Adipokines as emerging mediators of immune response and inflammation

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SUMMARY
The scientific interest in the biology of white adipose tissue (WAT) has increased since the discovery of leptin in 1994. The description of the product of the gene obese (ob) demonstrated the role of adipose tissue in the physiopathology of obesity-related diseases, and helped to increase the identification of numerous other adipokines, many of a pro-inflammatory nature. It has become increasingly evident that WAT-derived adipokines can be considered as a hub between obesity-related exogenous factors, such as nutrition and lifestyle, and the molecular events that lead to metabolic syndrome, inflammatory and/or autoimmune conditions, and rheumatic diseases. In this Review, we will discuss the progress in adipokine research, focusing particular attention to the roles of leptin, adiponectin, resistin, visfatin, and other recently identified adipokines in inflammatory, autoimmune and rheumatic diseases.

KEYWORDS adipokines, articular degenerative diseases, immune system, inflammation

REVIEW CRITERIA
Papers discussed in this review were identified from the authors’ own databases and were supplemented with searches on PubMed and online journals. Only peer-reviewed, English-language journals were included in the search. The following keywords were used in various combinations: "adipokines", "adipocytokines", "osteoarthritis", "rheumatoid arthritis", "matrix degradation", "immunity", "leptin", "adiponectin", "resistin", "visfatin", "apelin", "vaspin", "hepcidin", "omentin", and "chondrocytes". We have also included experimental data from our own research aimed at identifying the molecular mechanisms of leptin and other relevant adipokines in experimental model systems and patients.

INTRODUCTION
The two faces of white adipose tissue
The theory that white adipose tissue (WAT) could be an active contributor to whole-body homeostasis rather than just a fat depot became tangible with the discovery of leptin in 1994.1 This 16 kDa protein was found to be the product of the gene obese (ob), which is mutated in the murine form of hereditary obesity. WAT has since been found to produce more than 50 cytokines and other molecules (Figure 1). These adipokines engage, through endocrine, paracrine, autocrine or juxtacrine mechanisms of action, in a wide variety of physiological or pathological processes, including immunity and inflammation.2

It is important to underline that the term ‘adipokine’ is generally applied to biologically active substances found in the adipocytes of WAT; however, these factors might be synthesized at other sites and participate in functions unrelated to those within WAT.3 Obesity, the condition initially spurring the flood of research...
on WAT, is now regarded as a pro-inflammatory state, and several markers of inflammation have been found to be elevated in obese subjects. Adipokines include a variety of pro-inflammatory peptides (including tumor necrosis factor [TNF]), the secretion of which by adipocytes was observed even before the discovery of leptin). These pro-inflammatory adipokines appear to contribute strikingly to the ‘low-grade inflammatory state’ of obese subjects, setting up a cluster of metabolic aberrations including cardiovascular complications and autoimmune inflammatory diseases. It is noteworthy that adipokine production by WAT in obesity is strongly influenced by the presence of infiltrating macrophages, through mutual crosstalk. Macrophages are an additional source of soluble mediators and might contribute and perpetuate local and systemic inflammation. WAT also produces, presumably as an adaptive response, anti-inflammatory factors such as interleukin (IL)-1 receptor antagonist (IL-1RA), which binds competitively to the IL-1 receptor without triggering activity within the cell, and IL-10 (circulating levels of which are also elevated in obese individuals). IL-1RA is markedly increased in human obese patients; data from rodents suggest that this endogenous antagonist has important central and peripheral functions including increased adipogenesis and acquired resistance to leptin. In addition, the ratio of IL-1RA to IL-1 is in favor of IL-1RA, and interferon (IFN)-β is likely to be the best inducer of IL-1RA in WAT. Curiously, IFN-β is unable to modulate either leptin or adiponectin in WAT.

This Review will address the recent findings concerning the involvement of adipokines in inflammatory and immune responses, and will concentrate on the roles of the more recently discovered agents in articular degenerative diseases, such as rheumatoid arthritis (RA) and osteoarthritis.

LEPTIN: THE FORERUNNER OF THE ADIPOKINE SUPERFAMILY

Leptin is a 16kDa non-glycosylated peptide hormone encoded by the gene obese (ob), the murine homolog of the human gene LEP. It belongs to the class I cytokine superfamily. It is mainly produced by adipocytes, and circulating leptin levels are directly correlated with WAT mass. It decreases food intake and increases energy consumption by inducing anorexigenic factors (e.g. CART [cocaine and amphetamine-regulated transcript], POMC [pro-opiomelanocortin]) and suppressing orexigenic neuropeptides (e.g. NPY [neuropeptide Y], AgRP [agouti-related peptide] and orexin). Leptin levels are gender-dependent, and are higher in women than in men even when adjusted for BMI, which might be relevant to the influence of sex on the development or frequency of certain diseases, such as osteoarthritis.

