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Review

Towards a pro-inflammatory and immunomodulatory emerging role of leptin

M. Otero[1,*], R. Lago[1], R. Gomez[1], C. Dieguez[2], F. Lago[3], J. Gómez-Reino[1] and O. Gualillo[1]

Leptin is a 16 kDa adipocyte-secreted hormone that regulates weight centrally and links nutritional status with neuroendocrine and immune function. Since its cloning in 1994, leptin's role in regulating immune and inflammatory response has become increasingly evident. Actually, the increase of leptin production that occurs during infection and inflammation strongly suggests that leptin is a part of the cytokines loop which governs the inflammatory-immune response and the host defence mechanism. Indeed, leptin stimulates the production of pro-inflammatory cytokines from cultured monocytes and enhances the production of Th1 type cytokines from stimulated lymphocytes. Several studies have implicated leptin in the pathogenesis of autoimmune inflammatory conditions such as type 1 diabetes, rheumatoid arthritis and chronic bowel disease. Obesity is characterized by elevated circulating leptin levels which might contribute significantly to the so called low-grade systemic inflammation, making obese individuals more susceptible to the increased risk of developing cardiovascular diseases, type II diabetes or inflammatory articular degenerative disease such as osteorathritis (OA). As a matter of fact, a key role for leptin in OA has been recently demonstrated since leptin exhibits, in synergy with other pro-inflammatory cytokines, a detrimental effect on articular cartilage cells by promoting nitric oxide synthesis. This review will focus prevalently on the complex relationships existing among leptin, inflammatory response and immunity, trying to provide surprising insights into leptin's role and to discuss challenges and prospects for the future.

Biology of leptin and its receptors at a glance

Leptin: synthesis, secretion and main biological actions

The discovery of leptin, in 1994, changed completely the traditional view of white adipose tissue (WAT). Actually, WAT was considered for decades as only a triglyceride reservoir with a passive or null endocrine role. The discovery of leptin, followed by many other adipocyte-derived molecules, called adipokines, identifies the adipose tissue as one of the main endocrine organs with an active and relevant role in regulating energy homeostasis, metabolism as well as immune-inflammatory processes [1].

Leptin is a 16 kDa non-glycosylated peptide hormone, encoded by the obese (ob) gene and mainly produced by adipocytes [2, 3]. Structurally, leptin belongs to the type 1 cytokine superfamily. Leptin is an anorexic peptide which is primarily known for its role as a hypothalamic modulator of food intake, body weight and fat stores. Circulating leptin levels are directly correlated to adipose tissue mass and act at hypothalamic central level as a satiety factor inducing a decrease in food intake and an increase in energy consumption [4, 5].

Due to its early discovered function as a satiety signal, exogenous leptin administration was expected to be a good therapeutic strategy to treat obese individuals. In fact, it has been shown that exogenous leptin administration leads to neuroendocrine normalization and decrease in food intake both in rodents and in rare leptin-deficient human obese patients. However, in human clinical trials with obese subjects, the effect of exogenous leptin administration was modest compared with the expected, and the weight loss was unspectacular, though the hormone's flurry of fame as a potential wonder drug petered out [6]. Notably, human obese individuals almost have high leptin concentrations, which is in agreement with the high amount of adipose tissue in obesity. Nonetheless, high leptin levels have no effect in appetite suppression, revealing a reduced response to leptin in obese people. Reduced leptin transport into the brain has been postulated to be one of the main factors related with the under-responsiveness to leptin actions. This decreased leptin transport across the blood brain barrier (BBB) has been shown to be related with a deficit in short leptin receptor isoforms as well as with the development of obesity [7]. However, an additional hypothesis regarding under-responsiveness to leptin is the desensitization for the leptin signal. In terms of signalling, leptin resistance is likely due to the overexpression of different leptin target genes, such as suppressor of cytokine signalling (SOCS)-3, which has been shown to limit leptin actions both *in vitro* and *in vivo*. The increased expression of SOCS-3, due to high leptin levels,

[1]Santiago University Clinical Hospital, Research Laboratory 4 (NEIRID LAB, Laboratory of Neuro Endocrine Interactions in Rheumatology and Inflammatory Diseases), Santiago de Compostela, Spain, [2]University of Santiago de Compostela, Department of Physiology, Santiago de Compostela, Spain and [3]Santiago University Clinical Hospital, Research Laboratory 1 (Molecular and Cellular Cardiology), Santiago de Compostela, Spain.

