

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



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

Morena Scotece¹, Javier Conde¹, Veronica Lopez¹, Rodolfo Gómez¹,
Francisca Lago², Juan J Gómez Reino¹ and Oreste Gualillo¹
¹SESGAS, Santiago University Clinical Hospital, Research laboratory 9
(NEIRID LAB: Neuroendocrine Interactions in Rheumatology and Inflammatory
Diseases), Institute of Medical Research (IDIS), Santiago de Compostela,
²SESGAS, Santiago University Clinical Hospital, Research Laboratory 7
(Molecular and Cellular Cardiology),
Institute of Medical Research (IDIS), Santiago de Compostela,
Spain

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 (Toussirot 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.

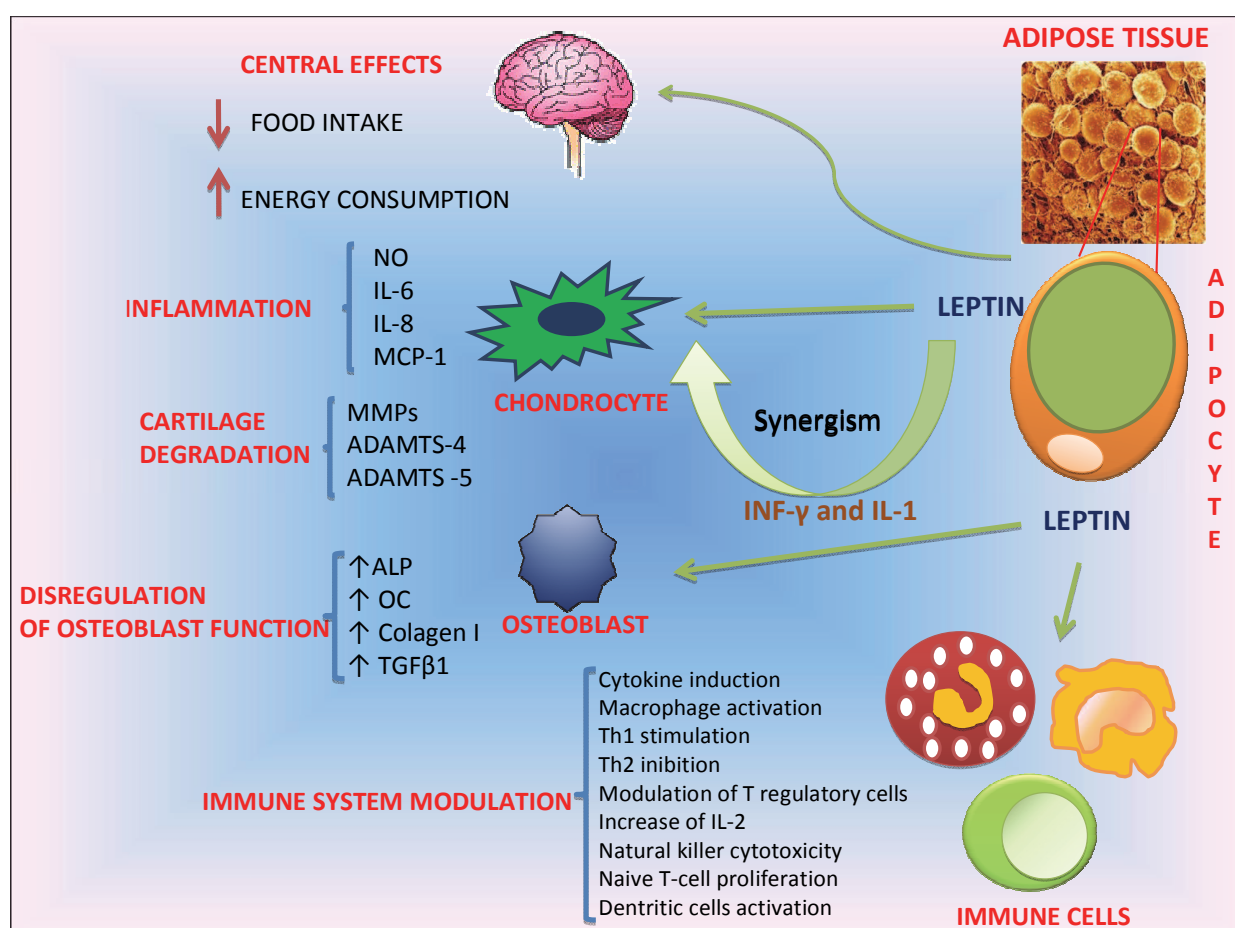


Fig. 1. Schematic representation of the effects of leptin in the brain, immune system, and articular cartilage.

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.

