Review

Leptin as an immunomodulator

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Abstract

Leptin is an adipocyte-derived hormone/cytokine that links nutritional status with neuroendocrine and immune functions. In humans, leptin influences energy homeostasis and regulates neuroendocrine function primarily in states of energy deficiency. Initially described as an antiobesity hormone, leptin has subsequently been shown also to influence basal metabolism, hematopoiesis, thermogenesis, reproduction, and angiogenesis. As a cytokine, leptin can affect thymic homeostasis and the secretion of acute-phase reactants such as interleukin-1 (IL-1) and tumor-necrosis factor-alpha (TNF-α). Leptin links nutritional status and proinflammatory T helper 1 (Th1) immune responses and the decrease in leptin plasma concentration during food deprivation leads to impaired immune function. Similar to other pro-inflammatory cytokines, leptin promotes Th1-cell differentiation and can modulate the onset and progression of autoimmune responses in several animal models of disease. Here, we review the advances and controversy for a role of leptin in the pathophysiology of immune responses and discuss novel possible therapeutic implications for leptin modulators.

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1. Introduction

The past few years of research on leptin – the product of the obese (ob) gene – has provided important insights into the intricate network that links nutrition, metabolism and immune homeostasis (Friedman and Halaas, 1998). The neuroendocrine and immune systems communicate bidirectionally through common ligands and receptors. The hypothalamic–pituitary–adrenal (HPA) axis is one of the main structures that is responsible for this communication, and HPA hormones (corticotrophin-releasing hormone, CRH, adenocorticotrophic hormone, ACTH, and glucocorticoids) secreted during stress responses and inflammation control immune responses. Acute-phase reactants – interleukin-1 (IL-1), IL-6 and tumor-necrosis factor-α (TNF-α) can influence the secretion of HPA hormones and also the contrary holds true, indeed leptin, a cytokine/hormone, can also influence the HPA axis. It is mainly produced by the adipose tissue in proportion to the body fat mass and, at lower levels, by tissues such as the stomach, skeletal muscle and placenta (Friedman and Halaas, 1998). In the hypothalamus, leptin regulates appetite, autonomic nervous system outflow, bone mass and the secretion of HPA hormones (Friedman and Halaas, 1998). Although an important role of leptin is to regulate body weight through the inhibition of food intake and stimulation of energy expenditure by increased thermogenesis, recent evidence has indicated that leptin is much more than a ‘fat-o-stat’ sensor (Matarese et al., 2002a). Indeed, leptin-deficient (ob/ob) mice and leptin-receptor-deficient (db/db) mice are not only severely obese, but also have a series of marked abnormalities that are secondary to the effects of leptin on reproduction (Chehab et al., 1996), hematopoiesis (Bennett et al., 1996), angiogenesis (Sierra–Honigmann et al., 1998; Park et al., 2001), metabolism of bone (Ducy et al., 2000), lipids and glucose (Friedman and Halaas, 1998) and, last but not least, innate and adaptive immunity (Lord et al., 1998; Sanchez-Margalet et al., 2003). This review analyses the role of leptin in immune homeostasis, and the direct and indirect influences of leptin on inflammation and autoimmunity.

2. Leptin in innate and adaptive immune response

Mice lacking leptin or its functional receptor have a number of defects in both cell-mediated and humoral immunity (Mandel and Mahmoud, 1978). Similarly, humans with congenital leptin deficiency have a much higher incidence of infection-related death during childhood (Ozata et al., 1999), whereas recombinant human leptin (rmetHuLeptin) administration in two children with congenital leptin deficiency normalized absolute numbers of naive CD4+CD45RA+ T cells and nearly restored the proliferation response and the cytokine release profile from their lymphocytes (Farooqi et al., 2002). A number of studies in mice have shown that the effect of leptin on the immune system is both direct and indirect, i.e., via modulation of central or peripheral pathways (Fraser et al., 1999; Zhang et al., 2002).

Leptin has a well-established role in all cells involved in innate immunity, which senses either specific pathogen-associated molecular patterns, formally not expressed by host tissues, or endogenous molecules released from “stressed” cells (Table 1). In macrophages/monocytes, leptin up-regulates phagocytic function (Mancuso et al., 2002) via phospholipase activation (Mancuso et al., 2004) as well as proinflammatory cytokine secretion, such as TNF-α (early), IL-6 (late), and IL-12 (Loffreda et al., 1998; Gainsford et al., 1996). Leptin stimulates the proliferation of human circulating monocytes in vitro and up-regulates expression of activation markers, such as CD25 (α-chain of IL-2 receptor), CD71 (transferring receptor), CD69, and CD38, while it further increases the expression of other activation markers already present at high levels on the surface of resting monocytes, such as HLA-DR, CD11b, and CD11c (Zarkesh-Esfahani et al., 2001). A recent study on mouse macrophages has demonstrated that leptin is a potent chemoattractant for monocytes and macrophages and that leptin-mediated chemotaxis requires the presence of full-length leptin receptors on migrating cells (Gruen et al., 2007), suggesting that the canonical cell motility machinery is activated upon macrophage exposure to leptin.