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Correspondence to: Oreste Gualillo, PhD PharmD, Santiago University Clinical Hospital, Research Laboratory 4 NEIRID LAB, Research Area, Travesía Choupana sin numero, 15705 Santiago de Compostela, Spain. E-mail: gualillo@usc.es

*Present address: Beth Israel Deaconess Medical Center, New England Baptist Bone & Joint Institute, Harvard Institutes of Medicine, Boston MA, USA.

could explain the diminished response to leptin actions in obese subjects [8, 9].

Leptin expression is mainly regulated by food intake and hormones, but also by different inflammatory mediators [10]. It has been shown that leptin levels are directly correlated with insulin levels [11] and inversely related with glucocorticoid ones [12]. Acute infection, sepsis and a wide range of inflammatory mediators increase leptin synthesis [13, 14]. However, it is worthy to mention that in contrast to the acute stimulation with pro-inflammatory cytokines, a chronic stimulation with pro-inflammatory cytokines cause a suppression of leptin [15, 16]. Furthermore, it has been observed that the expression of this hormone is inhibited by testosterone and increased by ovarian sex steroids, suggesting a gender-related leptin regulation [17].

Leptin could be easily defined as a cytokine-like hormone with pleiotropic actions. Indeed, apart from its early discovered function as a central adipostatin, leptin has been shown to participate in a wide range of peripheral biological functions, including glucose metabolism. For instance, *ob*/*ob* leptin-deficient mice are hyperglycaemic and insulin-resistant. However, it is unknown if this is a direct result of leptin deficiency or a result of increased fat mass. Interestingly, peripheral administration of leptin to *ob*/*ob* mice reverses hyperglycaemia and hyperinsulinaemia even before weight loss occurs [18]. Leptin has also been shown to stimulate Krebs cycle activity in rodent adipocytes [19]. Intriguingly, various glycolytic substrates and amino acids entering either glycolysis or the tricarboxylic acid cycle are able to modulate leptin secretion in the presence or absence of insulin. Indeed, it has been demonstrated that glycolytic substrates are necessary to maintain basal leptin secretion but are not sufficient *per se* to stimulate leptin secretion to the same extent as does insulin. Interestingly, several amino acid precursors of tricarboxylic acid cycle intermediates also maintained basal leptin secretion, but were also able to acutely and potently stimulate leptin secretion in the absence of insulin [20].

Leptin is also involved in $CD4^+$ T lymphocyte proliferation, cytokine secretion, reproduction, angiogenesis, hypothalamic–pituitary–adrenal axis regulation and glucocorticoid synthesis [10]. Obesity, in humans, is often associated with an increased production and accelerated degradation of cortisol, and it is characterized by clinical features of hypercortisolism. Genetically obese mice and rats demonstrate hypercorticosteronaemia, which is corrected after leptin administration [4]. Notably, leptin and its receptors are also expressed in the pituitary where the former was shown to be most abundant in corticotrophic cells [21]. *In vitro* leptin was shown to blunt the release of corticotropin-releasing hormone (CRH) induced by hypoglycaemia in isolated hypothalamic neurons without altering the adrenocorticotropin (ACTH) secretion from isolated pituitary cells [22]. Glucocorticoids are potent regulators of leptin expression. *In vitro* studies on isolated adipocytes showed a clear stimulatory effect of glucocorticoids on leptin synthesis and secretion [23]. Peripheral infusion of glucocorticoids to rats induced *ob* gene expression in adipose tissue and hyperleptinaemia [24]. In patients with leptin deficiency, plasma ACTH and cortisol levels are slightly elevated, especially in the afternoon and evening hours, with a consequent loss of the normal circadian rhythm [25]. Leptin secretion also exhibits circadian fluctuations with an increase in hormone levels during night-time in both females and males, and its spontaneous 24 h secretion was shown to be inversely related to that of cortisol and ACTH [13]. In addition, leptin reduces cortisol synthesis in the adrenal by down-regulating the steroid-producing enzyme cascade in the cortical cell [26]. It is noteworthy that highly selective lesions of the suprachiasmatic nucleus (SCN) in rats, a central nervous system area which contains the biological clock of the brain that controls daily changes in autonomic nervous system activity, abolished the diurnal variation in serum concentrations of leptin. This effect was independent of diurnal changes in serum corticosterone or the diurnal pattern of food intake. Moreover, the mean serum concentrations of leptin were increased by SCN lesions indicating a possible inhibitory control of WAT via its autonomic innervation. Finally, it has been documented that these lesions also increased mRNA levels of leptin in WAT, indicating that the CNS affects leptin gene expression in WAT. Thus, sympathetic innervation of WAT modulates hormone production by WAT in addition to its well-established stimulatory role in lipolysis [27].

