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Adipokines and Systemic Rheumatic Diseases: Linking Inflammation, Immunity and Metabolism

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1. Introduction

The cloning of leptin in 1994 introduced a novel concept about white adipose tissue (WAT) (Zhang et al., 1994). Actually, WAT has been recognized as an active tissue able to produce a wide variety of factors, called adipokines. These molecules participate through endocrine, paracrine, autocrine or juxtacrine cross-talk in a great variety of physiological or physiopathological processes, including food intake, insulin sensitivity, immunity and inflammation (Trayhurn & Wood, 2004, 2005).

Moreover, 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. Adipokines include classic pro-inflammatory proteins such as TNF- α and IL-6, both secreted by adipocytes, but synthesized also by immune cells infiltrating WAT, such as macrophages (Flower et al., 2003; Hotamisligil et al., 1993; Trayhurn et al., 2006).

These pro-inflammatory adipokines appear to significantly contribute to the so-called “low grade inflammation” of obese subjects, a condition associated with increased risk of cancer, type 2 diabetes, cardiovascular complications, autoimmune and inflammatory diseases including rheumatic diseases such as rheumatoid arthritis (RA), osteoarthritis (OA) and systemic lupus (SLE) (Ahima et al, 1996). For instance, it has been reported that obesity that is characterized by abnormal fat accumulation and dysfunction increases the incidence of osteoarthritis (OA). A prevailing hypothesis is that obesity increases mechanical loading on the articular cartilage that finally leads to its degeneration. However, obesity is also associated with OA in non-weight bearing joints such as hand joints, which suggest that metabolic factors, as adipokines, contribute to the high prevalence of OA in obese subjects

(Felson, 2005; Oliveria et al., 1999). Furthermore, adipokines play a pivotal role in other autoimmune and rheumatic diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).

In this book chapter we review the role of adipokines in inflammation and immune response in the context of rheumatic diseases.

2. Leptin

Leptin is the protein product of the *ob* gene, the murine homologue of the human gene LEP, cloned in 1994 (Zhang et al., 1994). This adipokine is mainly produced by white adipose cells 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) that belong to the class 1 cytokine receptor superfamily, and are encoded by the gene diabetes (*db*). Alternative splicing of the *db* gene produce 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, immune responses and others. Recent evidence demonstrates an involvement of leptin in promoting the pathogenesis of different autoimmune and rheumatic diseases such as rheumatoid arthritis, multiple sclerosis and SLE. Several authors have demonstrated a dependence between the risk of aggressive course of RA and leptin levels (Kadowaki & Yamauchi, 2005; Lee et al., 2007; Targonska-Stepniak et al., 2008; Whitehead et al., 2006). It is widely accepted that leptin levels are elevated in patients with RA and that there is a correlation between serum leptin and synovial fluid/serum leptin ratio and disease duration and parameters of RA activity (Olama et al., 2010). Generally, leptin is considered to be pro-inflammatory, but this hormone has been also reported to reduce radiographic joint damage (Rho et al., 2009). This effect could be related to some leptin anabolic effects, such as the stimulation of 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 (Dumond et al., 2003).

The actions of leptin in RA are not only targeted to articular tissues, this adipokine also exerts direct modulatory effects on activation, proliferation, maturation and production of inflammatory mediators in a variety of immune cells, including lymphocytes, NK cells, monocytes/macrophages, dendritic cells, neutrophils and eosinophils (Lam & Lu, 2007). In particular, it is known that leptin is able to modulate T regulatory cells that are potent suppressors of autoimmunity. The group of Matarese et al., has recently demonstrated that leptin secreted by adipocytes sustains Th1 immunity by promoting effector T cell proliferation and by constraining Treg cells expansion. Weight loss, with concomitant reduction in leptin levels, induces a reduction in effector T cell 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 other hand, an increase in adipocyte mass leads to high leptin secretion, which results in expansion of effector T cells and reduction of T_{Reg} cells. This effect determines an overall enhancement of the pro-inflammatory immunity and of T cell-mediated autoimmune disorders. These data suggests that leptin can be considered as a link between immune tolerance, metabolic function and autoimmunity and that 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 the mammalian target of rapamycin (mTOR) and regulate the proliferative capacity of regulatory T (T_{Reg}) cells. The study of Procaccini et al describes the leptin-mTOR signalling pathway as an important link between host energy status and T_{Reg} cell activity. The authors conclude that oscillating mTOR activity is necessary for T_{Reg} cell activation and suggest that this may explain why T_{Reg} cells are unresponsive to TCR stimulation in vitro, where high levels of leptin and nutrients may sustain mTOR activation (De Rosa et al., 2007; Procaccini et al., 2010).