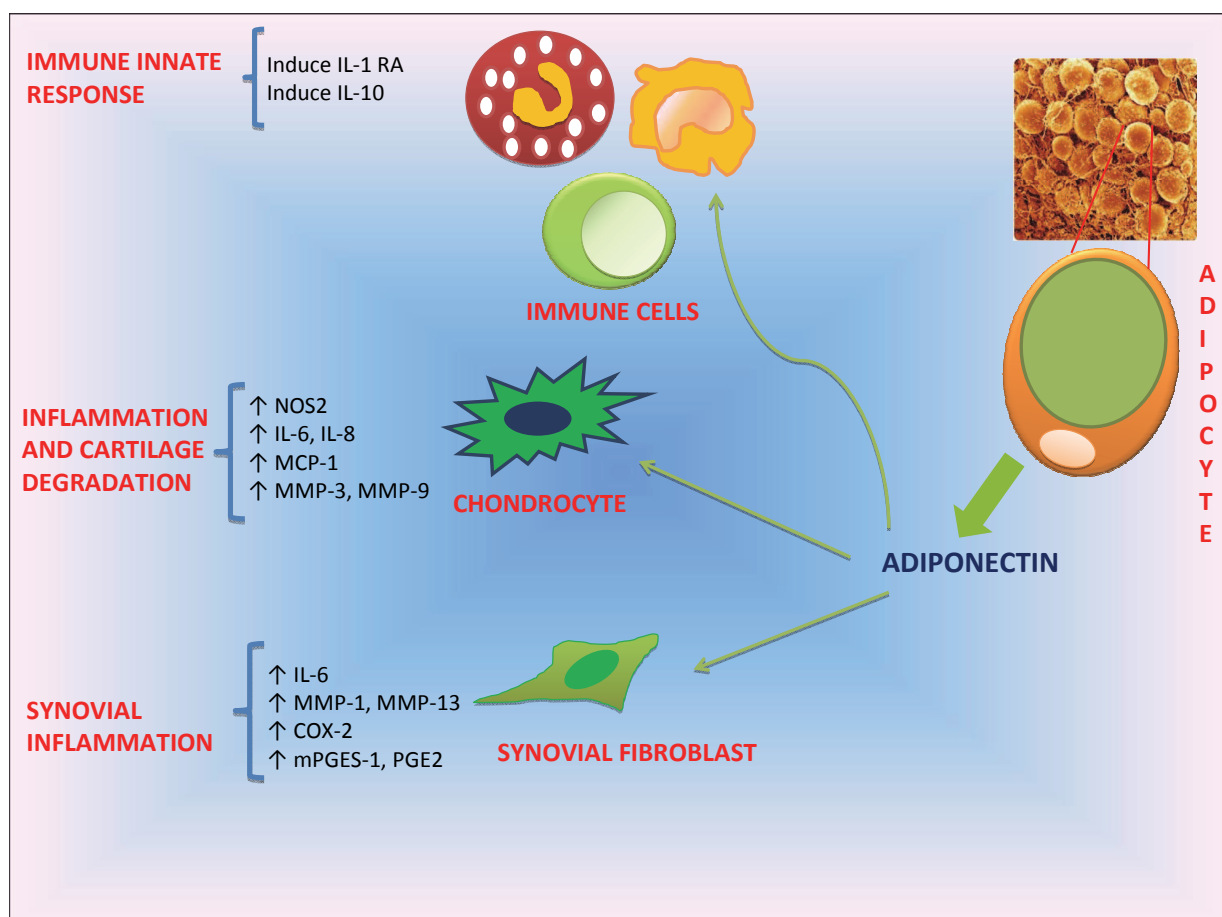


Fig. 2. Schematic representation of the interaction of adiponectin with immune cells, chondrocytes, and synovial fibroblasts.

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).

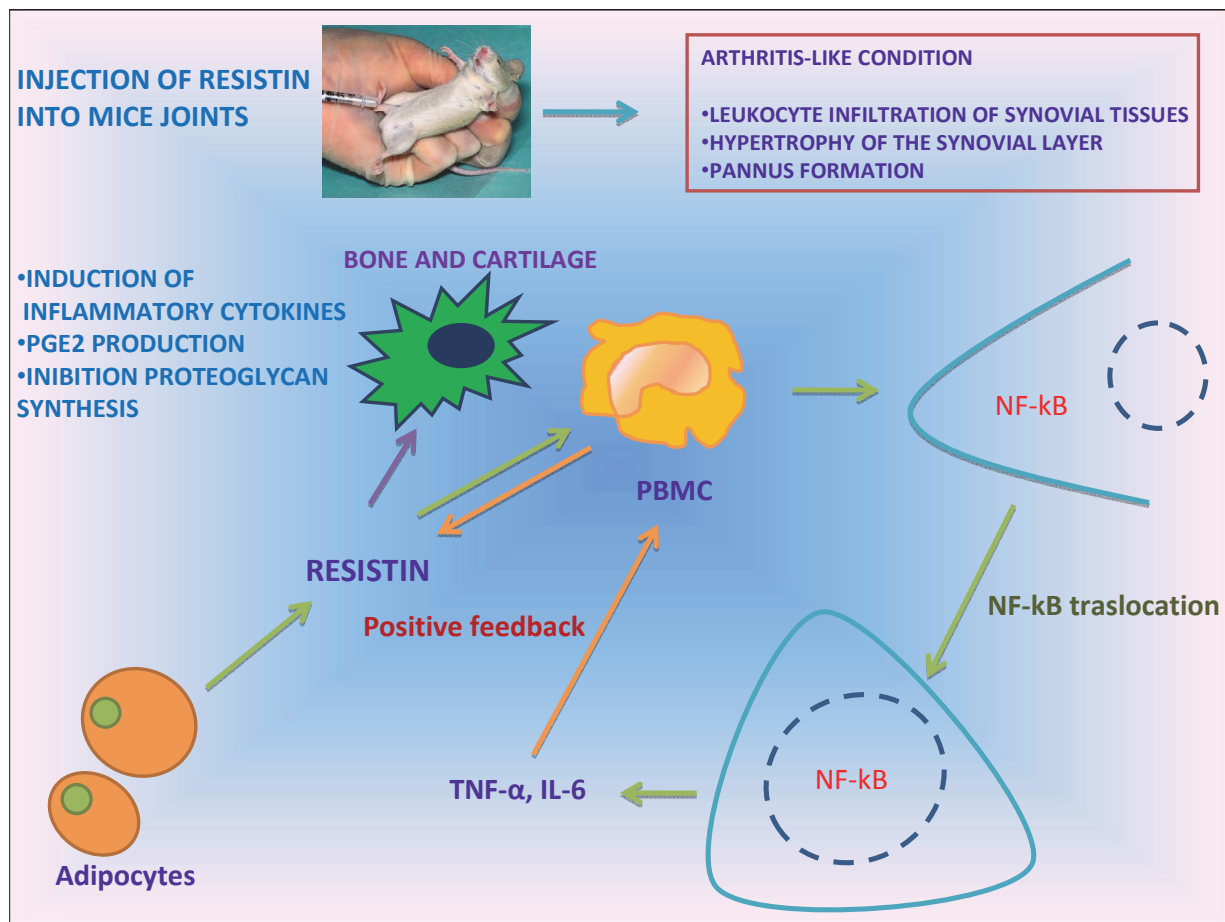


Fig. 3. Schematic representation of resistin interaction among adipocytes, immune cells and bone and cartilage cells.