Leptin can, therefore, be described as a cytokine-like hormone with pleiotropic actions (Figure 2). Leptin exerts its biological influences by binding to its receptors, which are encoded by the gene diabetes (db) and belong to the class I cytokine receptor superfamily. Alternative splice variants of the db gene give rise to multiple isoforms, but only the long form Ob-Rb appears to be capable of transducing the leptin signal. The JAK-STAT pathway seems to be the main route by which Ob-Rb transmits the extracellular signal it receives. Other alternative pathways, however, are also involved.

LEPTIN: IMMUNE SYSTEM AND INFLAMMATORY RESPONSE

Db/db mice, which lack leptin receptors, are affected by thymus atrophy, and ob/ob mice, which lack leptin, are immunodecient. These findings might explain why the murine immune system is depressed by starvation and reduced caloric intake, both of which result in low leptin levels, and why this depression is reversed by administration of exogenous leptin. Known actions of leptin on immune responses have been recently reviewed and include modulation of monocytes/macrophages, neutrophils, basophils, eosinophils, and natural killer and dendritic cells. Furthermore, leptin modifies T-cell balance, induces T-cell activation, and changes the pattern of T-cell cytokine production by driving T-cell differentiation towards a Th1-like response, accounting for a pro-inflammatory role of leptin in several animal models of autoimmune/inflammatory conditions (Table 1).

A remarkable aspect of the effects of leptin on the immune system is its action as a pro-inflammatory cytokine: it is produced by inflammatory cells, and leptin mRNA and circulating leptin levels are increased by a number of inflammatory stimuli, including IL-1, IL-6 and lipopolysaccharide (LPS). Leptin-deficient mice are less prone than non-leptin-deficient mice to develop inflammatory diseases, regardless of whether these involve innate or adaptive immunity; reported conditions include experimentally induced colitis, experimental autoimmune diabetes, and rheumatoid arthritis.

The JAK-STAT signaling pathway transmits information from extracellular signals to the nucleus resulting in DNA transcription and expression of genes involved in immunity, proliferation, differentiation, apoptosis and oncogenesis. Disrupted or dysregulated JAK-STAT functionality can result in immune deficiency syndromes and cancers.
P38 mitogen-activated protein kinases are a class of mitogen-activated protein kinases that are responsive to stress stimuli, such as cytokines, ultraviolet irradiation, heat shock, and osmotic shock, and are involved in cell differentiation, apoptosis and autophagy. P38 inhibitors are being sought for possible therapeutic effect on autoimmune diseases and inflammatory processes.

Encephalomyelitis, type I diabetes and experimentally induced hepatitis. De Rosa et al. demonstrated that leptin neutralization directly reversed anergy and T-cell receptor hyporesponsiveness of regulatory T cells, providing new insights about the role of leptin in autoimmunity. 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 (Table 2). In patients with RA, circulating leptin levels have been described as either higher or unmodified in comparison to healthy controls. In RA patients, a fasting-induced fall in circulating leptin is associated with CD4+ lymphocyte hyporeactivity and increased IL-4 secretion. 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. In osteoarthritis, leptin production is much higher in osteoarthritic human cartilage than in normal cartilage. The finding that administration of exogenous leptin increases IGF1 and TGFβ1 production by rat knee-joint cartilage has suggested that high circulating leptin levels in obese individuals might protect cartilage from osteoarthritic degeneration. Under pathological conditions, however, control of matrix homeostasis by chondrocytes in the joint is lost, and most of the evidence points the other way (Figure 3). In cultured human and murine chondrocytes, type 2 nitric oxide synthase (NOS2) is activated by the combination of leptin plus IFNγ, and NOS2 activation by IL-1 is increased by leptin via a mechanism involving JAK2, PI3K, MEK1 and p38. Recently, it has been demonstrated that leptin is also able to induce the synthesis of relevant matrix metalloproteinases (MMPs) involved in cartilage damage, such as MMP9 and MMP13. Notably, small interfering RNA against leptin directly deactivated MMP13, which was upregulated after the epigenetic reactivation of leptin.

