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REVIEW

LEPTIN, A RAILROAD SWITCH ENABLING CROSSOVER SIGNALS AMONG INFLAMMATION, IMMUNITY AND METABOLISM

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Abstract

White adipose tissue is currently considered as an active endocrine organ that secretes a plethora of factors named adipokines, some of them being of pro-inflammatory nature that likely contribute to the low-level systemic inflammation, a status that is often present in metabolic syndrome-associated chronic pathologies such as obesity, type 2 diabetes, and atherosclerosis. Leptin is historically indisputably one of the most important adipokine secreted by fat cells, with a variety of physiological roles ranging from to the control of metabolism, energy homeostasis and inflammatory response to cognition. Leptin is also implicated in the connection between nutritional status and immune competence, modulating both the innate and adaptive immune responses in normal as well as pathological conditions. It has been shown that conditions characterized by low leptin levels are associated with increased infection susceptibility. Conversely, immune-mediated disorders such as autoimmune diseases are associated with increased secretion of leptin and production of proinflammatory cytokines. Thus, leptin can be easily considered as a frank mediator of metabolic and inflammatory/immune responses.

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Introduction

White adipose tissue plays a very important role in the energetic balance of mammals. This tissue has been specialized along millions of years in storing lipids and supplying energy stores to the whole body whenever it is necessary. In order to face energetic requirements, fat cells regulate fatty acid mobilization in response to alterations of homeostatic status. However, adipose tissue is not only a reservoir of fats; it is also an endocrine organ able to release hormones, peptides, and cytokines collectively named adipokines; they exert relevant actions both on metabolism and the immune system (1). Leptin is the forerunner of adipokines superfamily and it is one of the most important hormones secreted by adipose tissue (2) whose implications in energy homeostasis at central level has been previously described (3).

Leptin levels signal starvation to the body, in that a falling in serum leptin concentration leads to neuroendocrine modifications aimed to preserve energy stores for vital functions. Thus, during fasting period and after reduc-

tion of body fat mass, there is a decrease in leptin levels that provokes a reduction of total energy expenditure (4-5). Even these effects of low leptin levels are designed to increase the survival chances under starving conditions, the fall in leptin levels may lead to deep immune suppression (6), in addition to other neuroendocrine alterations affecting adrenal axis, and reproductive function in both genders (7). In fact, both *ob/ob* mice (lacking leptin gene) and *db/db* mice (lacking leptin receptor gene) are not only obese and diabetic but they present deep immune/endocrine alterations observed during starvation (6-8).

In humans, it has been found that leptin levels are associated with immune response in malnourished babies, which have low plasma leptin and impaired immune response (9). It is relevant to stress that leptin signalling deficiency impairs both humoral and cellular immune responses. The long form of leptin receptor Ob-Rb (that is able to transduce the signal) is expressed in B and T lymphocytes, suggesting that leptin regulates directly the B and T cell responses (10). Modulation of the immune system by leptin is exerted at several levels including development, proliferation, anti-apoptotic, maturation, and activation levels (11). Indeed, leptin receptors have been found in almost all the cell blood populations including neutrophils, monocytes, and lymphocytes. Leptin receptor belongs to the superfamily of class I cytokine receptors and signals through a canonical pathway involving the Jak2/STATs transducers. However, other relevant signal transduction pathways such as the Shc/GRB2 pathway has been described upon activation of leptin receptors long form (12).

Leptin activity on the immune system is fundamentally proinflammatory. Indeed leptin activates proinflammatory cells, promotes T-helper I responses, and mediates the production of proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1) or IL-6 (13).

Leptin, inflammation and innate immunity

Consistent with the role of leptin in the mechanisms of immune response and host defense, circulating leptin levels are increased in infective processes and experimental models of inflammation (14-15). Studies of rodents with genetic alteration in leptin or leptin receptors revealed a strong deficit in macrophage phagocytosis and on the expression of proinflammatory cytokines both *in vivo* and *in vitro*, whereas exogenous leptin administration upregulated both phagocytosis and the production of cytokines (16-17). Leptin deficiency increases susceptibility to infectious and inflammatory stimuli and is associated with dysregulation of cytokine production (17-18). Though, leptin levels increase acutely during infection and inflammation, and may represent a protective component of the host response to inflammation (19). Recently, Guilak *et al* (20) carried experiments in leptin deficient (*ob/ob*) and leptin receptor deficient (*db/db*) female mice to test the hypothesis that obesity may result in increased knee osteoarthritis (OA), systemic inflammation, and altered subchondral bone morphology. Authors concluded that extreme obesity due to impaired leptin signaling induced alterations in subchondral bone morphology without increasing the incidence of knee OA. In addition, adiposity in the absence of leptin signaling is insufficient to induce systemic inflammation and knee OA in female C57BL/6J mice. These results imply a pleiotropic role of leptin in the development of OA by regulating both the skeletal and immune systems (20).

Human leptin was found to stimulate proliferation and activation of human circulating monocytes *in vitro*, promoting the expression of several markers of macrophage activation. Moreover, leptin (*i*) increases the expression of monocytes surface markers (21,22), (*ii*) enhances the stimulatory effect of lipopolysaccharide (LPS) or phorbol myristate acetate (PMA) on the proliferation and activation of human monocytes, (*iii*) stimulates the production of proinflammatory TNF-α and IL-6 by monocytes (21), and (*iv*) increases chemokine expression in cultured murine macrophage, through activation of long form of leptin receptor and via the JAK2-STAT3 pathway (23). Noteworthy, in lung macrophages leptin increases leukotriene synthesis (24).

Leptin regulates monocyte function as assessed by *in vitro* experiments evaluating free radical production; it was shown to stimulate the oxidative burst in control monocytes (25). In addition, leptin binding at the macrophage cell surface increases lipoprotein lipase expression through oxidative stress- and PKC-dependent pathways. In this line, leptin has been found to increase oxidative stress in macrophages (26). Finally, leptin might act as a monocyte/macrophage chemoattractant by inducing *in vitro* chemotactic responses (27), by mediating the inflammatory infiltrate composition (28) and by inducing tissue factor expression in human peripheral blood mononuclear cells (29). On the other hand, human leptin seems to downregulate oxidative burst in previously activated monocytes (25).

Leptin has been found to augment the production of several cytokines and interleukins whereas it decreases MIP-1α production by dendritic cells. In the same way to leptin effect on monocytes, it increases the survival of dendritic cells, and it may also increase the expression of specific surface molecules (30). Leptin is able to induce functional and morphological changes in human dendritic cells driving them towards Th1 priming and promoting cell survival via the PI3K-Akt signaling pathway (31). Leptin receptor deficient mice displayed a marked reduction of co-stimulatory molecules and a Th2-type cytokine pro-

file, with poor capacity to stimulate allogenic T cell proliferation. To note the activity of the PI3K/Akt pathway as well as STAT-3 and IkappaB-alpha in dendritic cells of *db/db* mice is also down-regulated. Furthermore, the low number of dendritic cells in *db/db* bone marrow culture was attributed to a significant increase in apoptosis rate, which is also associated with dysfunctional expression of Bcl-2 family genes (32).

Human polymorphonuclear neutrophils (PMN) have been found to express leptin receptor *in vitro* and *in vivo* and it is likely to act as a survival cytokine for PMN (33-34). Leptin has a stimulating effect on intracellular hydrogen peroxide production in PMN, although this effect seems to be mediated by the activation of monocytes (35). Leptin could upregulate cell surface expression of the adhesion molecules ICAM-1 but suppress ICAM-3 and L-selectin in eosinophils. Moreover, leptin could also stimulate the migration of eosinophils, and provoke the release of inflammatory cytokines (36).

Leptin receptors can signal also in Natural Killer (NK) cells, given that leptin activates STAT3 phosphorylation in these cells. Consistent with the role of leptin regulating NK cells, *db/db* mice have been found to have impaired NK cell function (37-38). Leptin actions in NK cells include cell differentiation, maturation, activation, and cytotoxic activity (16). Leptin increases both the development and the activation of NK cells, by increasing IL-12 production and by reducing the expression of IL-15 (37-38). Further, leptin mediates the activation of NK cells indirectly by modulation of IL-1 by monocytes and macrophages (29).

Leptin, inflammation and adaptive immunity

Most of the data about the role of leptin in adaptive immunity came from studies carried on in *ob/ob* mice. These mice have a diminished sensitivity of T cells to triggering stimuli. In addition, these animals show thymus atrophy and other lymphoid organs (6-8), with a reduction in the number of circulating T cells, and an increase in the number of monocytes. The ability of exogenous leptin in preventing thymic atrophy is due to a direct antiapoptotic effect on T cells (8). Thus, leptin administration increases thymic expression of important soluble thymocyte growth factors such as IL-7. Leptin has also a trophic role in sustaining thymic epithelium and promoting thymopoiesis.

Acute deficiency of leptin has potent effects on the immune system, in some cases higher than that observed in *ob/ob* mice. Indeed, acute hypoleptinemia in mice induces a strong decrease in the total number of thymocytes, and a strong increase of the number of apoptotic cells much more than that observed in ob/ob mice. Both *ob/ob* and *db/db* mice show defects in cell-mediated immune response which lead to impaired reaction of delayed hypersensibility, suppression of skin allograft rejection, and inhibition of footpad swelling by antigen recall (7,39-41). Lord *et al* (6) demonstrated that mouse lymphocytes express the long form of leptin receptor, and that leptin modulates in these cells cytokine production. In addition, leptin also regulates the number and activation of T lymphocytes. The proliferative response to leptin in mice seems to be produced in naïve T cells (CD4+CD45RA+), whereas it has been shown that leptin inhibit proliferation of memory T cells (CD4+CD45RO+) (6). Leptin provides a survival signal in double positive T cells (CD4+CD8+) and simple positive CD4+CD8- thymocytes during thymic maturation (8). Furthermore, this adipokine induces the expression of adhesion molecules in CD4+ T cells, such as VLA-2 (CD49b), or ICAM-1 (CD54) (6-13).

Leptin increases T cell response, shifting cytokine responses towards a Th1 phenotype in mice (8). The effect of leptin polarizing T cells towards a Th1 response seems to be mediated by stimulating the synthesis of IL-2, IL-12 and IFN-gamma and the inhibition of the production of IL-10 and IL-4 production (29). In addition to the above reviewed immune regulatory actions, recent evidence shows that leptin acts as a proinflammatory cytokine. It has been shown that different inflammatory stimuli, including IL-1, IL-6 or LPS, regulate leptin mRNA expression as well as circulating leptin levels (14). 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 (42). 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 (EAE), type I diabetes and experimentally induced hepatitis (1). The leptin-dependent resistance to the development of innate immune-mediated inflammation remains unknown, but it has been reported an imbalance between pro- and anti-inflammatory cytokines (43) which suggests that leptin is able to modify monocytes/macrophages cytokine secretion pattern through a STAT-3 activated pathway (44). In models of adaptive immune-mediated inflammation, leptin deficiency implies an imbalance between T_{H1} and T_{H2} lymphocytes (10), causing an altered cytokine secretion which could lead to the above mentioned resistance to inflammation. In any case, the precise role of leptin in the development of inflammation remains incompletely understood.

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 (45). 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 (46). It has also been shown that serum leptin levels are elevated in adult males with acute ulcerative colitis, and that inflamed colonic epithelial cells secrete leptin to the intestinal lumen, where it is able to activate the NF-kB (47). These data suggest that leptin plays a key role in intestinal inflammation as well as in the development of anorexia associated to this inflammatory state.

Concerning 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 (48). 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 (49). 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 (49). Noteworthy, Matarese *et al* (42) showed that leptin is expressed by both macrophages and T cells infiltrated into the central nervous system (CNS) during EAE. 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. However, it has been recently demonstrated that T cell-derived leptin has only a marginal role in the regulation of the inflammatory process (50). The authors showed that there were no differences between *ob/ob* and wild type T cells regarding their ability to induce inflammation, suggesting that other sources of leptin, different than T-cells, must be critical in leptin modulation of inflammatory responses. The reason for these discrepant findings remains unclear, but might be related to differences in experimental settings (i.e the model of autoimmune encephalitis, and the transfer model of colitis), and deserves further investigations. In addition, a recent report by Palmer *et al* (51) pushes on the importance of the global neuroendocrine alterations, rather than local effects of leptin on T-cells, in the immune defects observed in *ob/ob* and *db/db* mice. Indeed, to study the relative contributions of direct and indirect effects of leptin on the immune system in a normal environment, these authors generated bone marrow chimeras by transplantation of leptin receptor-deficient *db/db*, or control *db/+*, bone marrow cells (BMC) into wild-type (WT) recipients. According this experimental set, the size and cellularity of the thymus, as well as cellular and humoral immune responses, were similar in *db/db* to WT and *db/+* to WT BMC. Thus, authors suggested that the immune phenotype of *db/db* mice is not explained by a cell autonomous defect of *db/db* lymphocytes. Conversely, thymus weight and cell number were decreased in the reverse graft setting in WT to *db/db* BMC, indicating that expression of the leptin receptor in the environment is important for T cell development. Finally, normal thymocyte development occurred in fetal *db/db* thymus transplanted into WT hosts, indicating that direct effects of leptin are not required locally in the thymic microenvironment.

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 (52). Furthermore, it has been demonstrated that leptin administration increases both inflammatory infiltrates and IFN-gamma production in peripheral T cells, which speeds-up the destruction of pancreatic beta-cells, and anticipates the onset of the disease, suggesting that leptin promotes the development of type 1 diabetes through a T_{H1} response. Finally, it has been shown that leptin administration increases both inflammatory and platelet responses in humans during caloric deprivation (53). In addition, it has been demonstrated that leptin increases susceptibility to hepatotoxicity through its regulation on T cell activation and cytokine secretion (54).

Leptin receptor is highly expressed on the cell surface of regulatory T - T(reg) - cells. Leptin can act as a negative signal for the proliferation of human Foxp3 (+) CD4 (+) CD25 (+) T(reg) cells. *In vitro* neutralization with leptin monoclonal antibody (mAb), during anti-CD3 and anti-CD28 stimulation, resulted in T(reg) cell proliferation, which was IL-2 dependent. Together with the finding of enhanced proliferation of T(reg) cells observed in leptin- and ObR-deficient mice, these results suggest a potential for therapeutic interventions in immune and autoimmune diseases (55, for other diseases, see 56-58). These authors (55) also reported that in monocytes, leptin induces expression and secretion of the IL-1 receptor using the MAPK pathway that activates NF-κB. Likewise, the expansion of T(reg) cells following anti-leptin neutralization is mediated by the induction of ERK 1/2 phosphorylation (59).

Conclusions

Leptin plays an important role in the activation of the immune system, and it is a mediator of inflammation. In this context, leptin is unquestionably one of the mediators responsible for the

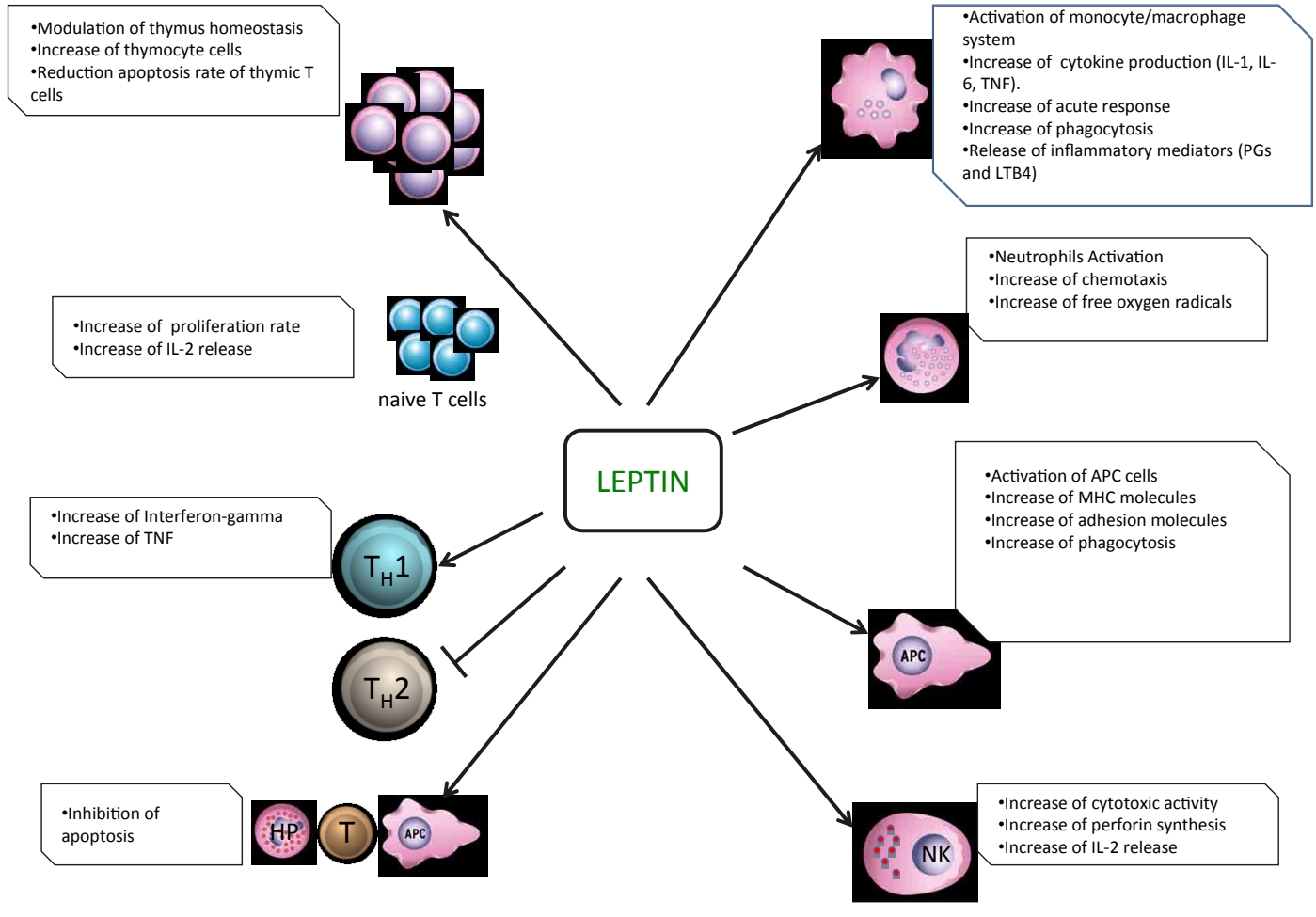

Figure 1. Schematic representation of the pleiotropic nature of leptin on the immune system.

low-grade systemic inflammation that is present in the pathogenesis of cardiometabolic diseases including atherosclerosis, hypertension, obesity, type 2 diabetes and metabolic syndrome. Hence, leptin may be considered a potential therapeutic target in some clinical situations, such as proinflammatory states or autoimmune diseases.

During the last 16 years, leptin has been proven to be a pleiotropic factor that is able to signal, among several organs, the amount of energy stores and to regulate neuroendocrine axes, immune function, and energy substrates metabolism. Several lines of evidence indicates that leptin (or its synthetic or semisynthetic analogues) can be a useful therapeutic target in a variety of dysfunction, most of them characterized by the hormonal deficiency such as amenorrhea or lipodystrophy. Other potential therapeutic targets, such as infertility and anorexia, are currently under intense investigation and hold promising options. A novel intriguing pharmacological perspective is represented by the development of a class of drugs that could act as leptin sensitizers are anticipated with great expectations. Another emerging aspect regarding leptin as potential therapeutic target is coming from the idea of leptin as a factor enhancing the production of proinflammatory factors in cartilage and as an agent contributing to the obesity-associated increased risk for osteoarthritis. Results coming from our laboratory and others suggest that manipulation of leptin levels is a promising novel mechanism to be directed in the search and development of novel anti-inflammatory and anti-erosive compounds having the good efficacy. So, the control of the amount of bioavailable leptin by using a specific soluble receptor (in a similar strategy than that used with TNF-α in rheumatoid arthritis) 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, could be another potential way to antagonize leptin actions (57,58). Obviously, it will be needed that these antibodies will not influence food intake to avoid the

development of hyperphagia and obesity. However, the fact that leptin actions on food intake are exerted at central level after crossing the BBB while its effects on inflammation are exerted at peripheral level opens up this possibility. Unfortunately, the current anti-leptin therapy has been developed focusing prevalently on leptin actions as an adipostatin, which implies trespassing the BBB. So that, very little is known about protein-based anti-leptin therapy at present. Nonetheless, considering that most of leptin effects on immunity and inflammation are mediated through peripheral receptors, it is conceivable that the development of the above mentioned strategies could be useful as a novel therapeutic approach. The applications of leptin continue to grow and will hopefully soon be used therapeutically.

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