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
↑ RA patients	IL-1 β , adipokines and dexamethasone increase LCN2 expression	IL-1 β increase chemerin expression
↑ IL-6, MMP-1 and MMP-3 in RA synovial fibroblasts	↑ matrix degradation	↑ TNF- α , IL-1 β , IL-6 and IL-8
↑ IL-6 and TNF- α in monocytes	↑ RA synovial fluid	↑ MMP-1, MMP-2, MMP-3, MMP-8 and MMP-13
↑ 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
↓ 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.

9. Acknowledgements

Javier Conde is a predoctoral fellow from IDICHUS Foundation. Morena Scotece is a predoctoral fellow funded by the FPU programme of Spanish Ministry of Education. Rodolfo Gómez is a post-doctoral fellow funded by National Institute of Health "Carlos III", Programme "Sara Borrell". The Instituto de Salud Carlos III and the Xunta de Galicia (SERGAS), through a research-staff stabilization contract, fund the work of O.G. and F.L. OG and FL research is supported by Instituto de Salud Carlos III and Xunta de Galicia. This work was also partially supported by RETICS Program, RD08/0075 (RIER) and REDINSCOR from Instituto de Salud Carlos III (ISCIII), within the VI NP of R+D+I 2008-2011.

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).

11. References

- Ahima, R.S., Prabakaran, D., Mantzoros, C., Qu, D., Lowell, B., Maratos-Flier, E., & Flier, J.S. (1996). Role of leptin in the neuroendocrine response to fasting. *Nature*, 382, 6588, 250-2, 0028-0836 (Print). 0028-0836 (Linking)
- Almehed, K., d'Elia, H.F., Bokarewa, M., & Carlsten, H. (2008). Role of resistin as a marker of inflammation in systemic lupus erythematosus. *Arthritis Res Ther*, 10, 1, R15, 1478-6362 (Electronic). 1478-6354 (Linking)
- Bao, J.P., Chen, W.P., Feng, J., Hu, P.F., Shi, Z.L., & Wu, L.D. (2010). Leptin plays a catabolic role on articular cartilage. *Mol Biol Rep*, 37, 7, 3265-72, 1573-4978 (Electronic). 0301-4851 (Linking)

- Berg, V., Sveinbjornsson, B., Bendiksen, S., Brox, J., Meknas, K., & Figenschau, Y. (2010). Human articular chondrocytes express ChemR23 and chemerin; ChemR23 promotes inflammatory signalling upon binding the ligand chemerin(21-157). *Arthritis Res Ther*, 12,6, R228, 1478-6362 (Electronic). 1478-6354 (Linking)
- Berry, P.A., Jones, S.W., Cicuttini, F.M., Wluka, A.E., & Maciewicz, R.A. (2011). Temporal relationship between serum adipokines, biomarkers of bone and cartilage turnover, and cartilage volume loss in a population with clinical knee osteoarthritis. *Arthritis Rheum*, 63, 3, 700-7, 1529-0131 (Electronic). 0004-3591 (Linking)
- Bokarewa, M., Nagaev, I., Dahlberg, L., Smith, U., & Tarkowski, A. (2005). Resistin, an adipokine with potent proinflammatory properties. *J Immunol*, 174,9, 5789-95, 0022-1767 (Print). 0022-1767 (Linking)
- Bozaoglu, K., Bolton, K., McMillan, J., Zimmet, P., Jowett, J., Collier, G., Walder, K., & Segal, D. (2007). Chemerin is a novel adipokine associated with obesity and metabolic syndrome. *Endocrinology*, 148,10, 4687-94, 0013-7227 (Print). 0013-7227 (Linking)
- Brentano, F., Schorr, O., Ospelt, C., Stanczyk, J., Gay, R.E., Gay, S., & Kyburz, D. (2007). Pre-B cell colony-enhancing factor/visfatin, a new marker of inflammation in rheumatoid arthritis with proinflammatory and matrix-degrading activities. *Arthritis Rheum*, 56,9, 2829-39, 0004-3591 (Print). 0004-3591 (Linking)
- Busso, N., Karababa, M., Nobile, M., Rolaz, A., Van Gool, F., Galli, M., Leo, O., So, A., & De Smedt, T. (2008). Pharmacological inhibition of nicotinamide phosphoribosyltransferase/visfatin enzymatic activity identifies a new inflammatory pathway linked to NAD. *PLoS One*, 3,5, e2267, 1932-6203 (Electronic). 1932-6203 (Linking)
- Catalan, V., Gomez-Ambrosi, J., Rodriguez, A., Ramirez, B., Silva, C., Rotellar, F., Cienfuegos, J.A., Salvador, J., & Fruhbeck, G. (2011). Association of increased Visfatin/PBEF/NAMPT circulating concentrations and gene expression levels in peripheral blood cells with lipid metabolism and fatty liver in human morbid obesity. *Nutr Metab Cardiovasc Dis*, 21,4, 245-53, 1590-3729 (Electronic). 0939-4753 (Linking)
- Choi, H.M., Lee, Y.A., Lee, S.H., Hong, S.J., Hahm, D.H., Choi, S.Y., Yang, H.I., Yoo, M.C., & Kim, K.S. (2009). 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*, 11,6, R161, 1478-6362 (Electronic). 1478-6354 (Linking)
- Chu, S.T., Lin, H.J., Huang, H.L., & Chen, Y.H. (1998). The hydrophobic pocket of 24p3 protein from mouse uterine luminal fluid: fatty acid and retinol binding activity and predicted structural similarity to lipocalins. *J Pept Res*, 52,5, 390-7, 1397-002X (Print). 1397-002X (Linking)
- Chung, C.P., Long, A.G., Solus, J.F., Rho, Y.H., Oeser, A., Raggi, P., & Stein, C.M. (2009). Adipocytokines in systemic lupus erythematosus: relationship to inflammation, insulin resistance and coronary atherosclerosis. *Lupus*, 18,9, 799-806, 0961-2033 (Print). 0961-2033 (Linking)
- Conde, J., Gomez, R., Bianco, G., Scotece, M., Lear, P., Dieguez, C., Gomez-Reino, J., Lago, F., & Gualillo, O. (2011). Expanding the adipokine network in cartilage:

- identification and regulation of novel factors in human and murine chondrocytes. *Ann Rheum Dis* , 70,3, 551-9, 1468-2060 (Electronic). 0003-4967 (Linking)
- Cowland, J.B.&Borregaard, N. (1997). Molecular characterization and pattern of tissue expression of the gene for neutrophil gelatinase-associated lipocalin from humans. *Genomics* , 45,1, 17-23, 0888-7543 (Print). 0888-7543 (Linking)
- Curat, C.A., Wegner, V., Sengenès, C., Miranville, A., Tonus, C., Busse, R.,& Bouloumie, A. (2006). Macrophages in human visceral adipose tissue: increased accumulation in obesity and a source of resistin and visfatin. *Diabetologia* , 49,4, 744-7, 0012-186X (Print). 0012-186X (Linking)
- De Palma, G., Castellano, G., Del Prete, A., Sozzani, S., Fiore, N., Loverre, A., Parmentier, M., Gesualdo, L., Grandaliano, G.,& Schena, F.P. (2011). The possible role of ChemR23/Chemerin axis in the recruitment of dendritic cells in lupus nephritis. *Kidney Int* , 79,11, 1228-35, 1523-1755 (Electronic). 0085-2538 (Linking)
- De Rosa, V., Procaccini, C., Cali, G., Pirozzi, G., Fontana, S., Zappacosta, S., La Cava, A.,& Matarese, G. (2007). A key role of leptin in the control of regulatory T cell proliferation. *Immunity* , 26,2, 241-55, 1074-7613 (Print). 1074-7613 (Linking)
- Degawa-Yamauchi, M., Bovenkerk, J.E., Juliar, B.E., Watson, W., Kerr, K., Jones, R., Zhu, Q.,& Considine, R.V. (2003). Serum resistin (FIZZ3) protein is increased in obese humans. *J Clin Endocrinol Metab* , 88,11, 5452-5, 0021-972X (Print). 0021-972X (Linking)
- Devireddy, L.R., Teodoro, J.G., Richard, F.A.,& Green, M.R. (2001). Induction of apoptosis by a secreted lipocalin that is transcriptionally regulated by IL-3 deprivation. *Science* , 293, 5531, 829-34, 0036-8075 (Print). 0036-8075 (Linking)
- Dumond, H., Presle, N., Terlain, B., Mainard, D., Loeuille, D., Netter, P.,& Pottie, P. (2003). Evidence for a key role of leptin in osteoarthritis. *Arthritis Rheum* , 48,11, 3118-29, 0004-3591 (Print). 0004-3591 (Linking)
- Ebina, K., Fukuhara, A., Ando, W., Hirao, M., Koga, T., Oshima, K., Matsuda, M., Maeda, K., Nakamura, T., Ochi, T., Shimomura, I., Yoshikawa, H.,& Hashimoto, J. (2009). Serum adiponectin concentrations correlate with severity of rheumatoid arthritis evaluated by extent of joint destruction. *Clin Rheumatol* , 28,4, 445-51, 1434-9949 (Electronic). 0770-3198 (Linking)
- Felson, D.T. (2005). Relation of obesity and of vocational and avocational risk factors to osteoarthritis. *J Rheumatol* , 32,6, 1133-5, 0315-162X (Print). 0315-162X (Linking)
- Filkova, M., Liskova, M., Hulejova, H., Haluzik, M., Gatterova, J., Pavelkova, A., Pavelka, K., Gay, S., Muller-Ladner, U.,& Senolt, L. (2009). Increased serum adiponectin levels in female patients with erosive compared with non-erosive osteoarthritis. *Ann Rheum Dis* , 68,2, 295-6, 1468-2060 (Electronic). 0003-4967 (Linking)
- Flower, L., Gray, R., Pinkney, J.,& Mohamed-Ali, V. (2003). Stimulation of interleukin-6 release by interleukin-1beta from isolated human adipocytes. *Cytokine* , 21,1, 32-7, 1043-4666 (Print). 1043-4666 (Linking)
- Forsblad d'Elia, H., Pullerits, R., Carlsten, H.,& Bokarewa, M. (2008). Resistin in serum is associated with higher levels of IL-1Ra in post-menopausal women with rheumatoid arthritis. *Rheumatology (Oxford)* , 47,7, 1082-7, 1462-0332 (Electronic). 1462-0324 (Linking)
- Friebe, D., Neef, M., Kratzsch, J., Erbs, S., Dittrich, K., Garten, A., Petzold-Quinque, S., Bluher, S., Reinehr, T., Stumvoll, M., Bluher, M., Kiess, W.,& Korner, A. (2011).