Leptin receptor and signal transduction

Leptin receptors (Ob-R) are encoded by the diabetes (db) gene and belong to the class I cytokine receptor superfamily, which includes receptors for interleukin 6 (IL-6), Leukaemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), oncostatin M (OSM), granulocyte-colony stimulating factor (G-CSF) and gp130. These receptors typically contain fibronectin type III domains and two cytokine-like binding domains in the extracellular region [28–30].

The alternative splicing of the db gene gives rise to six receptor isoforms with cytoplasmic domains of different length, including one soluble form (Ob-Re), four short forms (Ob-Ra, Ob-Rc, Ob-Rd and Ob-Rf) and one long-functional isoform, known as Ob-Rb [31, 32], whose expression is almost ubiquitous [10].

The classical and alternative signalling pathways for leptin receptor. Cytoplasmic domain of Ob-Rb is essential for the signal transduction that, as it occurs within the other members of the class 1 cytokine receptor family, involves a classical Janus Kinase (JAK)-STAT pathway. JAK-2 activation leads to the phosphorylation of the conserved cytoplasmic-residues which act as binding-sites for different transcription factors, including STAT (signal transducers and activators of transcription)-1, STAT-3 and STAT-5 [33–36]. Notably, it has been demonstrated that leptin-induced STAT-3 activation regulates the expression of different genes, including SOCS-3, which participates in an inhibitory feedback loop of leptin signalling [8, 9].

Besides its signalling through the JAK-STAT pathway, Ob-Rb is able to transduce signals by using alternative signalling pathways [34, 37]. Another alternative pathway was recently demonstrated. Indeed, leptin is able to induce tyrosine phosphorylation of the SH(2)-containing SHC protein and, upon its tyrosine phosphorylation, SHC associates with the adaptor protein Grb-2. This pathway might directly link tyrosine phosphorylation events to Ras activation representing probably a critical step in cell proliferation and/or differentiation [38].

Pharmacological studies have demonstrated that some metabolic effect of leptin cannot be explained by its effect on food intake alone. Indeed, accumulating evidences indicates that leptin has direct action also on lipid metabolism via adenosine 5′-monophosphate (AMP) kinase (AMPK) (Fig. 1). The activation of this kinase is a critical step in regulating fatty acid oxidation and it is noteworthy that in the hypothalamus leptin inactivates AMPK, increases acetyl-CoA carboxylase activity (ACC) activity and decreases the food intake. On the other side, in skeletal muscle, the activation of AMPK by leptin reduces ACC activity, lowers malonyl-CoA levels and stimulates fatty acid oxidation. Another important intracellular signal component of leptin's metabolic activity is hepatic stearoyl-CoA desaturase 1 (SCD-1). SCD-1 catalyses the conversion of saturated fatty acids (FA) to monounsaturated FA, a rate-limiting step in triglyceride synthesis. Leptin-driven inhibition of hepatic SCD-1 reduces liver triglyceride and ultimately change membrane fluidity, lipoprotein metabolism and adiposity [6].