A pro-inflammatory effect of leptin on cartilage would be in keeping with the fact that, in comparison with men, women have both higher circulating leptin levels and a greater propensity to develop osteoarthritis. It would also explain the association between obesity and inflammatory conditions, especially those related to alterations of cartilage homeostasis. Finally, in patients with ankylosing spondylitis, serum leptin was decreased compared to healthy controls, whereas in female patients with systemic lupus erythematosus (SLE), leptin levels were higher than in healthy controls.

**ADIPONECTIN**

Adiponectin (also known as GBP28, apM1, Acrp30, or AdipoQ) is a 244-residue protein that is produced largely by WAT. Adiponectin has...
structural homology with collagens VIII and X and complement factor C1q, and circulates in the blood in relatively large amounts in different molecular forms.23,24

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. 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.23,24

Adiponectin acts via two recently described receptors, one (AdipoR1) found predominantly in skeletal muscle and the other (AdipoR2) in the liver. Transduction of the adiponectin signal by AdipoR1 and AdipoR2 involves the activation of the protein kinase AMPK, PPAR (peroxisome proliferator-activated receptor) α, PPAR γ and other signaling molecules.

Adiponectin and inflammatory processes

Although adiponectin was discovered almost at the same time as leptin, its role in protection against obesity and obesity-related disorders has only recently begun to be recognized.25 Adiponectin has a wide range of effects in pathologies with immune and inflammatory components, such as cardiovascular disease, type 2 diabetes, metabolic syndrome and RA.26 Adiponectin exerts relevant actions on innate and adaptive immunity (Table 1). It interferes with macrophage function by inhibiting phagocytic activity and IL-6 and TNF production. In addition, it reduces B-cell lymphopoiesis, decreases T-cell response, and induces the production of important anti-inflammatory factors such as IL-10 and IL-1RA by human monocytes, macrophages and dendritic cells.5

Adiponectin and cartilage

Adiponectin levels in synovial fluid are higher in patients with RA than in patients with osteoarthritis.14,26 High levels of adiponectin have been found also in patients with SLE in comparison with healthy controls; intriguingly, among the SLE patients, patients with insulin resistance showed significantly lower adiponectin levels than patients without insulin resistance.27
In human synovial fibroblasts, adiponectin induces two of the main mediators of RA via the p38 MAPK pathway: IL-6 and MMP1. Chondrocytes also present functional adiponectin receptors, activation of which leads to the induction of NOS2 via a signaling pathway that involves PI3 kinase; and adiponectin-treated chondrocytes similarly increase IL-6, TNF and MCP1 (monocyte chemotactic protein 1) synthesis (but not release of prostaglandin E2 or leukotriene B4). Taken together, these results suggest that it might be worth considering adiponectin as a potential target of treatment for degenerative joint diseases. On the other hand, the high adiponectin levels of patients with RA can also be interpreted as an attempt to overcome the well-known pro-inflammatory effect of leptin, for example by counteracting the pro-inflammatory effects of TNF and reducing the production of IL-6 and C-reactive protein in RA.

**RESISTIN**

Resistin is a dimeric protein that received its name from its apparent induction of insulin resistance in mice. It belongs to the FIZZ (found in inflammatory zones) family (also known as RELMs, i.e. resistin-like molecules). Resistin (FIZZ3) has been found in adipocytes, macrophages and other cell types.

It has been postulated that resistin mediates insulin resistance, but this role may be limited.
Earlier excitement about this theory, which provides a direct connection between adiposity and insulin resistance, was rapidly extinguished by contradictory findings in both mice and humans.

**Resistin and inflammation**

It is suggested that resistin is engaged in inflammatory conditions in humans by means of its secretion in substantial quantities by mononuclear cells. Also, resistin levels are mutually correlated with those of cell adhesion molecules such as ICAM1 in patients with obstructive sleep apnea, and in atherosclerotic patients are positively associated with other markers of inflammation, such as soluble TNF-R type II and lipoprotein-associated phospholipase A2.\(^{31,32}\) Furthermore, LPS has been reported to induce resistin gene expression in primary human and murine macrophages via a cascade involving the secretion of pro-inflammatory cytokines, and in human peripheral blood mononuclear cells resistin seems both to induce and be induced by IL-6 and TNF (induction of these cytokines by resistin occurring via the NF\(\kappa\)B pathway).\(^{33,34}\)

Resistin might also be involved in the pathogenesis of RA: it has been found in the plasma and the synovial fluid of RA patients, and injection of resistin into mice joints induces an arthritis-like condition, with leukocyte infiltration of synovial tissues, hypertrophy of the synovial layer and pannus formation.\(^{34,35}\) Plasma resistin levels in patients with RA, however, seem to be similar to those found in healthy controls; and although in some studies RA patients’ resistin levels were higher in synovial fluid than in serum (which shows that circulating levels of adipokines do not necessarily reflect the situation in the joint), the discrepancy might be due simply to the increased permeability of inflamed synovial membrane, or could simply be an epiphenomenon.\(^{14,27,34}\)

**VISFATIN**

Visfatin is an insulin-mimetic adipokine that was originally discovered in liver, skeletal muscle and bone marrow as a growth factor for B lymphocyte precursors (whence its alternative name, pre-B-colony enhancing factor, or PBEF).\(^{36,37}\) It is upregulated in models of acute lung injury and sepsis.\(^{37}\) Circulating visfatin levels are closely correlated with WAT accumulation, visfatin mRNA levels increase in the course of adipocyte differentiation, and visfatin synthesis is regulated by several factors, including glucocorticoids, TNF, IL-6 and growth hormone. Visfatin is not only produced by WAT, but also by endotoxin-challenged neutrophils, in which it prevents apoptosis through a mechanism mediated by caspases 3 and 8.\(^{37}\) Also, patients with inflammatory bowel diseases have elevated circulating visfatin levels and increased levels of visfatin mRNA in their intestinal epithelium. Visfatin has been shown to induce chemotaxis and the production of IL-1\(\beta\), TNF, IL-6 and costimulatory molecules by CD14\(^+\) monocytes, and to increase their ability to induce alloproliferative responses in lymphocytes, effects which are mediated intracellularly by p38 and MEK1.\(^{38}\) In addition, circulating visfatin is higher in patients with RA than in Table 2: Adipokines in rheumatic diseases.

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<th>RA</th>
<th>Osteoarthritis</th>
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<tr>
<td>Leptin</td>
<td>Leptin levels ↑ or ↓ regardless of correlation with CRP and IL-6</td>
<td>Leptin expression in cartilage ↑ with severity of osteoarthritis</td>
<td>In ankylosing spondylitis, leptin levels ↑ compared with healthy controls</td>
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<td>1 NOS2 (synergy with IFN-γ and IL-1) 1 MMPs 9–13 1 IGF-1, 1 TGFβ 1 In synovial fluid versus serum</td>
<td>In systemic lupus erythematosus, leptin levels ↑</td>
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<td>Adiponectin</td>
<td>↑ levels in RA</td>
<td>↑ Synovial versus serum 1 IL-6 and 1 MMP1 by synovial fibroblast</td>
<td>Not modified in ankylosing spondylitis 1 in systemic lupus erythematosus</td>
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<tr>
<td>Visfatin</td>
<td>↑ levels in RA</td>
<td>N/A</td>
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<tr>
<td>Resistin</td>
<td>Levels unchanged in RA</td>
<td>Induces osteoarthritis when injected into mouse knee joints</td>
<td>N/A</td>
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Abbreviations: CRP, C-reactive protein; IFN, interferon; IL, interleukin; MMP, matrix metalloproteinase; N/A, not available; NOS, nitric oxide synthase; RA, rheumatoid arthritis.
The physiological role or relevance of visfatin in the context of RA is currently unclear; it might involve modulation of the inflammatory or immune response by visfatin, or it might be part of a compensatory mechanism, or the increased levels could simply be an epiphenomenon.

**NOVEL ADIPOKINES IN RHEUMATIC DISEASES**

The previous sections of this Review describe considerable advances in understanding the roles of the most relevant adipokines in inflammation and rheumatic diseases. This section provides a quick overview of novel adipokines that have been supposed to exert certain interesting actions in inflammation and immunity; these agents might possibly be involved in rheumatic diseases or other inflammatory arthropathies.

**Apelin**

Apelin is a bioactive peptide that was originally identified as the endogenous ligand of the orphan G-protein-coupled receptor APJ. TNF increases both apelin production in adipose tissue and blood plasma apelin levels when administered to mice. Intriguingly, in mice with diet-induced obesity, macrophage counts and the levels of pro-inflammatory agents such as TNF rise progressively in adipose tissue. One can, therefore, 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.

**Vaspin**

Vaspin was discovered by Hida et al. as a serpin (serine protease inhibitor) that was produced in visceral adipose tissue. 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.

**Hepcidin**

Hepcidin was discovered in 2001 as a urinary antimicrobial peptide synthesized in the liver and was later identified as an adipokine. It has been described as a key regulator of iron homeostasis. Hepatic hepcidin production, however, depends not only on iron homeostasis, but also on hypoxia and inflammatory stimuli. It is of particular relevance that hepcidin levels rise in disorders involving generalized inflammation, which results in hypoferremia due to a combination of decreased duodenal iron absorption and increased sequestration of iron by macrophages. The induction of hepcidin in cultured cell lines and in a murine model by acute inflammatory stimuli has been shown to be mediated mainly by IL-6 via a STAT3 mechanism. The resulting decrease in plasma iron levels eventually limits iron availability to erythropoiesis and contributes to the anemia associated with infection and inflammation. On the other hand, decrease in extracellular iron concentrations due to hepcidin probably limits iron availability to invading microorganisms, thereby contributing to host defense.

**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 Ca²⁺-dependent
lectin with affinity to galactofuranosyl residues (the last are constituents of pathogens and dominant immunogens). It was suggested, therefore, that a biological function of omentin/interlectin was the specific recognition of pathogens and bacterial components, an important role in the innate immune response to parasite infection. Intriguingly, 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.

POSSIBLE AVENUES FOR THERAPEUTIC ACTION AND CONCLUSIONS

It is now clear that adipokines have multiple important roles in the body, and the increasing research effort in this area is gradually revealing the intricate adipokine-mediated interplay between WAT, metabolic disorders and inflammatory (auto)immune disorders. Although many issues remain hazy, in this section we outline some potential prospects for therapeutic action.

There is now a huge amount of data on the promotion of inflammation by high circulating leptin levels. It might be conceivable to control the amount of bioavailable circulating leptin, and hence to prevent leptin-induced inflammation, by means of a soluble, high-affinity leptin-binding molecule analogous to the soluble TNF receptors used to treat RA. Alternatively, it might be possible to thwart the leptin receptor with monoclonal humanized antibodies or mutant leptins that are able to bind to the receptor withoutactivating it. An obvious proviso here is that receptors mediating the influence of leptin on food intake should not be blocked, lest the patient develop hyperphagia and obesity; however, the fact that this influence is exerted in the brain, on the other side of the blood-brain barrier, would seem to make such discrimination possible. At present, little is known in this area because current anti-leptin agents were developed to control the adipostatic effects of leptin, and hence to cross the blood brain barrier.

The anti-atherosclerotic and vasoprotective effects of adiponectin are another source of inspiration for possible pharmacological approaches. In particular, one strategy against diabetes and relevant cardiovascular and metabolic diseases might be to tackle the hypo-adiposecretinemia associated with these conditions. Given the high levels of adiponectin in the blood, exogenous administration of the adipokine itself would probably have little effect; but drugs that specifically enhance endogenous adiponectin production, such as thiazolidinediones, might well prove to be effective. It should not be forgotten that the primary causes of obesity and its inflammatory complications are generally nutritional and lifestyle factors such as overeating and physical inactivity, and that front line treatment of obesity-related illnesses and obesity-related hyperproduction of detrimental adipokines, therefore, essentially includes the correction of these factors.

Understanding of the actions of the newer adipokines dealt with in this review is generally still too incomplete to generate well-supported therapeutic hypotheses. The rate at which their roles are being clarified, however, makes it certain that adipokines, too, will soon be pivotal to pharmacotherapeutic approaches to obesity-induced inflammatory diseases.

KEY POINTS

- Adipokines are soluble factors produced prevalently by white adipose tissue that have emerged as modulators of inflammation and the immune response.
- Although definitive conclusions are awaited, recent evidence points to involvement of adipokines in relevant degenerative diseases such as rheumatoid arthritis and osteoarthritis.
- Although many functions of these molecules remain to be investigated, adipokines stand at the interface between metabolism and immunity in modulating not only inflammation, but also immune and autoimmune reactivity.

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Acknowledgments

Part of the research described in this Review was supported by the Spanish Ministry of Health through the Fondo de Investigación Sanitaria, Instituto de Salud Carlos III (contracts PI05/0525, PI030115, PI050419, PI060919 and G03/152), by the Spanish Ministry of Education & Science (BUF 2005) and/or by the Xunta de Galicia. The work of O Guallio and F Lago is funded by the Instituto de Salud Carlos III and the Xunta de Galicia (SERGAS) through a research staff stabilization contract. The authors would like to thank R Gomez Bahamonde for his help with drawing tables and figures. Désirée Lie, University of California, Irvine, CA, is the author of and is solely responsible for the content of the learning objectives, questions and answers of the Medscape-accredited continuing medical education activity associated with this article.

Competing interests

The authors declared no competing interests.

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