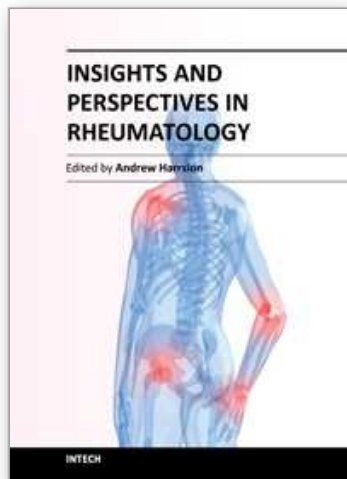
- Leucocytes are a major source of circulating nicotinamide phosphoribosyltransferase (NAMPT)/pre-B cell colony (PBEF)/visfatin linking obesity and inflammation in humans. *Diabetologia* , 54,5, 1200-11, 1432-0428 (Electronic). 0012-186X (Linking)
- Fukuhara, A., Matsuda, M., Nishizawa, M., Segawa, K., Tanaka, M., Kishimoto, K., Matsuki, Y., Murakami, M., Ichisaka, T., Murakami, H., Watanabe, E., Takagi, T., Akiyoshi, M., Ohtsubo, T., Kihara, S., Yamashita, S., Makishima, M., Funahashi, T., Yamanaka, S., Hiramatsu, R., Matsuzawa, Y., & Shimomura, I. (2005). Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. *Science* , 307,5708, 426-30, 1095-9203 (Electronic). 0036-8075 (Linking)
- Fukuhara, A., Matsuda, M., Nishizawa, M., Segawa, K., Tanaka, M., Kishimoto, K., Matsuki, Y., Murakami, M., Ichisaka, T., Murakami, H., Watanabe, E., Takagi, T., Akiyoshi, M., Ohtsubo, T., Kihara, S., Yamashita, S., Makishima, M., Funahashi, T., Yamanaka, S., Hiramatsu, R., Matsuzawa, Y., & Shimomura, I. (2007). Retraction. *Science* , 318,5850, 565, 1095-9203 (Electronic). 0036-8075 (Linking)
- Giles, J.T., Allison, M., Bingham, C.O. 3rd, Scott, W.M. Jr, & Bathon, J.M. (2009). Adiponectin is a mediator of the inverse association of adiposity with radiographic damage in rheumatoid arthritis. *Arthritis Rheum* , 61,9, 1248-56, 0004-3591 (Print). 0004-3591 (Linking)
- Gomez, R., Scotece, M., Conde, J., Gomez-Reino, J.J., Lago, F., & Gualillo, O. (2011). Adiponectin and leptin increase IL-8 production in human chondrocytes. *Ann Rheum Dis* , 1468-2060 (Electronic). 0003-4967 (Linking)
- Gosset, M., Berenbaum, F., Salvat, C., Sautet, A., Pigenet, A., Tahiri, K., & Jacques, C. (2008). Crucial role of visfatin/pre-B cell colony-enhancing factor in matrix degradation and prostaglandin E2 synthesis in chondrocytes: possible influence on osteoarthritis. *Arthritis Rheum* , 58 ,5, 1399-409, 0004-3591 (Print). 0004-3591 (Linking)
- Griffin, T.M., Huebner, J.L., Kraus, V.B., & Guilak, F. (2009). Extreme obesity due to impaired leptin signaling in mice does not cause knee osteoarthritis. *Arthritis Rheum* , 60,10, 2935-44, 0004-3591 (Print). 0004-3591 (Linking)
- Gupta, K., Shukla, M., Cowland, J.B., Malesud, C.J., & Haqqi, T.M. (2007). Neutrophil gelatinase-associated lipocalin is expressed in osteoarthritis and forms a complex with matrix metalloproteinase 9. *Arthritis Rheum* , 56,10, 3326-35, 0004-3591 (Print). 0004-3591 (Linking)
- Hao, D., Li, M., Wu, Z., Duan, Y., Li, D., & Qiu, G. (2010). Synovial fluid level of adiponectin correlated with levels of aggrecan degradation markers in osteoarthritis. *Rheumatol Int* , 1437-160X (Electronic). 0172-8172 (Linking)
- Hinze, C.H., Suzuki, M., Klein-Gitelman, M., Passo, M.H., Olson, J., Singer, N.G., Haines, K.A., Onel, K., O'Neil, K., Silverman, E.D., Tucker, L., Ying, J., Devarajan, P., & Brunner, H.I. (2009). Neutrophil gelatinase-associated lipocalin is a predictor of the course of global and renal childhood-onset systemic lupus erythematosus disease activity. *Arthritis Rheum* , 60,9, 2772-81, 0004-3591 (Print). 0004-3591 (Linking)
- Honsawek, S., & Chayanupatkul, M. (2010). Correlation of plasma and synovial fluid adiponectin with knee osteoarthritis severity. *Arch Med Res* , 41,8, 593-8, 1873-5487 (Electronic). 0188-4409 (Linking)