Leptin links energy homeostasis and immune system.

It is well-known that immune responses requires an optimal balance between energy intake and consumption [39]. Early studies, focused on leptin's anorexigenic action, showed that this hormone is able to maintain an adequate energy homeostasis by integrating different orexigenic and anorexigenic signals.

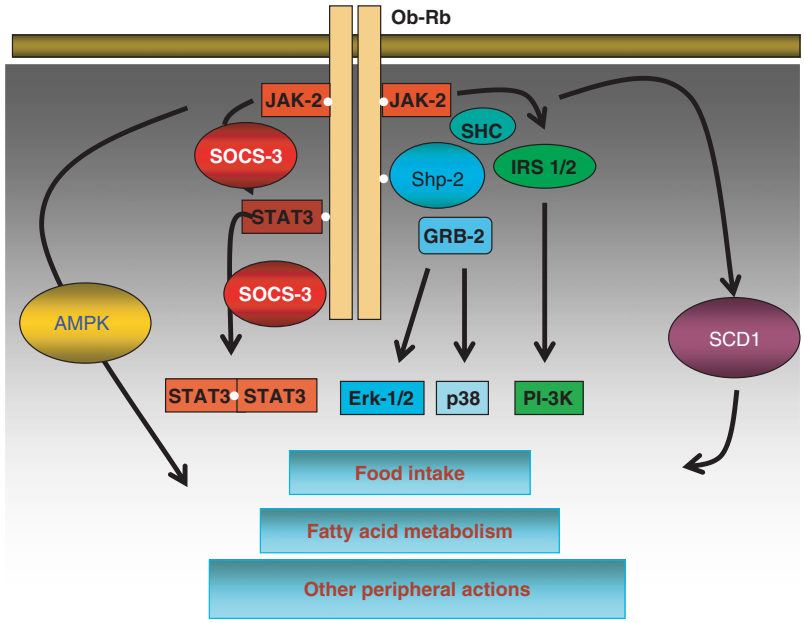

FIG. 1. Schematic representation of the main signalling pathways activated by the leptin receptor. The long form of the receptor is the only isoform able to transduce signal intracellularly. Upon leptin binding, the early limiting step in the signalling cascade is the activation, by auto or cross phosphorylation, of the associate Janus kinase type 2. Jak2 phosphorylates tyrosine residues in the receptor in order to create docking sites for adaptor proteins or transcription factors. Most of these intracellular levels might be considered as potential therapeutic target to manipulate leptin action.

Furthermore, it has been shown that leptin receptor deficient (*db*/*db*) mice suffer from thymus atrophy [40], indicating a relevant role of leptin in immunity, not only by maintaining energy homeostasis but also by regulating the function of immune cells. Later studies showed a wide range of direct leptin's actions on immune responses, reinforcing the concept that leptin could be involved in immune modulation [10, 41, 42].

Regarding leptin's regulatory actions on innate immunity, it has been demonstrated that leptin promotes phagocytic function and induces eicosanoid synthesis as well as nitric oxide and several pro-inflammatory cytokine production in macrophages and monocytes [43, 44]. Moreover, leptin stimulates the production of growth hormone by peripheral-blood mononuclear cells through protein kinase C (PKC)- and nitric oxide-dependent pathways [45]. In addition, leptin increases IFN-γ-induced expression of nitric oxide synthase (NOS) in murine macrophages [46]. In neutrophils, leptin induces chemotaxis and the release of reactive oxygen species [47, 48]. Finally, leptin has a wide regulatory action on natural killer (NK) cells by affecting proliferation, differentiation, activation and cytotoxicity [49].