Interesting reports have shown that also dendritic cells (DCs), the major antigen presenting cells (APCs) involved in T lymphocyte priming, are affected in obese mice (Table 1), in which both their function and their steady-state number are

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<td>Effects of leptin on the different cell populations of both innate and adaptive immune response.</td>
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<td><strong>Cell type</strong></td>
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<tr>
<td>Monocytes/macrophages</td>
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<td>Neutrophils</td>
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disturbed (Macia et al., 2006). Indeed it has been shown that DCs from ob/ob mice are less potent in stimulation of allogenic T cells in vitro. This impaired functionality is not associated with altered expression of phenotypic markers but rather with the secretion of immunosuppressive cytokines such as TGF-β (Macia et al., 2006). Moreover Mattioli et al. have shown that leptin induces functional and morphological changes in human DCs, licensing them towards Th1 priming and promoting DC survival (Mattioli et al., 2005), by triggering the activation of nuclear factor-kappa B (NF-kappa B) and a parallel up-regulation of bcl-2, bcl-XL gene expression and Akt activation (Mattioli et al., 2009). From the same group comes the finding showing that leptin increases immature DC migratory performance both by favoring cytoskeleton dynamics and by up-regulating CCR7 surface expression, thus favoring their chemotactic responsiveness (Mattioli et al., 2008).

Moreover, leptin can induce chemotaxis of neutrophils and the release of oxygen radicals (such as superoxide anion and hydrogen peroxide) (Caldefie-Chezet et al., 2001, 2003) (Table 1). These mediators can be particularly harmful to cells, as they can denature proteins and damage membrane lipids (by peroxidation of unsaturated fatty acids), carbohydrates and nucleic acids. The role of leptin in neutrophils function has been well characterized in ob/ob, db/db and WT mice injected intraperitoneally with a septic dose of lipopolysaccharide (LPS) (Rummel et al., 2010). Indeed Rummel et al., have shown that this treatment induced a dramatic increase in the number of neutrophils entering the brain of WT mice, an effect that was almost totally abolished in the mutant mice and correlated with a significant reduction in the mRNA levels of interleukin-1beta, intracellular adhesion molecule-1 and neutrophil-specific chemokines. These effects were reversed with leptin replenishment in ob/ob mice leading to recovery of neutrophil recruitment into the brain. Moreover, 48 h food deprivation in WT mice, which decreased circulating leptin levels, attenuated the LPS-induced neutrophil recruitment in the brain.

At least in human neutrophils, leptin seems to mediate its effects through an indirect mechanism, probably involving the release of TNF-α from monocytes (Zarkesh-Esfahani et al., 2004).

In addition, leptin is involved in all processes of NK cell development, differentiation, proliferation, activation, and cytotoxicity (Tian et al., 2002) (Table 1). Tian et al., demonstrated that the percentage of NK cells and total amount of NK cells in the liver, spleen, lung, and peripheral blood were declined in leptin-receptor deficient mice (db/db mice), indicating that NK cell development was vigorously influenced by leptin receptor deficiency. Moreover both basal and poly IC-stimulated NK cell activation (CD69 surface marker expression) were retarded in db/db mice (Tian et al., 2002). The effect is mediated at least via Signal transducer and activator of transcription 3 (STAT-3) activation and up-regulated expression of perforin and IL-2 genes (Zhao et al., 2003). Adaptive immunity, on the other hand, is characterized by antigen-specific responses. T and B cells produce cytokines and antibodies as result of their activation following antigen recognition through specific receptors.

A great impact of leptin deficiency has been found on the B cell compartment (Table 1). Indeed Claycombe et al., have shown that ob/ob mice displayed a significant reduction in lymphopoiesis, as testified by 70% fewer B cells than normal controls, as well as a reduction in the absolute number of pre-B and immature B cells. Seven days of provision of recombinant leptin promoted an increased number of B cells in the marrow of the obese mice twofold, while doubling and tripling, respectively, the numbers of pre-B and immature B cells (Claycombe et al., 2008). Similar results have been also detected in the bone marrow of fasted mice, in which intracerebroventricular leptin injection was sufficient to prevent the alteration of B-cell development (Tanaka et al., 2011). Moreover leptin activates human B cells to secrete cytokines, such as IL-6, IL-10, and TNF-α, via activation of JAK2/STAT3 and p38MAPK/ERK1/2 signaling pathways, which may contribute to its immunostimulatory and immunoregulatory properties (Agrawal et al., 2011).

The effects of leptin on adaptive immune responses have been extensively investigated also on human CD4+ T cells (Table 1). Addition of physiological concentrations of leptin to a mixed lymphocyte reaction (MLR) induces a dose-dependent increase in CD4+ T cell proliferation (Lord et al., 1998).

Studies in humans have further delineated the role of leptin in activation of lymphocytes. In contrast to macrophages/monocytes, leptin alone is unable to induce proliferation and activation of mature human peripheral blood lymphocytes unless it is co-administered with other nonspecific immunostimulants, in which case leptin results in induction of early (CD69) and late activation markers (CD25, CD71) in both CD4+ and CD8+ lymphocytes (Martin-Romero et al., 2000). However, leptin has different effects on proliferation and cytokine production by human naive (CD45RA) and memory (CD45RO) CD4+ T cells (both of which express the long spliced form of the leptin receptor, Ob-Rb). Leptin promotes the proliferation and IL-2 secretion by naive T cells, through the activation of the mitogen-activated protein kinase (MAPK) and phosphatididylinositol-3-kinase (PI3-K) pathways. On memory T cells, leptin promotes the switch towards T helper (Th1)-cell immune responses by increasing interferon-γ (IFN-γ) and TNF-α secretion (Fig. 1), IgG2a production from B cells, and by promoting delayed-type hypersensitivity (DTH) responses, a process sustained by an autocrine loop of leptin secretion from Th1 cells (Lord et al., 1998).

Leptin also increases the expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1, CD54) and very late antigen-2 (VLA-2, CD49b) on CD4+ T cells, possibly through the induction of pro-inflammatory cytokines such as IFN-γ. Increased expression of adhesion molecules could possibly be responsible for the activation and migration of immune cells to sites of inflammation (La Cava and Matarese, 2004). Recent evidence indicates that leptin also affects the generation, maturation and survival of thymic T cells by decreasing their rate of apoptosis (Howard et al., 1999). Indeed, acute caloric deprivation causes a rapid decrease of serum leptin concentration accompanied by reduced DTH responses and thymic atrophy, which are reversible with administration of leptin (Howard et al., 1999).

Recently, it has been reported that leptin can act as a negative signal for the expansion of human naturally occurring Foxp3+CD4+CD25hi regulatory T cells (Treg) (De Rosa et al., 2007), a cellular subset which suppress autoreactive response mediated by CD4+25- T cells (Fig. 1) (Table 1). De Rosa et al. showed that freshly isolated Treg cells produce leptin and...
express high levels of leptin receptor (ObR). In vitro neutralization with anti-leptin monoclonal antibody (mAb) following anti-CD3/CD28 stimulation resulted in Treg cells proliferation. This phenomenon was secondary to the modulation of selected molecular pathways of T cell activation and anergy in the Treg cells, as indicated by the downmodulation of the cyclin-dependent kinase inhibitor p27kip1 and the phosphorylation of the extracellular-related kinases 1/2 (ERK1/2) (De Rosa et al., 2007). Together with the finding of enhanced numbers and proliferation of Treg cells observed in leptin- and ObR-deficient mice, these results suggest a potential for therapeutic interventions in immune and autoimmune diseases, by transfer of anti-leptin-expanded antigen-specific T reg cells. Very recently a paper by the same group has shown that leptin activates the mammalian target of rapamycin (mTOR) pathway to control Treg cells responsiveness (Procaccini et al., 2010). mTOR is an evolutionarily conserved 289-kDa serine/threonine protein kinase that is inhibited by rapamycin and integrates environmental cues from nutrients, energy and growth factors to direct cell growth, proliferation and differentiation (Laplante and Sabatini, 2010). At the immune level, it has been shown that mTOR is able to program the generation of CD8+ effector, to
control T cell trafficking, and T cell activation versus anergy, thus suggesting that mTOR provides a direct link between T cell metabolism and function (Araki et al., 2009; Rao et al., 2010; Pearce et al., 2009). More specifically, in the paper by Procaccini et al., leptin has been shown to inhibit rapamycin-induced proliferation of Tregs, by increasing activation of the mTOR pathway. In addition, under normal conditions, Tregs secreted leptin, which activated mTOR in an autocrine manner to maintain their state of hyporesponsiveness. Finally, Tregs from db/db mice exhibited a decreased mTOR activity and increased proliferation compared with that of wild-type cells (Procaccini et al., 2010). Together, these data suggest that the leptin–mTOR axis sets the threshold for the responsiveness of Tregs and that this pathway might integrate cellular energy status with metabolic-related signaling in Treg cells that use this information to control immune tolerance.

3. Leptin and autoimmunity

A growing body of evidence indicates that leptin acts as a pro-inflammatory cytokine in immune responses. Although pro-inflammatory factors are critical mediators of host defense mechanisms, these cytokines sustain and enhance the development of autoimmune diseases (La Cava and Matarese, 2004). Indeed, leptin has been shown to enhance immune reactions in autoimmune diseases that are commonly associated with inflammatory responses. Increased peripheral secretion of leptin in humans is associated with chronic inflammatory and autoimmune conditions, whereas decreased leptin levels generally inhibit autoimmune disease onset. Indeed starvation, not only associates with hyperleptinemia, but also with an increased concentration of glucocorticoids and decreased levels of thyroid and growth hormones (which can result in immune suppression). In this context it has been shown that ob/ob mice have reduced secretion of IL-2, IFN-γ, TNF-α and IL-18, and increased production of Th2-type cytokines, such as IL-4 and IL-10, after mitogenic stimulation (Lord et al., 1998), indicating that leptin is involved in the dysregulated balance between Th1 and Th2 cytokine. As a result, ob/ob mice are resistant to the induction of several experimentally induced autoimmune diseases. The prevalence of autoimmune diseases, such as Rheumatoid Arthritis (RA), is increased with serum leptin levels, indeed fasting RA patients exhibiting significantly improved clinical disease activity correlated with a marked reduction in serum leptin and a shift towards Th2 cytokine production (Fraser et al., 1999). Consistently, less severe autoimmune arthritis has been observed in both ob/ob and db/db mice following the immunization of methylated Bovine Serum Albumin (BSA) into knee joints, and the antigen-specific T cell proliferative responses are markedly decreased in ob/ob mice, thus suggesting an involvement of leptin signaling in antigen-induced arthritis (Busso et al., 2002). The immunomodulatory effects of leptin have also been linked to enhanced susceptibility to other autoimmune disease such as experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis (Matarese et al., 2001a). Recent studies have shown that leptin is involved in the induction and progression of EAE (Matarese et al., 2001a,b; Sanna et al., 2003). The ob/ob mice are resistant to EAE induction with increased IL-4 and a lack of IFN-γ secretion after myelin-specific stimulation of T cells. Interestingly, leptin replacement renders these mice susceptible to the disease secondary to a shift towards a Th1-type cytokine pattern and to the reversal of IgG1 to the Th1-dependent IgG2a (Matarese et al., 2001a,b). Notably, leptin is expressed by T cells and macrophages in both the lymph nodes and active inflammatory lesions of the CNS (Central Nervous System) during acute and relapsing EAE, but not during remission (Sanna et al., 2003). The role of leptin in EAE is further established with leptin neutralization experiments in WT mice. This kind of treatment significantly improves clinical score and delayed disease progression by inhibiting T cell autoreactivity during EAE progression (De Rosa et al., 2006). Finally, increased leptin expression has recently been described in active inflammatory lesions of the CNS in patients with multiple sclerosis (Lock et al., 2002) (MS) and in the sera of patients with MS before relapses after treatment with IFN-β (Baticchi et al., 2003). In human studies, Matarese et al. also demonstrated that leptin production was significantly increased in both serum and CSF (cerebrospinal fluid) of RRMS (relapsing–remitting multiple sclerosis) patients and that this increase correlated with IFN-γ secretion in the CSF. Finally they showed that leptin increase in MS patients associated with reduced frequency of Treg cells (Matarese et al., 2005). Moreover recent evidence has shown that the adipose tissue, through leptin, has a key role in the survival of autoreactive CD4+ T cells in vivo. It has been found that leptin regulates the survival of autoantigen-specific CD4+ T cells directly through the activation of mTOR and the survival gene Bcl-2, and indirectly through a reduced secretion of cytokines important for autoreactive CD4+ T cell survival (IL-6, IL-15, IL-21, and GM-CSF) (Galgi et al., 2010). Protection of ob/ob mice from autoimmune damage is also observed in experimentally induced hepatitis (EIH), in which leptin deficiency protects against the T-cell-mediated liver damage induced by administration of concanavalin A (ConA) or Pseudomonas aeruginosa exotoxin A (Siegmund et al., 2002a; Faggioni et al., 2000). Also in this case, leptin administration restores responsiveness of ob/ob mice to ConA. Of note, the liver of ob/ob mice with EIH shows reduced production of TNF-α, IFN-γ and IL-18 (Faggioni et al., 2000). Finally, ob/ob mice are resistant to acute and chronic intestinal inflammation induced by dextran sodium sulfate and to colitis induced by trinitrobenzene sulfonic acid (experimentally induced colitis, EIC) (Siegmund et al., 2002b). In acute EIC, ob/ob mice do not develop intestinal inflammation and show decreased secretion of pro-inflammatory cytokines and chemokines (Siegmund et al., 2002b). Again, as expected, leptin replacement increases cytokine production to the same levels observed in control mice (Siegmund et al., 2002b). Of interest, recent reports have shown that leptin secreted by the gastric mucosa is not completely degraded by proteolysis and can therefore reach the intestine in an active form, where it can control the expression of sodium/glucose and peptide transporters on intestinal epithelial cells (Buyse et al., 2001, 2002). As a result, leptin might have a dual nature: on the one hand, leptin could function as a growth factor for the intestine, because of its involvement in the absorption of carbohydrates and proteins; on the other hand, leptin could function as a mediator of intestinal inflammation (Buyse et al., 2001, 2002).
More recently, protection from autoimmunity in ob/ob mice has been observed also in experimentally induced glomerulonephritis (Tarzi et al., 2004). In this immune-complex-mediated inflammatory disease induced by the injection of sheep antibodies specific for mouse glomerular basement membrane into mice pre-immunized against sheep IgG, Tarzi et al. (2004) have observed renal protection of ob/ob mice associated with reduced glomerular crescent formation and reduced macrophage infiltration. These protective effects were associated with concomitant defects of both adaptive and innate immune responses (testified by reduced in vitro proliferation of splenic T cells and reduced humoral responses to sheep IgG, respectively).

Beside experimentally-induced autoimmune diseases, leptin is also involved in spontaneous autoimmune disease such as Type 1 Diabetes (T1D) in the non-obese diabetic (NOD) mice. Leptin accelerates the disease onset and progression by stimulating autoimmune destruction of β-cells and significantly increased IFN-γ production in peripheral T-cells (Matarese et al., 2002b). A recent study has shown that a spontaneous mutation of the leptin receptor in normally type 1 diabetes-prone NOD mice suppresses T1D development in the NOD mice by inhibiting activation of T-effector cells, demonstrating the important role of leptin signaling in the disease pathogenesis (Lee et al., 2006). Finally, leptin appears to also play a role in chronic graft-versus-host disease (cGVHD) in patients who receive hematopoietic stem cell transplantation (Tauchmanova et al., 2004), in which increased serum leptin levels are associated with the development of cGVHD. In relation to the important role of leptin in autoimmunity, women are 2–3 times higher in serum leptin levels than men adjusted for age and BMI, and are predisposed to autoimmune diseases such as multiple sclerosis, RA, or systemic lupus erythematosus. Therefore, leptin might play a part in the prevalence of autoimmune conditions in females. Of note, the sex steroid hormones could be particularly implicated for the different leptin levels in males and females; indeed before puberty, plasma leptin levels are similar in boys and girls, and during puberty plasma leptin levels increase in parallel with estrogens production in girls. In rodents, after immunization, females have more vigorous T-cell and antibody responses than males, produce higher levels of Th1 cytokines (because of the presence of estrogens) than males and show consistent in vitro secretion of IFN-γ and IL-1 (Whitacre, 2001). Conversely, androgens and testosterone promote the production of IL-4 and IL-5, and a switch to protective Th2 responses (Whitacre, 2001). In this sense, leptin could add to the list of hormones, such as oestradiol and prolactin, that have long been known to have a role in favouring the predisposition of females to the development of autoimmunity (Matarese et al., 2001b). In particular, only hyperleptinemic female mice develop autoimmunity, whereas hypoleptinemic mice are protected, and treatment of EAE-resistant SJL/J males with recombinant leptin renders them susceptible to EAE (Matarese et al., 2001b). Recent clinical studies on autoimmune disease patients demonstrate that high serum leptin levels may either play a causal role in the disease progress or serve as a diagnostic marker for clinical application (Garcia-Gonzalez et al., 2002).

4. Leptin and infectious disease susceptibility

Epidemiological observations indicate an association between susceptibility to infection and malnutrition (Blackburn, 2001; Harbige, 1996). It is well established that nutritional deficiency impairs cell-mediated immunity, phagocyte function, and cytokine and antibody production (Matarese, 2000). Indeed, malnutrition is the most common cause of secondary immunodeficiency worldwide. More specifically, protein-energy malnutrition (PEM) (Cederholm et al., 1997; Soliman et al., 2000) a nutritional deficiency in which individuals suffer from protein but not caloric malnutrition, is one of the highest priority public-health concerns, affecting approximately one billion undernourished or malnourished people in the developing world (Blackburn, 2001). PEM results when the supply of energy from protein and micronutrients in the diet is insufficient to meet bodily needs. In experimental animal models, PEM selectively compromises components of the cellular immune response, such as the secretion of IFN-γ, TNF-α and nitric oxide (NO), which are all important for the control of infection with Mycobacterium tuberculosis (Chan et al., 1996). Strikingly, PEM causes a dramatic reduction of body-fat mass and decrease in the circulating concentrations of leptin, which, in turn, impairs the production of IFN-γ, TNF-α and NO (Chan et al., 1996; Fruhbeck and Gómez-Ambrosi, 2001), and increases the incidence of infectious diseases (Matarese, 2000; Ozata et al., 1999).

In this context, Mancuso and colleagues reported that leptin deficiency leads to weakened immune defense in mouse models of pneumonia. The increased susceptibility to Klebsiella pneumoniae in ob/ob mice was associated with reduced bacterial clearance and defective alveolar macrophage phagocytosis in vitro. The exogenous addition of leptin restored the defect in phagocytosis, by increasing leukotriene production (Mancuso et al., 2002). Similar results were obtained also in another study by Hsu et al., in which the authors showed that ob/ob mice exhibited enhanced lethality and reduced pulmonary bacterial clearance following Streptococcus pneumoniae challenge, due to defective polymorphonucleates (PMN) in vitro killing of S. pneumoniae. Again, exogenous leptin administration to ob/ob mice in vivo improved their survival and reconstituted H2O2 production (Hsu et al., 2007).

Other studies observed a weakened defense of leptin-deficient mice also against Mycobacterium tuberculosis; indeed their impaired immune response to pulmonary infection has been ascribed to a reduced capacity to produce IFN-γ at the site of the infection, altered lymphocyte trafficking and a disturbance in granuloma formation (Wieland et al., 2005). All this holds true also for humans, as van Crevel and colleagues have shown that leptin levels were reduced during active tuberculosis and therefore they may increase disease severity, especially in cachectic patients (van Crevel et al., 2002).
Interesting results come from studies on diet-induced obesity (DIO), which is a more physiologically relevant model of human obesity, as only a small number of individuals are obese due to mutations in the leptin gene. Leptin mRNA has been shown to be increased in obese humans relative to non-obese humans. As such, it has been suggested that obese humans may be insensitive, or ‘resistant’ to the leptin signal (Lin et al., 2000). Recent data indicate that DIO mice have a substantial reduction in NK cell cytotoxicity, associated with inability of the immune system to appropriately respond to Influenza virus infection (Smith et al., 2007), thus suggesting that obesity may lead to increased morbidity and mortality from viral infections. The authors found that leptin concentrations in lean mice transiently increased during influenza infection whereas in obese mice serum leptin decreased significantly during infection, impairing the innate immune responses. Moreover they found that obesity resulted in a notable delay in lung proinflammatory cytokine expression and a blunted induction of the antiviral cytokine response. They speculated that this may be due to impaired janus kinases/STAT signaling caused by an elevation in suppressor of cytokine signaling (SOCS) proteins in obese mice. In accordance with this finding, it has been clearly demonstrated that in obese animals, these suppressor proteins are persistently elevated (Ueki et al., 2004) and inhibit signaling by type I interferons (Dai et al., 2006; Vlotides et al., 2004). Concomitantly Karlsson et al. have also demonstrated that in male, diet-induced obese C57BL/6 mice, a secondary H1N1 influenza challenge following a primary H3N2 infection led to an increased mortality rate, lung pathology and lung viral titers, associated with a consistent reduction of the number of influenza-specific CD8+ T cells producing IFN-γ when compared to lean controls (Karlsson et al., 2010).

More recently, it has also been shown that specific polymorphisms of the leptin receptor are responsible for the high frequency of Entamoeba histolytica infection and represent one of the most common cause of death for diarrhea in the less developed world (Duggal et al., 2011).