- Hotamisligil, G.S., Shargill, N.S., & Spiegelman, B.M. (1993). Adipose expression of tumor necrosis factor- α : direct role in obesity-linked insulin resistance. *Science*, 259, 5091-5095, 87-91, 0036-8075 (Print). 0036-8075 (Linking)
- Kadowaki, T. & Yamauchi, T. (2005). Adiponectin and adiponectin receptors. *Endocr Rev*, 26, 3, 439-51, 0163-769X (Print). 0163-769X (Linking)
- Kanagas, J.J. & Hopfer, U. (1997). Effect of TGF- β 1 and TNF- α on the plasminogen system of rat proximal tubular epithelial cells. *J Am Soc Nephrol*, 8, 2, 184-92, 1046-6673 (Print). 1046-6673 (Linking)
- Katano, M., Okamoto, K., Arito, M., Kawakami, Y., Kurokawa, M.S., Suematsu, N., Shimada, S., Nakamura, H., Xiang, Y., Masuko, K., Nishioka, K., Yudoh, K., & Kato, T. (2009). Implication of granulocyte-macrophage colony-stimulating factor induced neutrophil gelatinase-associated lipocalin in pathogenesis of rheumatoid arthritis revealed by proteome analysis. *Arthritis Res Ther*, 11, 1, R3, 1478-6362 (Electronic). 1478-6354 (Linking)
- Kaur, J., Adya, R., Tan, B.K., Chen, J., & Randeve, H.S. (2010). Identification of chemerin receptor (ChemR23) in human endothelial cells: chemerin-induced endothelial angiogenesis. *Biochem Biophys Res Commun*, 391, 4, 1762-8, 1090-2104 (Electronic). 0006-291X (Linking)
- Kitahara, K., Kusunoki, N., Kakiuchi, T., Suguro, T., & Kawai, S. (2009). Adiponectin stimulates IL-8 production by rheumatoid synovial fibroblasts. *Biochem Biophys Res Commun*, 378, 2, 218-23, 1090-2104 (Electronic). 0006-291X (Linking)
- Koskinen, A., Vuolteenaho, K., Nieminen, R., Moilanen, T., & Moilanen, E. (2011). 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*, 29, 1, 57-64, 0392-856X (Print). 0392-856X (Linking)
- Ku, J.H., Lee, C.K., Joo, B.S., An, B.M., Choi, S.H., Wang, T.H., & Cho, H.L. (2009). Correlation of synovial fluid leptin concentrations with the severity of osteoarthritis. *Clin Rheumatol*, 28, 12, 1431-5, 1434-9949 (Electronic). 0770-3198 (Linking)
- Kusunoki, N., Kitahara, K., Kojima, F., Tanaka, N., Kaneko, K., Endo, H., Suguro, T., & Kawai, S. (2010). Adiponectin stimulates prostaglandin E₂ production in rheumatoid arthritis synovial fibroblasts. *Arthritis Rheum*, 62, 6, 1641-9, 1529-0131 (Electronic). 0004-3591 (Linking)
- Lago, R., Gomez, R., Otero, M., Lago, F., Gallego, R., Dieguez, C., Gomez-Reino, J.J., & Gualillo, O. (2008). A new player in cartilage homeostasis: adiponectin induces nitric oxide synthase type II and pro-inflammatory cytokines in chondrocytes. *Osteoarthritis Cartilage*, 16, 9, 1101-9, 1522-9653 (Electronic). 1063-4584 (Linking)
- Lam, Q.L. & Lu, L. (2007). Role of leptin in immunity. *Cell Mol Immunol*, 4, 1, 1-13, 1672-7681 (Print). 1672-7681 (Linking)
- Laurberg, T.B., Frystyk, J., Ellingsen, T., Hansen, I.T., Jorgensen, A., Tarp, U., Hetland, M.L., Horslev-Petersen, K., Hornung, N., Poulsen, J.H., Flyvbjerg, A., & Stengaard-Pedersen, K. (2009). Plasma adiponectin in patients with active, early, and chronic rheumatoid arthritis who are steroid- and disease-modifying antirheumatic drug-naïve compared with patients with osteoarthritis and controls. *J Rheumatol*, 36, 9, 1885-91, 0315-162X (Print). 0315-162X (Linking)