Leptin also may acts as a catabolic factor involved in the pathogenesis of osteoarthritis.

In fact, Otero et al have 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 , and NOS2 activation by IL-1 β is increased by leptin via a mechanism involving JAK2, PI3K, and mitogen activated kinases (MEK1 and p38) (Otero M et al., 2003, 2005). 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) activation.

Recently, it was demonstrated that leptin is able to induce also the expression of MMPs involved in OA cartilage damage, such as MMP-9 and MMP-13 (Toussirost et al., 2007). Leptin alone and in combination with IL-1 β up-regulates MMP-1 and MMP-3 production in human OA cartilage through the transcription factor NF- κ B, protein kinase C and MAP kinase pathways. This hormone is also correlated positively to MMP-1 and MMP-3 in synovial fluid (SF) from OA patients (Koskinen et al., 2011).

It is noteworthy that leptin was recently shown to increase IL-8 production in human chondrocytes (Lago et al., 2008).

Bao et al have defined that leptin enhanced both gene and protein levels of catabolic factors such as MMP-2 y MMP-9, while down-regulated the anabolic factors such as bFGF in articular cartilage of rats. Additionally, the gene expression of ADAMTS-4 and -5 were markedly increased and was observed a depletion of proteoglycan in articular cartilage after treatment with leptin (Bao et al., 2010)

Leptin also could contribute to abnormal osteoblast function in OA. In fact, the elevated production of leptin in OA abnormal subchondral osteoblast is correlated with the increased levels of ALP (alkaline phosphatase), OC, collagen type I and TGF- β 1 inducing a dysregulation of osteoblast function (Mutabaruka et al., 2010).

Leptin's and leptin receptor (Ob-Rb) expression levels were significantly increased in advanced OA cartilage and in SF. The induction by leptin of IL-1 β production y MMP-9 and

MMP-13 protein expression in chondrocytes indicates a pro-inflammatory and catabolic role of this hormone on cartilage metabolism (Simopoulou et al., 2007).

Ku et al have demonstrated a relation of SF leptin concentrations with the radiographic severity of OA in OA patients, suggesting a role of leptin as an effective marker for quantitative detection of OA (Ku et al., 2009).

All these data have focused on the pro-inflammatory effect of leptin *in vitro* that seems to have an adverse effect on cartilage homeostasis. 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). Nevertheless, in this study, no standard was set for the incidence of OA in obese control mice without leptin mutation (Griffin et al., 2009).

This recent result suggested that obesity alone is insufficient to induce systemic inflammation and knee OA and that leptin has a necessary role in the pathophysiology of OA associated with obesity.

It is also found a relationship between leptin and lupus disease related factors. 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 (Chung et al., 2009). Figure 1.

Fig. 1. Schematic representation of the effects of leptin in the brain, immune system, and articular cartilage.

3. Adiponectin

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) (Kadowaki & Yamauchi, 2005; Oh et al., 2007). It increases fatty acid oxidation and reduces the synthesis of glucose in the liver. Ablation of the adiponectin gene has no dramatic effect on knock-out 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 (Whitehead et al., 2006). 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 (Kadowaki & Yamauchi, 2005; Maeda et al., 2001).

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 (Kadowaki & Yamauchi, 2005). To note, targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and all its metabolic actions (Yamauchi et al., 2007).

There is evidence 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 (Matsuzawa, 2006). 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 (Kadowaki & Yamauchi, 2005).

In contrast to its previously described protective role in vascular diseases, there is evidence that adiponectin might act as a pro-inflammatory factor in joints and it could be involved in matrix degradation. Of note, these discrepancies in the functions of adiponectin are linked to the level of oligomerization of the protein and opposite actions have been described for both low molecular weight and high molecular isoforms (Neumeier et al., 2006).

Adiponectin levels in RA patients are higher than in healthy subjects (Otero M et al., 2006) and multiple studies correlated these adiponectin elevated levels with severity of RA (Ebina et al., 2009). Giles and collaborators identified a cross sectional association between serum adiponectin levels and radiographic damage in RA patients (Giles et al., 2009), 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 decreasing as adiposity increases. Therefore, considering that adiponectin may have negative effects on the joint, this adipokine could be a relevant mediator to the inverse relationship between increasing adiposity and radiographic damage observed in RA studies.

In human synovial fibroblasts adiponectin induces IL-6, one of the main mediators of RA, via AMPK, p38, IKK α - β and NF- κ B, (Tang et al., 2007). Similarly, IL-8 is induced by adiponectin through an intracellular pathway involving NF- κ B (Katano et al., 2009). A recent publication confirms the role of adiponectin in pathogenesis of RA. The authors showed that adiponectin is able to induce the expression of vascular endothelial growth

factor, MMP-1 and MMP-13, in synovial cells, at the same levels as IL-1 β (Choi et al., 2009). In line with this, it has been reported that adiponectin, in RA synovial fibroblasts (RASFs), increases cyclooxygenase 2 (COX-2), membrane-associated PGE synthase 1 (mPGES-1) and prostaglandin E₂ (PGE₂) mRNA and protein expression in a dose-dependent manner (Kusunoki et al., 2010). This increase was inhibited by siRNA against adiponectin receptors (AdipoR1 and AdipoR2) or using inhibitors of specific proteins involved in adiponectin signal transduction (Kusunoki et al., 2010).

Adiponectin is also implicated in OA pathogenesis. In chondrocytes this hormone is able to induce several pro-inflammatory mediators such as nitric oxide, IL-6, MCP-1, MMP-3 and MMP-9 as well as IL-8 (Gomez et al., 2011; Lago R et al., 2008), generating a pro-inflammatory environment at joint level. However, the implication of adiponectin in OA development is also supported by clinical observations. Laurberg TB et al have reported that plasma adiponectin levels were significantly higher in OA patients than in healthy subjects (Laurberg et al., 2009). Moreover, elevated plasma adiponectin levels were observed in female patients with erosive compared with non-erosive hand OA (Filkova et al., 2009). In addition, adiponectin levels in synovial fluid correlating with osteoarthritis severity (Honsawek & Chayanupatkul, 2010) and aggrecan degradation (Hao et al., 2010). Figure 2.

Fig. 2. Schematic representation of the interaction of adiponectin with immune cells, chondrocytes, and synovial fibroblasts.

4. Resistin

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 (Steppan et al., 2001). It was secreted by adipose tissue, but has been found also in macrophages, neutrophils and other cell types. Serum resistin levels increases with obesity in mice, rats and humans (Degawa-Yamauchi et al., 2003; McTernan et al., 2002). Increasing evidence indicates its important regulatory roles in various biological processes, including several inflammatory diseases.

There are demonstrations that resistin may be involved in the pathogenesis of RA. It has previously been observed increased levels of this adipokine in synovial fluid from patients of rheumatoid arthritis (RA) compared to patients with non-inflammatory rheumatic disorders (Schaffler et al., 2003). Resistin may be a significant mediator in the inflammatory process of RA, in fact the serum resistin levels are associated with disease activity and acute phase reactants, including C-reactive protein and IL-1Ra antagonizing IL-1 β (Forsblad d'Elia et al., 2008; Senolt et al., 2007).

Resistin has been found in the plasma and synovial fluid of RA patients, and injection of resistin into joints of mice induces an arthritis-like condition, with leukocyte infiltration of synovial tissues, hypertrophy of the synovial layer, and pannus formation (Bokarewa et al., 2005; Senolt et al., 2007). Bokarewa et al have showed that resistin induces and is induced by several pro-inflammatory cytokines, such as TNF- α or IL-6, in peripheral blood mononuclear cells, via NF- κ B pathway, indicating that resistin can increase its own activity by a positive feedback mechanism (Bokarewa et al., 2005).

The pro-inflammatory profile of resistin, together with its association with obesity, suggests 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 PGE2 production. Moreover, it inhibited proteoglycan synthesis in human cartilage explants (Lee et al., 2009). However, Berry et al have not identified any association between baseline serum levels of resistin and cartilage volume loss (Berry et al., 2011).

In addition, resistin has a role as a marker of inflammation in other rheumatic diseases, such as systemic lupus erythematosus (SLE). In fact, Almehed et al have demonstrated a positive correlation between serum resistin levels, inflammation, bone mineral density and renal functions in patients with SLE (Almehed et al., 2008). Figure 3.

5. Visfatin

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 (Fukuhara et al., 2005; Samal et al., 1994). 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 debate (Fukurara et al., 2005, 2007).

Fig. 3. Schematic representation of resistin interaction among adipocytes, immune cells and bone and cartilage cells.

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 (Catalan et al., 2011; Friebe et al., 2011). However, leucocytes are not the only non-fat cell-type that synthesizes visfatin. Macrophages have also been described as a source for visfatin production (Curat et al., 2006) and interestingly, this adipokine promoted macrophage survival by reducing apoptosis (Li et al., 2008).

Our group demonstrated that visfatin was increased in RA patients (Otero M et al., 2006), these data were also further confirmed by other authors (Rho et al., 2009). To note, enhanced visfatin levels are associated with augmented joint damage (Rho et al., 2009). 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- α in monocytes (Brentano et al., 2007), concluding that visfatin has relevant pro-inflammatory and catabolic roles in RA pathogenesis and it could be considered a potential therapeutic target.

A recently published study by Busso et al. shows 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- α .

inhibitor (Busso et al., 2008). Moreover, pharmacological inhibition of visfatin led to low levels of intracellular NAD in inflammatory cells and decreased the production of TNF- α and IL-6 in affected joints (Busso et al., 2008). However, the mechanism by which visfatin exerts its catabolic effect in arthritic joints is incompletely understood.

At cartilage level, OA chondrocytes are able to produce visfatin and its expression is increased after IL-1 β treatment (Gosset et al., 2008). Visfatin administration, like IL-1 β , enhances PGE₂ 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 (Gosset et al., 2008). Visfatin decreases aggrecan expression, probably due to this increase in the expression of matrix degradative enzymes (Gosset et al., 2008). Taken together, these data suggest that visfatin has a catabolic function in cartilage. Table 1.

6. Chemerin

Chemerin, also known as tazarotene-induced gene 2 and retinoic acid receptor responder 2 (RARRES2), is a novel identified chemoattractant adipokine (Wittamer et al., 2003). It is secreted as an 18 kDa inactive proprotein and activated by post-translational C-terminal cleavage (Zabel et al., 2005). Chemerin acts via the G-coupled receptor chemokine-like receptor 1 (CMKLR1 or ChemR23) (Wittamer et al., 2003). Chemerin and its receptor are mainly expressed, but not exclusively, in adipose tissue (Bozaoglu et al., 2007), for instance, dendritic cells and macrophages express chemerin receptor (Luangsay et al., 2009). Endothelial cells also express ChemR23 and it is up regulated by pro-inflammatory cytokines such as TNF- α , IL-1 β and IL-6 (Kaur et al., 2010). 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 (Kaur et al., 2010).

Interestingly, chondrocytes express chemerin and its receptor (Berg et al., 2010; Conde et al., 2011) and IL-1 β is able to increase chemerin expression (Conde et al., 2011). In the same way, Berg et al. have demonstrated that recombinant chemerin enhances the production of several pro-inflammatory cytokines (TNF- α , IL-1 β , 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 (Berg et al., 2010). These factors play a role in the degradation of the extracellular matrix, by causing a breakdown of the collagen and aggrecan framework, which results 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 (Vermi et al., 2005). *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 suggest that chemerin is involved in the migration of plasmacytoid DCs and the accumulation of this cells in inflamed tissues in SLE patients (Vermi et al., 2005). Moreover, De Palma et al. found chemerin expression in renal tubular epithelial cells from SLE patients with nephritis (De Palma et al., 2011). These authors, using a transendothelial chemotaxis assay, demonstrated that the recruitment of plasmacytoid DCs by TNF- α was mediated by chemerin/ChemR23 interaction, may be due to the induction of the cleavage of pro-

chemerin by TNF- α through the local production of serine proteases in proximal tubular epithelial cells (De Palma et al., 2011; Kanalas & Hopfer, 1997; Zabel et al., 2005). Table 1.

7. Lipocalin 2

Lipocalin 2 (LCN2), also termed siderocalin, 24p3, uterocalin and neutrophil gelatinase-associated lipocalin, is a 25 kDa glycoprotein isolated from neutrophil granules, although white adipose tissue (WAT) is thought to be the main source (Triebel et al., 1992). 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 (Devireddy et al., 2001). LCN2 is involved in apoptosis of haematopoietic cells (Devireddy et al., 2001), transport of fatty acids and iron (Chu et al.,1998), modulation of inflammation (Cowland & Borregaard, 1997) among other processes.

LCN2 has recently been identified in chondrocytes (Owen et al., 2008). In these cells IL-1 β , leptin, adiponectin, LPS and dexamethasone act as potent modulators of LCN2 expression (Conde et al., 2011). Lipocalin 2 is likely to be involved in matrix degradation since it forms molecular complexes with MMP-9 (Gupta et al., 2007).

Recently, Katano and colleagues 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 (Katano et al., 2009). These enzymes may contribute to the proliferation of synovial cells and infiltration of inflammatory cells inside the synovia (Katano et al., 2009).

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) is an excellent candidate as predictive biomarker for worsening of cSLE renal and global disease activity. (Hinze et al., 2009). Table 1.

Visfatin	LCN2	Chemerin
$\uparrow$ RA patients	IL-1 β , adipokines and dexamethasone increase LCN2 expression	IL-1 β increase chemerin expression
$\uparrow$ IL-6, MMP-1 and MMP-3 in RA synovial fibroblasts	$\uparrow$ matrix degradation	$\uparrow$ TNF- α , IL-1 β , IL-6 and IL-8
$\uparrow$ IL-6 and TNF- α in monocytes	$\uparrow$ RA synovial fluid	$\uparrow$ MMP-1, MMP-2, MMP-3, MMP 8 and MMP-13
$\uparrow$ PGE2, MMP-3, MMP-13, ADAMTS-4 and ADAMTS-5 in chondrocytes	GM-CSF upregulate LCN2 expression in synovial neutrophils	Chemotactic factor for plasmacytoid DCs
$\downarrow$ aggrecan expression in chondrocytes	Candidate biomarker of early detection of lupus nephritis	Involved in the migration and accumulation of plasmacytoid DCs

Table 1. Visfatin, LCN2 and Chemerin: effects relevant to rheumatic diseases.

8. Conclusions

It is now clear that adipokines have multiple relevant roles in the body, and many research efforts are driven to elucidate the intricate network among, metabolic disorders, inflammatory diseases and immune system. Although many aspects are still unclear, this chapter summarizes the present knowledge on the role of adipokines in certain rheumatic diseases.

Several adipokines have catabolic effects in articular cartilage, however some of them showed contradictory results and their involvement in the degeneration of the joint is not well understood.

The data presented here suggest that adipokines could be considered a link between metabolism and rheumatic diseases and their signalling pathways may represent innovative therapeutic strategies for autoimmune and rheumatic disorders.

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10. Abbreviations

Rheumatoid arthritis (RA), osteoarthritis (OA), white adipose tissue (WAT), interleukin (IL), systemic lupus erythematosus (SLE), cocaine amphetamine related transcript (CART), neuropeptide Y (NPY), insulin growth factor-1 (IGF-1), transforming growth factor- β (TGF- β), metalloprotease (MMP), synovial fluid (SF), nitric oxide (NO), alkaline phosphatase (ALP), C-reactive protein (CRP), prostaglandin E2 (PGE2), lipocalin 2 (LCN2).

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