Finally, the most common form of human obesity, characterized by hyperleptinemia causing central and peripheral leptin resistance (Friedman and Halaas, 1998), is associated with an increased frequency of infection (Dhandhar et al., 1997). In this context, leptin-receptor desensitization is perceived by T cells as a condition of leptin deficiency, leading to immune dysfunction in a similar manner to malnutrition and genetic leptin deficiency.

5. The correct balance between infection and autoimmunity susceptibility: the leptin hypothesis

During the past century, in the industrialized world, the incidence of infections has diminished greatly because of improved hygienic conditions, better nutrition, vaccination and the use of antibiotics (Matarese, 2000).

In severely malnourished patients, in which leptin levels are diminished, both acquired immunity – i.e., lymphocyte functions – as well as innate host defense mechanisms – i.e., macrophages and granulocytes – are affected. Severe protein malnutrition in newborns and small children causes atrophy of the thymus with reduced cell numbers and subsequently ill-developed peripheral lymphoid organs, i.e., lymph nodes and spleen (Savino, 2002). This causal chain leads to long-lasting immune defects characterized by leucopenia, decreased CD4 to CD8 ratio and increased numbers of CD4/CD8 double-negative T cells, and, therefore, the appearance of immature T cells in the periphery. Impaired immune functions render undernourished patients more susceptible to infections, notably those by opportunist pathogens commonly prevalent in patients with HIV/AIDS. Malnutrition causes immunosuppression through a variety of mechanisms, including the involvement of leptin and the hypothalamic–pituitary–adrenal axis. PEM reduces leptin concentrations and increases serum levels of stress hormones, i.e., glucocorticoids (Woodward, 1998). Thus, it is likely that the hypothalamic–pituitary–adrenal axis plays a critical role in malnutrition-associated immune deficiency.

Interestingly, in the more-developed societies, epidemiological studies have revealed a concomitant increase in the incidence of autoimmune diseases, whereas these diseases have become less common in the less-developed countries (Black, 2001; Fernandes, 1994; Bruining, 2000). This finding is associated with increased prevalence of obesity in more industrialized countries. Obesity in humans is correlated with high concentrations of leptin, often associated with leptin resistance. Patients with obesity present with increased TNF-α production, altered T cell subset ratios. As previously mentioned, leptin-induced production of proinflammatory cytokines by macrophages causes neutrophil activation and TH1-derived IFN-γ secretion, sustaining autoreactive cells proliferation and susceptibility to autoimmune disorders.

Thus, susceptibility to infection and autoimmunity seems to be inversely related (Fig. 1). Several factors, other than nutrition, might contribute to this relationship, such as the environment, genetic background and exposure to specific pathogens. Nevertheless, changes in diet and calorie intake and subsequently modification in serum leptin levels should be taken into account to fully understand and explain the complex network connecting nutritional status and susceptibility to autoimmune and infectious diseases. In some murine models of EAE, the induction and progression of disease can be prevented by starvation and/or reduced calorie intake, or by administering nutrients, such as polyunsaturated fatty acids, able to reduce the inflammatory response (Field et al., 2002; Berton et al., 2001; Karges et al., 1997; Harbige et al., 2000; Muthukumar et al., 2000; Piccio et al., 2008). In humans, a similar observation has been reported by Bruining (2000), who described an increased incidence of Insulin-Dependent Diabetes Mellitus (IDDM) at younger ages in affluent countries, where affluence is associated with increased postnatal growth and abundant nutrition. More specifically, children that developed diabetes had a greater gain in body-mass index (BMI) in the first year of life compared with healthy siblings and the early presence of autoantibodies specific for IA-2 (pancreatic islet tyrosine phosphatase) (Bruining, 2000). In conclusion, we can define leptin, with its pleiotropic functions, a good candidate for contributing to the pathogenesis and maintenance of autoimmunity in genetically predisposed individuals. Conversely, malnutrition and nutritional deficiency might protect individuals from autoimmunity by lowering...
categorizing leptin concentrations, but predispose to infections, such as candidiasis, tuberculosis, pneumonia, and bacterial and viral diarrhea (Matarese, 2000) (Fig. 1).

6. Role of central leptin signaling in the control of immune function

As previously mentioned, leptin has been shown to have a pivotal role in the modulation of immune function, indeed declining leptin levels might be responsible for the impaired immune response detected during starvation. However, most of these studies focused exclusively on putative peripheral effects of leptin, for example, via leptin receptors on lymphocytes or macrophages activation and/or proliferation (Gainsford et al., 1996; Lord et al., 1998; Caldefie-Chezet et al., 2001). In the past few years, emerging experimental evidence has highlighted the central role of central leptin signaling in the control of immune system, thus suggesting that the central nervous system (CNS), which is inherent to integrate information from throughout the organism, is able to directly modulate immune function (Fig. 1). Supporting this hypothesis, in a recent paper, Tanaka et al., have demonstrated that leptin signaling deficiency reduced renal macrophage infiltration in a model of unilateral ureteral obstruction (UOO) (Tanaka et al., 2010). Interestingly, central leptin administration in ob/ob mice effectively reversed this condition. Furthermore, this effect of leptin was abolished by central co-administration of a melanocortin-3 receptor (MC3R)/melanocortin-4 receptor (MC4R) antagonist. Taken together the data from this study suggest that leptin increases renal macrophage infiltration through the activation of the central melanocortin system, thereby highlighting a “central” leptin-mediated regulation of peripheral monocyte/macrophage function, in chronic inflammatory diseases (Tanaka et al., 2010). Another work by the same group has shown that the alteration of B-cell development in the bone marrow of fasted mice (characterized by decrease in pro-B, pre-B, and immature B cells and increase in mature B cells) was prevented by intracerebroventricular leptin injection, thus providing again an in vivo evidence for the role of central leptin signaling in the starvation-induced alteration of B-cell development (Tanaka et al., 2011). Finally, studies from Tschop group have shown that leptin-initiated neuroendocrine pathways are able to functionally coordinate the systemic immune response (Tschöp et al., 2010). More specifically, they observed that leptin deficiency was associated with an impaired immune response and lowered survival in a murine model of sepsis, mainly due to impaired neutrophil function. On the contrary, genetic rescue of leptin signaling exclusively and specifically within the CNS was sufficient to improve mortality and cytokine profiles in sepsis, thus suggesting that leptin-dependent neurocircuitry in the CNS is required for efficient coordination of the immune response in sepsis to limit organ damage and prevent mortality (Tschöp et al., 2010).

A CNS leptin-induced improvement of systemic immune response may be mediated by the autonomic nervous system (ANS) signaling, as suggested by studies focusing on cholinergic modulation of inflammatory pathways in sepsis (Tracey, 2007) and the known impact of CNS leptin action on peripheral metabolism via the efferent ANS. Therefore, the authors of this last study hypothesize that the amounts of peripherally administered leptin cross the blood–brain barrier, via active transport to achieve its effects on the immune system by acting in the CNS and affecting peripheral immune defense components through modulation of the ANS.

Taken together, all the observations presented here reveal the existence of a specific CNS leptin-signaling system that controls systemic immune defense in a functionally relevant manner. It is possible to speculate that leptin might act in the brain to directly regulate peripheral immune function and thereby contribute to better outcomes in different infectious diseases compared with states of relative or total leptin deficiency.

7. Concluding remarks and future directions

Since its discovery in 1994, leptin has attracted increasing interest in the scientific community for its pleiotropic functions. In immune cells, leptin acts as a proinflammatory cytokine that promotes Th1 responses on one side and inhibits Treg cell expansion on the other, setting the basis for exaggerated, immunoinflammatory responses to altered self or nonself and leading to autoimmunity in subjects with autoimmunity risk factors (i.e., genetic predisposition, HLA, environment, etc.). Future studies are needed to identify the precise relationship among leptin, metabolic state, and Treg cells in the context of autoimmune disease susceptibility. In this context, recent studies from Fontana et al. (2007) have shown that caloric restriction and consequent lowering of serum leptin are able in humans to reduce immunoinflammatory parameters (such as IL-6 and CRP) significantly, suggesting that nutritional intervention is able to dampen inflammatory responses. In view of its influence on food intake and metabolism, leptin situtates at the interface between metabolism and immunity in modulating not only inflammation but also immune and autoimmune reactivity. Recently, molecules with orexigenic activity such as ghrelin and NPY (La Cava and Matarese, 2004; Tilg and Moschen, 2006) have been shown to mediate effects opposite to leptin in the hypothalamic control of food intake and on peripheral immune responses. For example, ghrelin blocks leptin-induced secretion of proinflammatory cytokines by human T cells, and NPY ameliorates clinical score and progression of EAE (La Cava and Matarese, 2004; Tilg and Moschen, 2006). Thus, several metabolic regulators including leptin might broadly influence vital functions not only by tuning caloric balance but also by affecting immune responses.

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