- Lee, J.H., Ort, T., Ma, K., Picha, K., Carton, J., Marsters, P.A., Lohmander, L.S., Baribaud, F., Song, X.Y., & Blake, S. (2009). Resistin is elevated following traumatic joint injury and causes matrix degradation and release of inflammatory cytokines from articular cartilage in vitro. *Osteoarthritis Cartilage*, 17,5, 613-20, 1522-9653 (Electronic). 1063-4584 (Linking)
- Lee, S.W., Park, M.C., Park, Y.B., & Lee, S.K. (2007). Measurement of the serum leptin level could assist disease activity monitoring in rheumatoid arthritis. *Rheumatol Int*, 27,6, 537-40, 0172-8172 (Print). 0172-8172 (Linking)
- Li, Y., Zhang, Y., Dorweiler, B., Cui, D., Wang, T., Woo, C.W., Brunkan, C.S., Wolberger, C., Imai, S., & Tabas, I. (2008). Extracellular Nampt promotes macrophage survival via a nonenzymatic interleukin-6/STAT3 signaling mechanism. *J Biol Chem*, 283,50, 34833-43, 0021-9258 (Print). 0021-9258 (Linking)
- Luangsay, S., Wittamer, V., Bondue, B., De Henau, O., Rouger, L., Brait, M., Franssen, J.D., de Nadai, P., Huaux, F., & Parmentier, M. (2009). Mouse ChemR23 is expressed in dendritic cell subsets and macrophages, and mediates an anti-inflammatory activity of chemerin in a lung disease model. *J Immunol*, 183,10, 6489-99, 1550-6606 (Electronic). 0022-1767 (Linking)
- Maeda, N., Takahashi, M., Funahashi, T., Kihara, S., Nishizawa, H., Kishida, K., Nagaretani, H., Matsuda, M., Komuro, R., Ouchi, N., Kuriyama, H., Hotta, K., Nakamura, T., Shimomura, I., & Matsuzawa, Y. (2001). PPARgamma ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. *Diabetes*, 50,9, 2094-9, 0012-1797 (Print). 0012-1797 (Linking)
- Matsuzawa, Y. (2006). Therapy Insight: adipocytokines in metabolic syndrome and related cardiovascular disease. *Nat Clin Pract Cardiovasc Med*, 3,1, 35-42, 1743-4297 (Print). 1743-4297 (Linking)
- McTernan, P.G., McTernan, C.L., Chetty, R., Jenner, K., Fisher, F.M., Lauer, M.N., Crocker, J., Barnett, A.H., & Kumar, S. (2002). Increased resistin gene and protein expression in human abdominal adipose tissue. *J Clin Endocrinol Metab*, 87,5, 2407, 0021-972X (Print). 0021-972X (Linking)
- Mutabaruka, M.S., Aoulad Aissa, M., Delalandre, A., Lavigne, M., & Lajeunesse, D. (2010). Local leptin production in osteoarthritis subchondral osteoblasts may be responsible for their abnormal phenotypic expression. *Arthritis Res Ther*, 12,1, R20, 1478-6362 (Electronic). 1478-6354 (Linking)
- Neumeier, M., Weigert, J., Schaffler, A., Wehrwein, G., Muller-Ladner, U., Scholmerich, J., Wrede, C., & Buechler, C. (2006). Different effects of adiponectin isoforms in human monocytic cells. *J Leukoc Biol*, 79,4, 803-8, 0741-5400 (Print). 0741-5400 (Linking)
- Oh, D.K., Ciaraldi, T., & Henry, R.R. (2007). Adiponectin in health and disease. *Diabetes Obes Metab*, 9,3, 282-9, 1462-8902 (Print). 1462-8902 (Linking)
- Olama, S.M., Senna, M.K., & Elarman, M. (2010). Synovial/Serum leptin ratio in rheumatoid arthritis: the association with activity and erosion. *Rheumatol Int*, 1437-160X (Electronic). 0172-8172 (Linking)
- Oliveria, S.A., Felson, D.T., Cirillo, P.A., Reed, J.I., & Walker, A.M. (1999). Body weight, body mass index, and incident symptomatic osteoarthritis of the hand, hip, and knee. *Epidemiology*, 10,2, 161-6, 1044-3983 (Print). 1044-3983 (Linking)
- Otero, M., Gomez Reino, J.J., & Gualillo, O. (2003). 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* , 48,2, 404-9, 0004-3591 (Print). 0004-3591 (Linking)
- Otero, M., Lago, R., Gomez, R., Lago, F., Dieguez, C., Gomez-Reino, J.J.,& Gualillo, O. (2006). Changes in plasma levels of fat-derived hormones adiponectin, leptin, resistin and visfatin in patients with rheumatoid arthritis. *Ann Rheum Dis* , 65,9, 1198-201, 0003-4967 (Print). 0003-4967 (Linking)
- Otero, M., Lago, R., Lago, F., Reino, J.J.,& Gualillo, O. (2005). Signalling pathway involved in nitric oxide synthase type II activation in chondrocytes: synergistic effect of leptin with interleukin-1. *Arthritis Res Ther* , 7,3, R581-91, 1478-6362 (Electronic). 1478-6354 (Linking)
- Owen, H.C., Roberts, S.J., Ahmed, S.F.,& Farquharson, C. (2008). Dexamethasone-induced expression of the glucocorticoid response gene lipocalin 2 in chondrocytes. *Am J Physiol Endocrinol Metab* , 294,6, E1023-34 , 0193-1849 (Print). 0193-1849 (Linking)
- Procaccini, C., De Rosa, V., Galgani, M., Abanni, L., Cali, G., Porcellini, A., Carbone, F., Fontana, S., Horvath, T.L., La Cava, A.,& Matarese, G. (2010). An oscillatory switch in mTOR kinase activity sets regulatory T cell responsiveness. *Immunity* , 33,6, 929-41, 1097-4180 (Electronic). 1074-7613 (Linking)
- Rho, Y.H., Solus, J., Sokka, T., Oeser, A., Chung, C.P., Gebretsadik, T., Shintani, A., Pincus, T.,& Stein, C.M. (2009). Adipocytokines are associated with radiographic joint damage in rheumatoid arthritis . *Arthritis Rheum* , 60,7, 1906-14, 0004-3591 (Print). 0004-3591 (Linking)
- Samal, B., Sun, Y., Stearns, G., Xie, C., Suggs, S.,& McNiece, I. (1994). Cloning and characterization of the cDNA encoding a novel human pre-B-cell colony-enhancing factor. *Mol Cell Biol* , 14,2, 1431-7, 0270-7306 (Print). 0270-7306 (Linking)
- Schaffler, A., Ehling, A., Neumann, E., Herfarth, H., Tarner, I., Scholmerich, J., Muller-Ladner, U.,& Gay, S. (2003). Adipocytokines in synovial fluid. *JAMA* , 290,13, 1709-10, 1538-3598 (Electronic). 0098-7484 (Linking)
- Senolt, L., Housa, D., Vernerova, Z., Jirasek, T., Svobodova, R., Veigl, D., Anderlova, K., Muller-Ladner, U., Pavelka, K.,& Haluzik, M. (2007). Resistin in rheumatoid arthritis synovial tissue, synovial fluid and serum. *Ann Rheum Dis* , 66,4, 458-63, 0003-4967 (Print). 0003-4967 (Linking)
- Simopoulou, T., Malizos, K.N., Iliopoulos, D., Stefanou, N., Papatheodorou, L., Ioannou, M.,& Tsezou, A. (2007). Differential expression of leptin and leptin's receptor isoform (Ob-Rb) mRNA between advanced and minimally affected osteoarthritic cartilage; effect on cartilage metabolism. *Osteoarthritis Cartilage* , 15,8, 872-83, 1063-4584 (Print). 1063-4584 (Linking)
- Steppan, C.M., Bailey, S.T., Bhat, S., Brown, E.J., Banerjee, R.R., Wright, C.M., Patel, H.R., Ahima, R.S.,& Lazar, M.A. (2001). The hormone resistin links obesity to diabetes. *Nature* , 409, 6818, 307-12, 0028-0836 (Print). 0028-0836 (Linking)
- Tang, C.H., Chiu, Y.C., Tan, T.W., Yang, R.S.,& Fu, W.M. (2007). Adiponectin enhances IL-6 production in human synovial fibroblast via an AdipoR1 receptor, AMPK, p38, and NF-kappa B pathway. *J Immunol* , 179 ,8, 5483-92, 0022-1767 (Print). 0022-1767 (Linking)
- Targonska-Stepniak, B., Majdan, M.,& Dryglewska, M. (2008). Leptin serum levels in rheumatoid arthritis patients: relation to disease duration and activity. *Rheumatol Int* , 28,6, 585-91, 0172-8172 (Print). 0172-8172 (Linking)

