGF- $\beta$ ) at both the messenger RNA (mRNA) and protein levels which can exert anabolic activities in cartilage metabolism [4].

By contrast, leptin has been demonstrated to act as a proinflammatory agent in osteoarthritis. Otero et al. showed that, in cultured human and murine chondrocytes, type 2 nitric oxide synthase (NOS2) is activated by the combination of leptin plus IFN $\gamma$ , and NOS2 activation by IL1 is increased by leptin via a mechanism involving JAK2, PI3K, MEK1, and p38 [5–7]. The costimulation of leptin plus IFN $\gamma$  induces nitric oxide, a well-known proinflammatory mediator on joint cartilage, where it triggers chondrocyte phenotype loss, apoptosis, and metalloproteinases (MMPs) activation.

Leptin, per se, is able to induce also the expression of MMPs involved in OA cartilage damage, such as MMP-9 and MMP-13 [8]. Recently, Koskinen et al. have suggested that leptin alone or in combination with IL-1 $\beta$  upregulates MMP-1 and MMP-3 production in human OA cartilage through the transcription factor NF- $\kappa$ B, protein kinase C, and MAP kinase pathways, and its levels correlate positively with MMP-1 and MMP-3 in synovial fluid (SF) from OA patients [9].

Noteworthy, very recently, Gómez et al. have showed that in human chondrocytes leptin increased IL-8 production, which is one of the major mediators of the inflammatory response [10].

Moreover, in articular cartilage of rats, gene expression of ADAMTS-4 and ADAMTS-5 (a disintegrin and metalloproteinase with thrombospondin motifs) was markedly increased after treatment with leptin inducing also a depletion of proteoglycans [11].

Leptin could also contribute to abnormal osteoblast function in OA. Indeed, the elevated production of leptin in OA abnormal subchondral osteoblast is correlated with the increased levels of ALP (alkaline phosphatase), OC (osteocalcin), collagen type I, and TGF- $\beta$ 1, inducing a dysregulation of osteoblast function [12]. Very recently, Griffin et al. showed that the incidence of OA was not higher in *ob/ob* and *db/db* female obese mice than in control background strain (C57BL/6J) [13]. Nevertheless, in this study, no standard was set for the incidence of OA in obese control mice (without leptin mutation) [12].

This recent finding suggests that obesity, as dysregulated body fat accumulation, per se, is not a risk factor for joint degeneration since adiposity in the absence of leptin signaling is insufficient to induce systemic inflammation and knee osteoarthritis in female mice.

### 2.3. Leptin and Rheumatoid Arthritis

Together with other neuroendocrine signals, leptin seems to play a role in autoimmune diseases such as RA, but whether leptin can harm or protect joint structures in RA is still unclear. In patients with RA, circulating leptin levels have been described as either higher or unmodified in comparison to healthy controls [8, 14]. In RA patients, a fasting-induced fall in circulating leptin is associated with CD4<sup>+</sup> lymphocyte hyporeactivity and increased IL-4 secretion [15]. 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 [16]. Several authors have also demonstrated that there may exist a close dependence between the risk of aggressive course of RA and leptin levels [17, 18]. In addition, a correlation between serum leptin and synovial fluid/serum leptin ratio and disease duration and parameters of RA activity has been reported [19].

The action of leptin in RA is not only targeted to articular tissue, but this adipokine also exerts direct modulatory effects on activation, proliferation, maturation, and production of inflammatory mediators in a variety of immune cells, including lymphocytes, natural killer cells, monocytes/macrophages, dendritic cells, neutrophils, and eosinophils [20].

In particular, it is known that leptin is able to modulate T regulatory cells that are potent suppressors of autoimmunity. The group of Matarese has recently demonstrated that leptin secreted by adipocytes sustains Th1 immunity by promoting effector T cell proliferation and by constraining T<sub>Reg</sub> cells expansion. Weight loss, with concomitant reduction in leptin levels, induces a reduction in effector T cells proliferation and an increased expansion of T<sub>Reg</sub> cells leading to a downregulation 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 of T<sub>Reg</sub> cells. This fact determines an overall enhancement of the proinflammatory immunity and of T-cell-mediated autoimmune disorders. Though, leptin can be considered as a link among immune tolerance, metabolic function, and autoimmunity and future strategies aimed at interfering with leptin signaling may represent innovative therapeutic tools for 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 (T<sub>Reg</sub>) cells. This study suggests that the leptin-mTOR signalling pathway is an important link between host energy status and T<sub>Reg</sub> cell activity. Authors conclude that oscillating mTOR activity is necessary for T<sub>Reg</sub> cell activation and suggest that this might explain why T<sub>Reg</sub> cells are unresponsive to TCR stimulation *in vitro* when high levels of leptin and nutrients may sustain mTOR activation [21, 22]. To note, both direct and indirect effects of leptin on the immune system have been described to account for the immune defects observed in leptin- and leptin-receptor-deficient rodents. Actually, Palmer et al. have also showed an indirect effect of leptin on the immune system, demonstrating that leptin receptor deficiency affects the immune system indirectly via changes in the systemic environment [23].

## 2.4. Leptin and Systemic Lupus Erythematosus (SLE)

Leptin has been suggested to have a role also in other rheumatic diseases such as systemic lupus erythematosus (SLE), in particular modulating the cardiovascular risk of SLE patients. Recently, the group of La Cava demonstrated that leptin and high-fat diet are able to induce proinflammatory high-density lipoproteins and atherosclerosis in BWF1 lupus-prone mice. These data suggest that environmental factors associated with obesity and metabolic syndrome can accelerate atherosclerosis and disease in a lupus-prone background [24].

A relationship between leptin and lupus-disease-related factors is also found. In fact, patients with SLE have increased concentrations of leptin and these concentrations are associated with insulin resistance, BMI (body mass index), and CRP (C-reactive protein) in these patients [25].

## 3. ADIPONECTIN

### 3.1. Adiponectin: A Short Overview

Adiponectin, also known as GBP28, apM1, Acrp30, or AdipoQ, is a 244-residue protein that is produced mainly by WAT. Adiponectin 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 (trimers, hexamers, and also 12-18-mer forms) [26, 27]. It increases fatty acid oxidation and reduces the synthesis of glucose in the liver. Ablation of the adiponectin gene has no dramatic effect in knockout mice on a normal diet, but when placed on a high-fat/sucrose diet they develop severe insulin resistance and exhibit lipid accumulation in muscles [28]. Circulating adiponectin levels tend to be low in morbidly obese patients and increase with weight loss and with the use of thiazolidinediones, which enhance sensitivity to insulin [26, 29].

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- $\alpha$ , PPAR- $\gamma$ , and other signalling molecules [26]. To note, targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and all its metabolic actions [30].

Actually, some evidences, indicates that adiponectin has a wide range of effects in pathologies with inflammatory component, such as cardiovascular disease, endothelial dysfunction, type 2 diabetes, metabolic syndrome, OA, and RA [31]. Adiponectin acts as a potent modulator of both B and T cells; moreover, it modulates the activity of immune innate response by inducing relevant anti-inflammatory factors such as IL-1 receptor antagonist and IL-10 [26].

### 3.2. Adiponectin and RA

The potential role of adiponectin in rheumatic diseases has been actively investigated. In general, low adiponectin levels have been associated with obesity, type 2 diabetes, atherosclerosis, and vessel inflammation, and 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 [14, 32]. Giles et al. identified a robust cross-sectional association between serum adiponectin levels and radiographic damage in patients with RA [33], suggesting that this adipokines 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 increase. Indeed, considering that adiponectin may have negative effects on joint, this adipokine could be a relevant mediator to the inverse relationship between increasing adiposity and radiographic damage observed in RA studies.

In contrast to its “protective” role against obesity and vascular diseases, at joint levels adiponectin might be proinflammatory and involved in matrix degradation. In synovial fibroblasts, adiponectin induces IL-6 production and metalloproteinase-1, two of the main mediators of RA via the p38 MAPK pathway [34]. Similarly, IL-8 is induced by adiponectin through an intracellular pathway involving NF- $\kappa$ B [10, 35].

Recent studies showed that adiponectin might also contribute to synovitis and joint destruction in RA by stimulating matrix metalloproteinase-1, matrix metalloproteinase-13, and vascular endothelial growth factor expression in synovial cells, surprisingly, more than conventional proinflammatory mediators (i.e, IL-1 beta) [36]. In addition adiponectin increases both cyclooxygenase-2 (COX-2) and membrane-associated PGE synthase-1 (mPGES-1) mRNA and protein expression, in RA synovial fibroblasts (RASFs) in a time- and concentration-dependent manner [37]. This increase was inhibited by siRNA against adiponectin receptor (AdipoR1 and AdipoR2) or using inhibitors of specific proteins involved in adiponectin signal transduction [37].

Recently, Frommer et al. have confirmed the proinflammatory role of adiponectin in RA by demonstrating that this adipokine promotes inflammation through cytokine synthesis, attraction of inflammatory cells to the synovium, and recruitment of prodestructive cells via chemokines, thus promoting matrix destruction at sites of cartilage invasion [38].

### 3.3. Adiponectin and OA

It is possible that adiponectin is also implicated in OA pathogenesis. Adiponectin has emerged as a regulator of immune responses and inflammatory arthritis. However, its role in OA and cartilage degradation is controversial and, under many aspects, poorly known. Nevertheless, in chondrocytes this adipokine induces proinflammatory mediators such as nitric oxide, IL-6, MCP-1, MMP-3 and MMP-9 as well as IL-8 [10, 39, 40].

Recent studies show a potential source of adipokines at articular level: the infrapatellar fat pad (IFP). Actually, recent evidence indicates an inflammatory phenotype of this adipose compartment in patients with OA showing that IFP could contribute to the pathophysiological changes in the OA joint via the local production of cytokines and adipokines [41–43]. In addition, the implication of adiponectin in OA pathogenesis is supported also by clinical observations. Lauberg et al. have reported that plasma adiponectin levels were significantly higher in OA patients than in healthy controls [44], and they also observed higher plasma adiponectin levels in female patients with erosive hand OA than those with nonerosive OA [45].

It is noteworthy that adiponectin-leptin ratio has been proposed as predictor of pain in OA patients [46]; in fact this adipokine has been detected in the OA synovial fluids correlating with osteoarthritis severity [47] and aggrecan degradation [48].

### 3.4. Adiponectin and SLE

The role of adiponectin in the SLE pathophysiology is not clear. High levels of adiponectin have been found in patients with systemic lupus erythematosus (SLE) in comparison with healthy controls [49]; intriguingly, among the SLE patients, patients with insulin resistance (IR) showed significantly lower adiponectin levels than patients without IR [50].

Rovin et al. have reported that plasma adiponectin levels are increased in patients with renal SLE compared to healthy controls and patients with nonrenal SLE. During renal but not nonrenal SLE flare, urine adiponectin levels increase significantly. For this reason, urine adiponectin may be a biomarker of renal SLE flare [51]. Intriguingly, the group of Arahamian has suggested that PPAR-gamma agonists may be useful agents for the treatment of SLE and also demonstrated that induction of adiponectin is the major mechanism underlying the immunomodulatory effects of PPAR-gamma agonists [52]. However, these authors obtained their data by using a murine model of lupus so that the reality regarding the potential therapeutic effect of PPAR gamma agonists in human SLE may be completely different.

In addition, the study of Vadacca et al. reported no difference of adiponectin levels in SLE patients in comparison to healthy subjects [53].

In addition, very recently, McMahon and colleagues have demonstrated that leptin levels confer increased risk of atherosclerosis in women with systemic lupus erythematosus and that there is no significant association between adiponectin and atherosclerotic plaques in SLE [24].

## 4. RESISTIN

### 4.1. Resistin: A Short Overview

Resistin, known as adipocyte-secreted factor (ADSF) or found in inflammatory zone 3 (FIZZ3), was discovered in 2001 and was proposed as potential link between obesity and diabetes [54]. It was secreted by adipose tissue but has been found also in macrophages, neutrophils, and other cell types. Serum resistin levels increase with obesity in mice, rats, and humans [55, 56]. Increasing evidence indicates its important regulatory role in various biological processes, including several inflammatory diseases.

### 4.2. Resistin and RA

There are demonstrations that resistin may be involved in the pathogenesis of RA. Increased levels of this adipokine in synovial fluid from patients of rheumatoid arthritis (RA) compared to patients with noninflammatory rheumatic disorders have previously been observed [57].

Actually, resistin has been found in the plasma and synovial fluid of RA patients, and injection of this adipokine into mice joints induce an arthritis-like condition, with leukocyte infiltration of synovial tissues, hypertrophy of the synovial layer, and pannus formation [58, 59]. Bokarewa et al. have showed also that resistin induces and is induced by several proinflammatory cytokines, such as TNF- $\alpha$  or IL-6, in peripheral blood mononuclear cells, via NF- $\kappa$ B pathway, indicating that resistin can increase its own activity by a positive feedback mechanism [58] Increased serum resistin in patients with rheumatoid arthritis correlated with both C-reactive protein (CRP) and DAS28, suggesting a role of this adipokine in the pathogenesis of rheumatoid arthritis [59]. Gonzalez-Gay et al. have confirmed this association between laboratory markers of inflammation, particularly CRP and resistin levels and have showed that anti-TNF-alpha therapy results in a rapid reduction of serum resistin levels in patients with RA [60].

There is also an association between resistin and increased inflammation, joint destruction and levels of interleukin 1 receptor antagonist (IL-1RA) in rheumatoid arthritis female patients [61].

### 4.3. Resistin and OA

The proinflammatory profile of resistin, together with its association with obesity suggest that this adipokine might be another potential mediator that links OA with inflammation and obesity. It was demonstrated that this adipokine is elevated in both serum and SF after traumatic joint injuries. Recombinant resistin stimulated proteoglycan degradation in mouse femoral head cultures and the induction of inflammatory cytokines and PGE<sub>2</sub> production. Moreover, it inhibited proteoglycan synthesis in human cartilage explants [62]. However, Berry et al. have not identified any association between baseline serum levels of resistin and cartilage volume loss [63].

Recently, Zhang and colleagues demonstrated that resistin has diverse effects on gene expression in human chondrocytes, affecting chemokines, cytokines, and matrix gene expression. Messenger RNA stabilization and transcriptional upregulation are also involved in resistin-induced gene expression in human chondrocytes [64].

### 4.4. Resistin and SLE

In addition, resistin has a role as a marker of inflammation in other rheumatic diseases, such as systemic lupus erythematosus (SLE). In fact, Almedhed et al. have demonstrated a positive correlation between serum resistin levels, inflammation, bone mineral density, and renal functions in patients with SLE [65].

## 5. VISFATIN

### 5.1. Visfatin: A Short Overview

Visfatin, also named pre-B-cell colony-enhancing factor (PBEF) and nicotinamide phosphoribosyltransferase (Nampt), was originally discovered in liver, skeletal muscle, and bone marrow as a growth factor for B-lymphocyte precursors; however, it is also secreted by visceral fat [66, 67]. It is supposed that visfatin had insulin mimetic properties, but the role of this adipokine in the modulation of glucose metabolism, as well as its binding to insulin receptors, is still a matter of debate [67, 68].

It has been reported that visfatin is increased in obesity. Moreover, leucocytes from obese patients produce higher amounts of visfatin compared with lean subjects, and, specifically, granulocytes and monocytes are the major visfatin-producing cells [69, 70]. However, leucocytes are not the only nonfat cell type that synthesizes visfatin. Actually, macrophages have been described as a source for visfatin production [71], and, interestingly, this adipokine promoted macrophage survival by reducing apoptosis [72].

### 5.2. Visfatin and RA

Visfatin may be considered another potential therapeutic target for RA with important proinflammatory and catabolic roles in RA pathogenesis. Our group demonstrated that circulating visfatin is higher in patients with RA than in healthy controls [14]. These data were also further confirmed by other authors [73]. To note, enhanced visfatin levels are associated with augmented joint damage [73]. Brentano and colleagues reported that visfatin was localized in the site of invasion of synovial tissue in joints of RA patients. Moreover, it is able to induce IL-6, MMP-1, and MMP-3 in RA synovial fibroblasts, as well as IL-6 and TNF- $\alpha$  in monocytes [74]. To note, PBEF knockdown in RASFs significantly inhibited basal and TLR ligand-induced production of IL-6, IL-8, MMP-1, and MMP-3 [74].

Very recently, Busso et al. have showed that visfatin is a key mediator in inflammatory arthritis.

The administration of a visfatin inhibitor to mice with collagen-induced arthritis reduced arthritis severity with similar effect to that produced by TNF- $\alpha$  inhibitor [75]. Moreover, pharmacological inhibition of visfatin led to reduced levels of intracellular NAD in inflammatory cells and decreased the production of TNF- $\alpha$  and IL-6 in affected joints [75]. However, the mechanisms by which visfatin exerts its catabolic effect in arthritic joints are still incompletely understood.

### 5.3. Visfatin and OA

At cartilage level, OA chondrocytes are able to produce visfatin and its expression is increased after IL-1 $\beta$  treatment [76]. Visfatin administration, like IL-1 $\beta$ , enhances PGE<sub>2</sub> release. In line with this, visfatin also increases MMP-3 and MMP-13 synthesis and release and ADAMTS-4 and ADAMTS-5 expression in mouse articular chondrocytes [76]. Probably due to this augment in the expression of matrix degradative enzymes, visfatin decreases aggrecan expression [76].

In addition, we showed that serum visfatin concentrations were higher in patients with OA compared to healthy controls [11]. Very recently, Duan et al. have reported that SF visfatin was positively correlated with degradation biomarker of collagen II, helix-II, and C-telopeptide of type II collagen (CTX-II) and degradation biomarker of aggrecan, aggrecanase-1 (AGG1), and aggrecanase-2 (AGG2), suggesting an involvement of adiponectin in cartilage matrix degradation [77].

Taken together, these data suggest that visfatin has a catabolic function in cartilage and may have an important role in the pathophysiology of osteoarthritis.

### 5.4. Visfatin and SLE

Recent findings report also an implication of visfatin in SLE pathophysiology. It was showed that, in SLE patients, visfatin levels were higher compared to healthy controls [49, 73]. However, further studies are needed for more precise elucidation of the role that this adipokine plays in the SLE.

## 6. CHEMERIN

Chemerin, also known as tazarotene-induced gene 2 and retinoic acid receptor responder 2 (RARRES2), is a novel identified chemoattractant adipokine [78]. It is secreted as an 18 kDa inactive proprotein and activated by posttranslational C-terminal cleavage [79]. Chemerin acts via the G-coupled receptor chemokine-like receptor 1 (CMKLR1 or ChemR23) [78]. Chemerin and its receptor are mainly expressed, but not exclusively, in adipose tissue [80], for instance, dendritic cells, and macrophages express chemerin receptor [81]. ChemR23 is also expressed by endothelial cells, and it is upregulated by proinflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 [82]. Moreover, chemerin exogenous challenge promotes *in vitro* angiogenesis by inducing cell proliferation, endothelial migration, and capillary tube formation, critical steps in the development of angiogenesis [82].

Interestingly, chondrocytes express chemerin and its receptor [83–85], and IL-1 $\beta$  is able to increase chemerin expression [84]. In the same way, Berg et al. have demonstrated that recombinant chemerin enhances the production of several proinflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-8), as well as different MMPs (MMP-1, MMP-2, MMP-3, MMP 8, and MMP-13) in human articular chondrocytes [83]. These factors play a role in the degradation of the extracellular matrix, by causing a breakdown of the collagen and aggrecan framework, and result in the irreversible destruction of the cartilage in OA and RA. Moreover, these authors reported that the intracellular signalling after ChemR23 activation occurs through p42/44 MAPK and Akt phosphorylation.

Chemerin and ChemR23 expression was found in SLE skin biopsies [85]. *In vitro* experiments showed that chemerin acts as a chemotactic factor for plasmacytoid DCs. The tissue distribution of this adipokine, located at the luminal side of inflamed blood vessels, suggests that chemerin is involved in



the migration of plasmacytoid DCs and the accumulation of these cells in inflamed tissues in SLE patients [85]. Moreover, De Palma et al. found chemerin expression in renal tubular epithelial cells from SLE patients with nephritis [86]. These authors, using a transendothelial chemotaxis assay, demonstrated that the recruitment of plasmacytoid DCs by TNF- $\alpha$  was mediated by chemerin/ChemR23 interaction, which may be due to the induction of the cleavage of prochemerin by TNF- $\alpha$  through the local production of serine proteases in proximal tubular epithelial cells [79, 86–88].

## 7. LIPOCALIN 2

Lipocalin 2 (LCN2), also termed siderocalin, 24p3, uterocalin, and neutrophil gelatinase-associated lipocalin (NGAL), is a 25 kDa glycoprotein isolated from neutrophil granules although white adipose tissue (WAT) is thought to be the main source [89]. The LCN2 protein has been isolated as a 25 kDa monomer, as a 46 kDa homodimer, and in a covalent complex with MMP-9, and its cellular receptor, megalin (GP330), was recently described [90]. LCN2 is involved in apoptosis of haematopoietic cells [90], transport of fatty acids and iron [91], modulation of inflammation [92], among other processes.

LCN2 has recently been identified in chondrocytes [93]. In these cells IL-1 $\beta$ , leptin, adiponectin, LPS, and dexamethasone act as potent modulators of LCN2 expression [84]. Lipocalin 2 is likely to be involved in matrix degradation since it forms molecular complexes with MMP-9 [94].

Recently, the group of Katano confirmed that the level of NGAL in SF was significantly higher in patients with RA than in those with osteoarthritis. Through proteome analysis Katano et al. have showed that GM-CSF may contribute to the pathogenesis of RA by the upregulation of LCN2 in neutrophils, followed by induction of Cathepsin D, transitional endoplasmic reticulum ATPase (TERA), and transglutaminase 2 (tg2) in synoviocytes [35]. These enzymes may contribute to the proliferation of synovial cells and infiltration of inflammatory cells inside the synovia [35].

Finally, LCN2 is also a candidate biomarker for the early detection of LN (lupus nephritis) that is an inflammation of the kidney caused by systemic lupus erythematosus (SLE), which is very common in childhood-onset SLE (cSLE). Hinze et al. have demonstrated that urinary and plasma NGAL (U-NGAL and P-NGAL) are excellent candidates for predictive biomarkers for worsening of cSLE renal and global disease activity, respectively [95].

## 8. SERUM AMYLOID A3

Serum amyloid A3 (SAA3) protein is an adipokine that belongs to the family of acute-phase serum amyloid A proteins (A-SAA) secreted in the acute phase of inflammation. In mice, all A-SAA proteins are actively transcribed [96–98] whereas, in humans, SAA3 is encoded by a pseudogene and its functional protein is unknown [99, 100]. In contrast to that, in other species, murine SAA3 expression is not confined to the liver but found in several cell types [101–103]. Murine SAA3 is involved in immune, metabolic, and cardiovascular homeostasis [103–105]. Certain factors (e.g., IL-1 $\beta$ , TNF, dexamethasone, IL-6, and bacterial LPS) and conditions such as obesity modulate SAA3 expression [101–103, 106]. SAA3 is induced by IL-1 $\beta$  in primary rabbit chondrocytes and can induce transcription of MMP-13 [107].

## 9. OTHER ADIPOKINES WITH A POTENTIAL ROLE IN RHEUMATIC DISEASES

### 9.1. Apelin, Vaspin, and Omentin

#### 9.1.1. Apelin

Apelin is a bioactive peptide that was originally identified as the endogenous ligand of the orphan G protein-coupled receptor APJ [108]. TNF increases both apelin productions in adipose tissue and blood plasma

apelin levels when administered to mice [109]. Intriguingly, in mice with diet-induced obesity, macrophage counts and the levels of proinflammatory agents such as TNF rise progressively in adipose tissue [110]. Thus, one can envisage that overproduction of apelin in the obese might be an adaptive response that attempts to forestall the onset of obesity-related disorders such as mild chronic inflammation.

Very recently, Hu et al. have suggested that apelin may play a catabolic role in cartilage metabolism and that it can be a risk factor in the pathophysiology of osteoarthritis. Apelin stimulates the proliferation of chondrocytes and significantly increases mRNA levels of MMP-1, MMP-3, MMP-9, and IL-1 $\beta$  in vitro. Intra-articular injection with apelin *in vivo* upregulates the expression of MMP-3, MMP-9, and IL-1 $\beta$  decreases the level of collagen II. In addition, after treatment with apelin, mRNA levels of ADAMTS-4 and ADAMTS-5 markedly increased and depletion of proteoglycan in articular cartilage was found [11].

### 9.1.2. Vaspin

Vaspin is a serpin (serine protease inhibitor) that was produced in the visceral adipose tissue [111]. Interestingly, administration of vaspin to obese mice improved glucose tolerance and insulin sensitivity and reversed altered expression of genes that might promote insulin resistance. The induction of vaspin by adipose tissue might constitute a compensatory mechanism in response to obesity and its inflammatory complications.

### 9.1.3. Omentin

Omentin is a protein of 40 kDa secreted by omental adipose tissue and highly abundant in human plasma that had previously been identified as intelectin, a new type of Ca<sup>2+</sup>-dependent lectin with affinity to galactofuranosyl residues (the last are constituents of pathogens and dominant immunogens) [112]. So, it was suggested that a biological function of omentin/intelectin was the specific recognition of pathogens and bacterial components, playing an important role in the innate immune response to parasite infection [113]. Moreover, several studies have shown that omentin gene expression is altered by inflammatory states and obesity [114]. Indeed, Kuperman et al. have found increased gene expression of omentin in airway epithelial cells of patients with asthma [115]. Intriguingly, a differential expression of omentin mRNA occurs in omental adipose tissue of patients with Crohn's disease, suggesting that omentin could be a new candidate factor potentially involved in chronic inflammatory diseases in humans [112].

Recently, Senolt et al. have found increased levels of vaspin and reduced levels of *omentin* in the synovial fluid of patients with RA compared with those with OA [116]. This finding suggests that these two adipokines are likely involved in OA pathophysiology.

## 10. CONCLUSIONS

The physiological role of adipokines is becoming much more clear and several clinical and experimental lines of evidence showed their contributions to inflammatory and rheumatic disorders. The complexity of the adipokine network in the pathogenesis and progression of rheumatic diseases raises, since the beginning, one important question of whether it may be possible to target the mechanism(s) by which adipokines contribute to disease selectively without suppressing their physiological actions. The data presented in this paper suggest that adipokines and their signalling pathways may represent innovative therapeutic strategies for autoimmune and rheumatic disorders (See Supplementary Tables S1 and S2). (See Supplementary Materials available at doi:10.1100/2011/290142).

Although, these data are almost incomplete to allow translation of these approaches to clinical practice, several potential approaches are likely feasible. For instance, the control of leptin levels by using antibodies in a similar way to anti-TNF therapy might be an interesting strategy. Only further insights that clarify the mechanisms by which adipokines are regulated and which are the concrete roles of them in the rheumatic pathology could propose new pharmacological approaches for this disease.

## CONFLICT OF INTERESTS

The authors declare no competing interests.

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