Leptin has also been demonstrated to have direct actions on T-cells. Indeed, Matarese *et al.* [42] had recently and extensively reviewed the direct actions of the leptin on adaptive immune responses that we briefly summarize here. Adaptive immunity is classically divided into T helper 1 (T_{H1}) and T helper 2 (T_{H2}) responses, focusing mainly on cytokine pattern secretion. In summary, T_{H1} cells produce pro-inflammatory cytokines, essential for macrophage activation and cell-mediated response, whereas T_{H2} lymphocytes synthesize anti-inflammatory modulators. Thus, an adequate balance between T_{H1} and T_{H2} cells is essential for an optimal adaptive immune response. It has also been shown that leptin prevents glucocorticoid-induced thymocytes apoptosis and increases thymic cellularity [50]. It has been recently reported that several T-cell antigens were expressed aberrantly in both *ob*/*ob* and *db*/*db* mice, suggesting that leptin may influence growth, differentiation and also T-cell activation by interacting with T-cell costimulatory antigens such as CTLA-4 and dipeptidyl peptidase IV [51]. Leptin induces T-cell activation and modifies T-cell cytokines production pattern by polarizing T-cell differentiation towards a T_{H1} response [52, 53]. Leptin deficiency, which signals low amounts of stored energy in the adipose tissue, is responsible for the immune-suppression observed in leptin-deficient (*ob*/*ob*) mice as well as during acute starvation and reduced caloric intake. Notably, this impaired immune response is reverted by exogenous leptin administration [53], revealing leptin as a link between energy homeostasis and immune system. It has been observed that both *ob*/*ob* and *db*/*db* mice are hyperglycaemic and have high cortisol levels as a consequence of obesity rather than direct effects of leptin. To clarify this issue, studies of food restriction, which can reduce cortisol and glucose levels in leptin-deficient mice, have shown that only leptin replacement completely restores normal immune response, whereas experimentally induced decrease of serum levels of cortisol and glucose cannot reverse immune abnormalities [53]. Very recently and curiously, it has been reported that leptin also enhances T-cell proliferation in birds [54], which is in concordant with results obtained in mammals and reveals that the immune-regulatory actions of leptin are conserved all along the evolution of taxa.

Leptin acts as a pro-inflammatory cytokine

In addition to the immune regulatory actions reviewed earlier, recent evidence shows that leptin acts as a pro-inflammatory cytokine. Indeed, leptin regulates several cytokine secretion patterns. It has been shown that different inflammatory stimuli, including interleukin (IL)-1, IL-6 or lipopolysaccharide (LPS), regulate leptin mRNA expression as well as circulating leptin levels [55]. Furthermore, leptin is produced by inflammatory-regulatory cells, suggesting that leptin expression could trigger or participate in the inflammatory process through direct para- or autocrine actions [56]. Indeed, circulating leptin levels are highly and promptly increased in experimental models of acute inflammation [10]. Even leptin from adipose tissue is stimulated by pro-inflammatory cytokines such as TNF-α and IL-1β, suggesting that these cytokines stimulate short-term release of stored leptin. Thus, supporting the concept that the acute cytokine-driven rise in leptin may support the initial pro-inflammatory

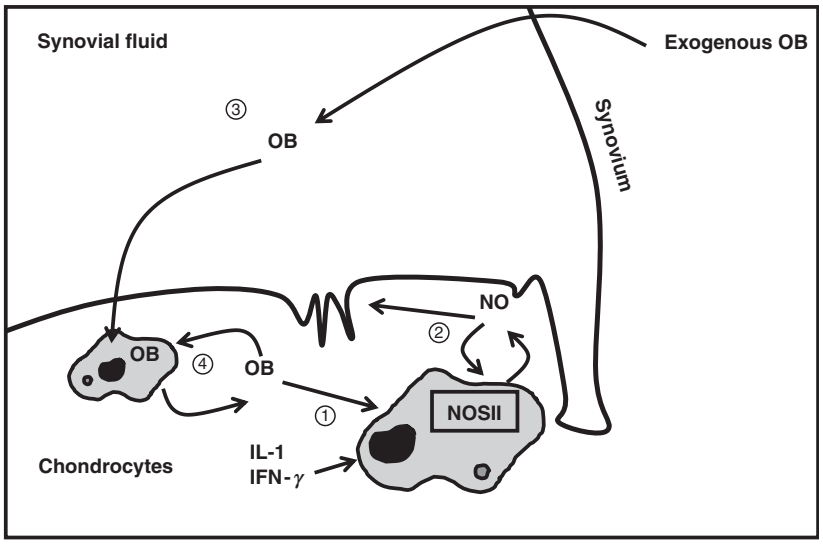

FIG. 2. Schematic view for leptin's direct pro-inflammatory action on chondrocytes. Leptin acts, in synergism with IL-1 or IFN-γ, on Nitric Oxide Synthase type II producing high amounts of nitric oxide (1) which modulates chondrocytes activity and matrix cartilage homeostasis (2) in a detrimental pro-inflammatory way. Increased leptin levels in synovial fluid (3), due to exogenous incoming, lead to an increase of endogenous leptin expression by acting directly on chondrocytes. OB, leptin; IL-1, interleukin-1; IFN-γ, interferon-γ NOS2, nitric oxide synthase type II; NO, nitric oxide.

response. Anyway, it has been proposed that long-term treatments with pro-inflammatory cytokines as well as chronic inflammation may lower plasma leptin concentrations [15].

It has been demonstrated that leptin-deficient mice showed resistance or less susceptibility to the development of both innate and adaptive immune-mediated inflammatory diseases, including experimentally induced colitis, experimental autoimmune encephalomyelitis, type I diabetes and experimentally induced hepatitis [10]. The leptin-dependent resistance to the development of innate immune-mediated inflammation remains unknown, but an imbalance between pro- and anti-inflammatory cytokines has been reported [57], which suggests that leptin is able to modify monocytes/macrophages cytokine secretion pattern through a STAT-3-activated pathway [58]. In models of adaptive immune-mediated inflammation, leptin deficiency implies an imbalance between T_{H1} and T_{H2} lymphocytes [59], causing an altered cytokine secretion which could lead to the aforementioned resistance to inflammation.

It has been reported that T-cells from leptin-resistant (*db*/*db*) mice were unable to develop colitis when transferred to T-cell deficient-mice [60]. Furthermore, circulating leptin is elevated in experimental models of intestinal inflammation, showing a correlation with the degree of inflammation, and an association with the development of anorexia [61]. Moreover, it has been shown that serum leptin levels are elevated in adult males with acute ulcerative colitis [62], and that inflamed colonic epithelial cells secrete leptin to the intestinal lumen, where it is able to activate the nuclear factor-κB (NF-κB). These data suggest that leptin plays a key role in intestinal inflammation as well as in the development of anorexia associated to this inflammatory stage.

Concerning experimental autoimmune encephalomyelitis (EAE), it has been shown that *ob*/*ob* mice are resistant to the development of this model of multiple sclerosis. This resistance is abolished by the administration of leptin, which is accompanied by a switch from a T_{H2} to T_{H1} pattern of cytokine release [63]. In addition, and in concordance with these reports, it has been noticed that the onset of the disease is preceded by an increase of circulating leptin [64]. Furthermore, it has been demonstrated that acute starvation, which is accompanied by a decrease in circulating leptin levels, delays the onset of the disease and attenuates the symptoms. Recently, it has been shown that leptin levels are negatively correlated with $CD4^+$ $CD25^+$ regulatory T-cells during multiple sclerosis, suggesting that this negative association may have major implications in the pathogenesis of multiple sclerosis, as well as in the development of different autoimmune diseases characterized by T_{H1} autoreactivity [64].

Noteworthy, it has been showed that leptin is expressed by both macrophages and T-cells infiltrated into the central nervous system during EAE [56]. This interesting report indicates that leptin is produced by immune cells during acute EAE, and suggests that this hormone could be participating in the development of CNS-inflammatory diseases not only in an endocrine fashion but also by an auto or paracrine way. Conversely, it has been recently demonstrated that T-cell-derived leptin has only a marginal role in the regulation of the hepatic and intestinal inflammatory process [65]. By using two well-described T-cell-dependent inflammatory models, Fantuzzi *et al*. [65] compared the ability of T-cells isolated from wild-type (wt) and *ob*/*ob* mice to induce inflammation. These authors showed that there were no differences between *ob*/*ob* and *wt* T-cells regarding their ability to induce inflammation, suggesting that other sources of leptin, rather than T-cells, must be critical in leptin modulation of inflammatory responses.

Leptin's actions have also been investigated in other models of immune-inflammation. In non-obese diabetic (NOD) female mice, increased serum leptin levels have been reported preceding the onset of the disease [66]. Furthermore, it has been demonstrated that leptin administration increases both inflammatory infiltrates and IFN-γ production in peripheral T-cells, speeding-up the destruction of pancreatic β-cells, and anticipating the onset of the disease [56],

Leptin's involvement in rheumatic diseases and cartilage homeostasis

The term rheumatic diseases includes a wide group of pathologies, such as rheumatoid arthritis (RA) and osteoarthritis (OA), which affect joints, bones and muscles, and might also involve internal organs. It has been shown that interactions between neuroendocrine and immune systems contribute to the pathogenesis of rheumatic diseases such as RA [67]. Among the different neuroendocrine mediators, leptin likely plays a major role in the pathogenesis of RA. Leptin-deficient *ob*/*ob* mice develop

Table 1.

Why is leptin a pro-inflammatory cytokine?
• Structurally, leptin belongs to the type I cytokine superfamily
• Leptin receptor (Ob-R) belongs to the class I cytokine receptor family
• Leptin expression is regulated by pro-inflammatory mediators
• Circulating leptin levels are increased in both acute and chronic inflammation
• Leptin modulates T_{H1}/T_{H2} balance, regulating cytokines expression pattern
• In synergy with other cytokines, leptin induces NOS type II activation in chondrocytes

resistance to experimental antigen-induced arthritis in comparison with wild-type mice [59]. In addition, it has been reported that fasting, which is associated with a dramatic decrease in circulating leptin, leads to a decreased $CD4^+$ lymphocyte activation and increased IL-4 secretion in patients with RA [68]. Our group has recently demonstrated that circulating leptin levels, as well as those of other adipokines, are increased in patients with RA [69]. This result is in agreement with a recent study of Bokarewa *et al*. [70], which reported increased plasma levels of leptin in patients with RA when compared with healthy controls. Notably, high leptin levels are also related with a higher prevalence of other immune diseases, such as systemic lupus erythematosus (SLE) [71], and also with increased susceptibility to the development of OA [72]. However, whether the increase of plasmatic leptin is a cause or a consequence of the development of those pathologies needs to be elucidated. In addition, in patients with SLE and RA clear evidence supports the known concept that leptin inhibits androstenedione secretion [73]. In chronic inflammatory diseases, this phenomenon may add to the well-known hypoandrogenicity. Because leptin is a pro-inflammatory mediator and androgens are anti-inflammatory, preponderance of leptin and hypoandrogenicity may help to perpetuate chronic inflammatory diseases.

Recent experimental evidence suggests a clear effect of leptin on the cartilage cellular component: the chondrocyte. Among the multiple connective tissues integrated in normal joint, the articular cartilage is the most affected during rheumatic diseases. Within the mature articular cartilage, chondrocytes, the single cellular component of this tissue, maintains a delicate balance between synthesis and degradation of the extracellular matrix [74, 75]. Under pathological conditions, this balance becomes altered and chondrocytes are capable of producing a host of mediators that are associated with inflammation, thus driving and perpetuating a complete loss of cartilage structure. Recently, it has been demonstrated that normal chondrocytes express leptin [76] and its long form cognate active receptor [77]. In addition, Dumond *et al*. [76] reported that leptin expression is increased in osteoarthritic chondrocytes as well as in the articular joints after leptin exogenous administration. Nonetheless, it has been recently hypothesized that the increased pre-disposition of females to develop OA could be due to the higher circulating leptin levels observed in females [72] in comparison with males.

Regarding leptin's direct activity on chondrocytes, it has been recently demonstrated that leptin induces, in synergy with IFN-γ, NOS type II activation in cultured chondrocytes [78] via the activation of JAK-2 kinase. NO, which is induced by a wide range of pro-inflammatory cytokines, is a well-known pro-inflammatory mediator in joint cartilage, where it triggers chondrocyte phenotype loss, apoptosis and metalloproteases activation [75].

Our group has reported very recently a synergistic effect of leptin also with IL-1 (probably the most relevant cytokine playing in degenerative articular inflammatory diseases such as OA) on NOS type II activation in chondrocytes by a signalling pathway that involves PI-3 kinase, MEK-1 and p38 kinase [79] (Fig. 2). Notably, this signalling cascade is convergent with the pathway evoked by the above described synergistic effect of leptin and IFN-γ in chondrocytes (Otero *et al*., unpublished data). Taken together, these data reinforce the view of leptin as a pro-inflammatory cytokine (Table 1) and suggest that it could be the link between obesity and inflammatory conditions, especially those related with alterations of cartilage homeostasis.

Future perspectives and conclusions

Many aspects concerning leptin's interactions with inflammation and immune system remains unclear. At the present, there is lots of evidence about leptin's actions on immune system that has enlightened leptin as an important link between nutritional status and immunity. In addition, leptin has been revealed as a new pro-inflammatory cytokine with direct actions on immune-inflammatory response. This adipokine could be considered as a new potential therapeutic target for rheumatic diseases, especially those related with energy homeostasis disorders such as cachexia and obesity.

As mentioned earlier, circulating leptin is increased under inflammatory conditions, both in acute and in chronic inflammatory diseases such as RA. Taking into consideration the detrimental effect of the increased circulating leptin on inflammation, it could be suggested that the control of the amount of bioavailable leptin by using a specific soluble receptor (in a similar strategy than that used with tumour necrosis factor-α in RA) might be a good way to avoid undesired leptin actions in autoimmune-inflammatory diseases.

The blockade of leptin receptor, by using monoclonal humanized antibodies or leptin mutants able to bind the leptin receptor without activating it [80], could be another potential way to antagonize leptin actions. Unfortunately, the current anti-leptin therapy has been developed focusing prevalently on leptin actions as an adipostatin, which implies trespassing the BBB. Hence, little is known about protein-based anti-leptin therapy at present. However, due to the fact that leptin investigations were initially focused on weight regulation, and considering that major leptin effect on food intake and energy expenditure occurs at the hypothalamic level and that all the aforementioned molecules do not cross the BBB, only little care has been given to the development of a protein-based anti-leptin therapy. Nonetheless, based on the recent observations supporting a major role of leptin in immunity, and considering that most of the effects on the immune system and inflammatory response are mediated directly by receptors on peripheral target cells, it should be auspicious that the development of such a molecule should be boosted as a promising therapeutic intervention for inflammatory degenerative diseases such as RA, OA and others. In addition, since the negative feedback loop via SOCS-3 is speculated to be central to the development of leptin resistance, it is quite reasonable that SOCS-3 may also constitute a target for pharmacological manipulation of leptin action. Understanding the leptin signalling mechanism has become crucial for design of novel therapeutic strategies for leptin-resistant/obese patients. The SH2-containing cytoplasmic tyrosine phosphatase Shp-2 has recently been shown to play a critical role in leptin signalling and functions in hypothalamic control of energy balance and metabolism. Shp-2 appears to down-regulate the LepRb-STAT3 pathway while promoting extracellular-regulated kinase activation by leptin. Overall, Shp-2 is a leptin signal enhancer, as evidenced by the obese and hyperleptinaemic phenotype of mutant mice with Shp-2 deleted in post-mitotic forebrain neurons. Pharmaceutical enhancement of Shp-2 activity may be a new valuable approach worthy of consideration in the clinical treatment of leptin-related diseases [81].

In conclusion, there is an increasing evidence that leptin is involved in the pathogenesis of inflammatory and autoimmune diseases. The evidence that leptin signalling deficiency impairs humoral and cellular immune response suggests that the blockade of leptin activity on specific target tissues could be a useful beneficial therapy in the near future.

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