- Toussiro, E., Streit, G., & Wendling, D. (2007). The contribution of adipose tissue and adipokines to inflammation in joint diseases. *Curr Med Chem*, 14,10, 1095-100, 0929-8673 (Print). 0929-8673 (Linking)
- Trayhurn, P., Bing, C., & Wood, I.S. (2006). Adipose tissue and adipokines--energy regulation from the human perspective. *J Nutr*, 136,7 Suppl, 1935S-9S, 0022-3166 (Print). 0022-3166 (Linking)
- Trayhurn, P. & Wood, I.S. (2004). Adipokines: inflammation and the pleiotropic role of white adipose tissue. *Br J Nutr*, 92,3, 347-55, 0007-1145 (Print). 0007-1145 (Linking)
- Trayhurn, P. & Wood, I.S. (2005). Signalling role of adipose tissue: adipokines and inflammation in obesity. *Biochem Soc Trans*, 33,Pt 5, 1078-81, 0300-5127 (Print). 0300-5127 (Linking)
- Triebel, S., Blaser, J., Reinke, H., & Tschesche, H. (1992). A 25 kDa alpha 2-microglobulin-related protein is a component of the 125 kDa form of human gelatinase. *FEBS Lett*, 314,3, 386-8, 0014-5793 (Print). 0014-5793 (Linking)
- Vermi, W., Riboldi, E., Wittamer, V., Gentili, F., Luini, W., Marrelli, S., Vecchi, A., Franssen, J.D., Communi, D., Massardi, L., Sironi, M., Mantovani, A., Parmentier, M., Facchetti, F., & Sozzani, S. (2005). Role of ChemR23 in directing the migration of myeloid and plasmacytoid dendritic cells to lymphoid organs and inflamed skin. *J Exp Med*, 201, 4, 509-15, 0022-1007 (Print). 0022-1007 (Linking)
- Whitehead, J.P., Richards, A.A., Hickman, I.J., Macdonald, G.A., & Prins, J.B. (2006). Adiponectin--a key adipokine in the metabolic syndrome. *Diabetes Obes Metab*, 8,3, 264-80, 1462-8902 (Print). 1462-8902 (Linking)
- Wittamer, V., Franssen, J.D., Vulcano, M., Mirjole, J.F., Le Poul, E., Migeotte, I., Brezillon, S., Tyldesley, R., Blanpain, C., Detheux, M., Mantovani, A., Sozzani, S., Vassart, G., Parmentier, M., & Communi, D. (2003). Specific recruitment of antigen-presenting cells by chemerin, a novel processed ligand from human inflammatory fluids. *J Exp Med*, 198,7, 977-85, 0022-1007 (Print). 0022-1007 (Linking)
- Yamauchi, T., Nio, Y., Maki, T., Kobayashi, M., Takazawa, T., Iwabu, M., Okada-Iwabu, M., Kawamoto, S., Kubota, N., Kubota, T., Ito, Y., Kamon, J., Tsuchida, A., Kumagai, K., Kozono, H., Hada, Y., Ogata, H., Tokuyama, K., Tsunoda, M., Ide, T., Murakami, K., Awazawa, M., Takamoto, I., Froguel, P., et al. (2007). Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. *Nat Med*, 13,3, 332-9, 1078-8956 (Print). 1078-8956 (Linking)
- Zabel, B.A., Allen, S.J., Kulig, P., Allen, J.A., Cichy, J., Handel, T.M., & Butcher, E.C. (2005). Chemerin activation by serine proteases of the coagulation, fibrinolytic, and inflammatory cascades. *J Biol Chem*, 280,41, 34661-6, 0021-9258 (Print). 0021-9258 (Linking)
- Zhang, Y., Proenca, R., Maffei, M., Barone, M., Leopold, L., & Friedman, J.M. (1994). Positional cloning of the mouse obese gene and its human homologue. *Nature*, 372,6505, 425-32, 0028-0836 (Print). 0028-0836 (Linking)



Insights and Perspectives in Rheumatology

Edited by Dr. Andrew Harrison

ISBN 978-953-307-846-5

Hard cover, 274 pages

Publisher InTech

Published online 13, January, 2012

Published in print edition January, 2012

This book offers a range of perspectives on pathogenesis, clinical features and treatment of different rheumatic diseases, with a particular focus on some of the interesting aspects of Sjögren's syndrome. It contains detailed and thorough reviews by international experts, with a diverse range of academic backgrounds. It will also serve as a useful source of information for anyone with a passive interest in rheumatology, from the genetic and molecular level, through to the psychological impact of pain and disability.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Morena Scotece, Javier Conde, Veronica Lopez, Rodolfo Gómez, Francisca Lago, Juan J Gómez Reino and Oreste Gualillo (2012). Adipokines and Systemic Rheumatic Diseases: Linking Inflammation, Immunity and Metabolism, Insights and Perspectives in Rheumatology, Dr. Andrew Harrison (Ed.), ISBN: 978-953-307-846-5, InTech, Available from: <http://www.intechopen.com/books/insights-and-perspectives-in-rheumatology/adipokines-and-systemic-rheumatic-diseases-linking-inflammation-immunity-and-metabolism>

INTECH

open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen