Published in final edited form as:
Brain Behav Immun. 2009 May ; 23(4): 405–410. doi:10.1016/j.bbi.2008.10.007.

Three questions about leptin and immunity

Giamila Fantuzzi
Department of Kinesiology and Nutrition, University of Illinois at Chicago, Chicago, IL

Abstract

Leptin is a protein produced by adipocytes (and other cell types) that acts in the brain to regulate appetite and energy expenditure accordingly to the amount of energy stored in adipose tissue. Leptin also exerts a variety of other functions, including important roles as a regulator of immune and inflammatory reactions. The present article is not meant to be a comprehensive review on leptin and immunity, but rather highlights a few controversial issues about leptin's place in the complex network of mediators regulating immune and inflammatory responses. Three issues are discussed: 1) Where am I going, or What is the cellular target of leptin for modulation of immune responses?; 2) Where am I coming from, or Is the cellular source important in determining leptin's effects on immune responses?; and 3) What am I doing, or What are leptin's effects on immune and inflammatory responses?

Introduction

Leptin, a protein mainly secreted by adipocytes and therefore classified as an adipokine, was discovered in 1994 as the long sought-after satiety factor missing in obese *ob/ob* mice (Friedman, 2002), a strain arising from a spontaneous mutation and identified in 1950 in the Jackson Laboratories (Ingalls et al., 1950). The leptin receptor (OBR) was identified shortly thereafter and confirmed to be the gene mutated in obese diabetic *db/db* mice, a strain also arising from a spontaneous mutation at the Jackson Laboratories (Hummel et al., 1966). Obese Zucker *fa/fa* rats also have a missense mutation in OBR (Phillips et al., 1996). Further analysis revealed the existence of several isoforms of OBR (Tartaglia, 1997), which likely exert disparate physiological functions. The long form of OBR (OBRb), the only one capable of signaling through the Signal Transducer and Activator of Transcription (STAT)-3 pathway and the only isoform missing in *db/db* mice, is required for leptin's regulation of appetite, while the function of the short OBR isoforms is still under debate (Myers et al., 2008).

Leptin released from adipocytes enters the circulation and reaches appetite-regulating centers in the Central Nervous System (CNS), where it acts as a satiety factor by binding to and activating OBRb expressed on neurons. Thus, leptin relays to the brain information about the size of adipose stores, allowing for appropriate regulation of food intake and energy expenditure in concert with a series of other hormones and neurotransmitters. For a detailed review of the leptin system in the regulation of appetite see (Myers et al., 2008).

In addition to regulation of food intake, leptin also affects a variety of other physiological functions, including fertility, bone metabolism, immune responses and others. There appears to be a threshold effect for leptin, which broadly reflects the amount of energy stored in adipose

tissue: below this critical threshold – which is likely different for the various systems regulated by leptin – the body perceives a state of starvation and reduces non-essential, energy-consuming functions (Grunfeld, 2002).

The interaction between leptin and the immune system is the focus of the present article. Excellent reviews have recently discussed various aspects of leptin's effects on immune and inflammatory responses and the reader is referred to these articles for a comprehensive coverage of this topic (Lam and Lu, 2007; Matarese et al., 2007). The present review will discuss three controversial issues in the interaction between leptin and immunity, specifically: 1) the cellular target(s) of leptin in modulating immune and inflammatory responses, 2) the cellular source(s) of leptin essential for immune responses, and 3) the overall effects of leptin on immunity and inflammation.

The three questions

Where am I going, or What is the cellular target of leptin for modulation of immune responses?

Leptin exerts its appetite-regulating activities by binding to and activating OBRb expressed in various areas of the brain, including the hypothalamus - where leptin is a critical factor in the homeostatic control of food intake and energy expenditure - as well as the cortex and limbic areas - where leptin regulates cognitive and reward responses to feeding (Ahima, 2008). However, OBRb are ubiquitously expressed in the periphery; most cell types, including each type of immune cell tested to date, are able to directly respond to stimulation with exogenous leptin *in vitro* (Lam and Lu, 2007). Although evidence for a direct effect of leptin on immune cells *in vitro* is extensive and uniformly convincing, the relative role played by different tissues and cells expressing OBR *in vivo* in modulating immune and inflammatory responses has only partly been investigated.

The CNS and PNS as potential targets for leptin's modulation of immunity and inflammation—Leptin exerts control of food intake by crossing the blood brain barrier and acting in the CNS, with major effects on homeostatic control of feeding mediated by modulation of POMC and NPY/AgRP neurons (Myers et al., 2008). Neuronal expression of OBRb and activation of STAT-3 through phosphorylation of Tyr1138 in the intracellular portion of OBRb are critical in determining leptin's inhibition of appetite (Myers et al., 2008). This same central pathway also regulates some of leptin-induced peripheral effects, such as hepatic insulin resistance (Buettner et al., 2006). However, the role of these and other centrally-mediated mechanisms in leptin's modulation of immune and inflammatory responses has not been formally investigated to date using available tools such as neuron-specific OBR-deficient mice. The important role of leptin in regulating CNS inflammation in multiple sclerosis is the topic of an excellent review (Matarese et al., 2008). However, it is likely that direct stimulation of immune cells, rather than neurons, by leptin is responsible for these effects (see below).

Activation of the vagus mediates important anti-inflammatory activities, which could potentially be modulated by leptin through its effects on vagal afferents (Wang et al., 1997). Nevertheless, the role of the vagus in mediating leptin's effects on inflammatory responses remains controversial. In fact, whereas induction of IL-1β expression in the hypothalamus by leptin is not affected by subdiaphragmatic vagotomy (Hosoi et al., 2002), the anti-inflammatory effects of leptin on acetic acid-induced colitis are abrogated by perivagal administration of capsaicin (Bozkurt et al., 2003). Furthermore, the anti-inflammatory activities of vanadyl sulfate, which are partly mediated by blocking communication of between the periphery and the CNS *via* the vagus, are still observed in *db/db* mice, indicating that the presence of OBR is not necessary for this response (Johnson et al., 2005). Therefore, whether direct effects of

leptin on the CNS and PNS are important for modulation of immunity and inflammation remains to be determined.

Immune cells as a target of leptin—*In vitro*, leptin exerts direct modulating effects on activation, proliferation, maturation and production of inflammatory mediators in a variety of immune cells, including lymphocytes, NK cells, monocytes/macrophages, dendritic cells, neutrophils and eosinophils (Lam and Lu, 2007). These effects are mediated by activation of a variety of signal transduction pathways, including STAT-3, PI3K, P38 MAPK and others, by binding of leptin to OBR expressed by immune cells (Lam and Lu, 2007). Despite clear and consistent *in vitro* data, whether direct binding of leptin is essential for regulation of immunity and inflammation *in vivo* remains to be conclusively determined, as discussed below.

Both *ob/ob* and *db/db* mice, as well as malnourished mice which have very low leptin levels, are characterized by profound thymic atrophy, which mostly affects double positive ($CD4^+$ $CD8^+$) immature thymocytes, a type of cell that requires leptin as a survival, anti-apoptotic factor (Howard et al., 1999). However, it remains unclear whether lack of leptin or its receptor specifically affects subpopulations of T lymphocytes in the periphery. In fact, leptin has differential effects *in vitro* on proliferation of naive *versus* memory T cells (Lord et al., 2002) and on Tregulatory (T_{reg}) *versus* T effector (T_{eff}) cells (see below for details) (De Rosa et al., 2007). It is thus possible that leptin or OBR deficiency is associated with specific changes in peripheral T cell subpopulations. The observation that administration of leptin to aged mice improves peripheral T cell receptor diversity indicates that leptin can significantly affect the peripheral T lymphocyte compartment (Dixit et al., 2007).

Short-term administration of leptin restores thymic cellularity in *ob/ob* mice and reverses LPS-induced thymic atrophy in lean mice (Gruver and Sempowski, 2008; Hick et al., 2006). Leptin administration is also effective at enhancing thymopoiesis and increasing the number of recent thymic emigrants in aged mice (Dixit et al., 2007). However, the cellular target of leptin in restoring thymic cellularity is still unclear. Bone marrow chimera experiments have generated conflicting results. In fact, whereas one group indicated that reconstitution of *db/db* mice with WT bone marrow did not restore thymic cellularity, the opposite results were reported by different investigators (Palmer et al., 2006; Trotter-Mayo and Roberts, 2008), leaving this issue open to further analysis. Our recent unpublished bone marrow transplant data support a direct, though not complete, effect of leptin on thymocytes.

Transfer of $CD4^+CD45RB^{high}$ effector cells into immunodeficient SCID or RAG-1 KO hosts is a widely used experimental model of inflammatory bowel disease, in which recipient mice develop chronic T cell-mediated colonic inflammation (Izcue et al., 2006). The principle of this model is based on depletion of immune-suppressive T_{reg} cells from the transferred lymphocyte population. Since recipient mice are lymphocyte-deficient, the only source of T lymphocytes in these mice are the aggressive T_{eff} transferred cells, whose activity cannot be counteracted by the suppressive activity of T_{reg} lymphocytes (Izcue et al., 2006). Using this model, a direct effect of leptin on T_{eff} cells can be demonstrated. In fact, mice receiving OBRb-deficient $CD4^+CD45RB^{high}$ cells have delayed-onset colitis compared to mice receiving OBRb-competent cells (Siegmund et al., 2004a). Since in this setting leptin is able to act on each cell type except for the transferred lymphocytes, these data indicate that immune cells can be a direct target of leptin's action *in vivo*. However, the effect of leptin on epithelial, endothelial and other non-bone marrow-derived cells also likely contributes to the overall *in vivo* activity of leptin on immunity and inflammation.

Where am I coming from, or Is the cellular source important in determining leptin's effects on immune responses?

White adipocytes are quantitatively the most important source of circulating leptin in the body (Friedman, 2002). However, other tissues, including the mammary, gastric and colonic epithelia, skeletal muscle, the placenta and lymphocytes can produce leptin, which may act in an autocrine/paracrine way in the microenvironment to modulate cellular responses (Lam and Lu, 2007). For example, leptin secreted by gastric mucosa may be involved in protection against peptic ulcers, while leptin produced by colonic epithelial cells could potentially contribute to cell proliferation and activation of goblet cells (Adeyemi et al., 2005; Hardwick et al., 2001). Evidence about the role of lymphocyte-derived leptin in regulation of immunity and inflammation is discussed below.

Effect of leptin on T regulatory cells: is lymphocyte-derived leptin necessary?—That both murine and human activated T lymphocytes express leptin mRNA and have the ability to synthesize and secrete bioactive leptin has been demonstrated in several settings (De Rosa et al., 2007; Sanna et al., 2003; Siegmund et al., 2004a). Data indicate that human $CD4^+CD25^+$ T_{reg} cells produce higher levels of leptin compared with $CD4^+CD25^-$ T_{eff} cells (De Rosa et al., 2007). Ample evidence discussed above demonstrates that T lymphocytes express functional OBR and there is indication that T_{reg} cells have higher OBR expression compared to T_{eff} cells (De Rosa et al., 2007; Lam and Lu, 2007). Thus T_{reg} cells may be more sensitive than T_{eff} cells to the modulating effects of leptin, possibly through an autocrine role.

The relative role of adipocyte- *versus* lymphocyte-derived leptin in regulating immunity and inflammation has been studied both *in vitro* and *in vivo*. Neutralization of T cell-derived leptin in cultures of human lymphocytes reversed the hyporesponsiveness of T_{reg} cells to proliferative stimuli, a typical characteristic of this population, while suppressing proliferation of T_{eff} cells (De Rosa et al., 2007). Importantly, leptin-neutralized proliferating T_{reg} cells maintained their suppressive capacity towards T_{eff} cells (De Rosa et al., 2007). Thus, *in vitro* experiments point to an important autocrine/paracrine role for T lymphocyte-derived leptin in regulating proliferation of T lymphocytes and modulating the balance between T_{reg} and T_{eff} cells. However, *in vivo* data obtained using murine models seem to contradict the importance of the autocrine leptin pathway for regulation of T_{reg} function. Although increased numbers of $CD4^+CD25^+$ $FoxP3^+$ T_{reg} lymphocytes have been described in both *ob/ob* and *db/db* mice (De Rosa et al., 2007; Matarese et al., 2005; Taleb et al., 2007), cell transfer experiments questioned the necessity for lymphocyte-derived leptin in regulation of T_{reg} expansion. In fact, transfer of WT T_{reg} cells - which are able to secrete and respond to leptin in an autocrine fashion - into the leptin-deficient environment of an *ob/ob* mouse led to a dramatic expansion of the transferred WT T_{reg} population compared with a parallel transfer into a leptin-competent host (De Rosa et al., 2007). Furthermore, administration of exogenous leptin to *ob/ob* mice that had received WT T_{reg} cells inhibited proliferation of the transferred population (De Rosa et al., 2007). These data indicate that lymphocyte-derived leptin is not sufficient to fully modulate T_{reg} cell proliferation *in vivo* in mice, suggesting that adipocyte-derived leptin might play an important role in this setting. Finally, the role of leptin (regardless of its cellular source) in regulating proliferation *versus* suppressive activity of T_{reg} cells *in vivo* remains contradictory, with one report indicating a selective role of leptin in modulating T_{reg} proliferative capacity (De Rosa et al., 2007), while others demonstrate no effect on proliferation (Matarese et al., 2005; Taleb et al., 2007), with instead a major outcome in terms of suppressive ability towards T_{eff} cells (Taleb et al., 2007).

Effect of leptin on T effector cells: is adipocyte-derived leptin sufficient?—Outside the realm of T_{reg} function, comparison of the ability of transferred WT *versus* leptin-deficient $CD4^+CD45RB^{high}$ effector cells in inducing colitis in SCID mice indicated no

significant role for T lymphocyte-derived leptin in regulating inflammatory responses (Fantuzzi et al., 2005). Comparable results were obtained using the model of ConA-induced fulminant autoimmune hepatitis (Fantuzzi et al., 2005). Complementing these data, transplantation of WT white adipose tissue into *ob/ob* mice effectively restored their ability to mount an inflammatory response in the model of dextran sulfate sodium-induced colitis (Sennello et al., 2006). These data indicate that adipocyte-derived leptin, which is the only source of leptin in *ob/ob* mice transplanted with WT adipose tissue, is sufficient to completely restore inflammatory responses as well as to reverse thymic atrophy in these mice (Sennello et al., 2006). In conclusion, although lymphocyte-derived leptin may contribute to modulation of the lymphoid microenvironment, adipocyte-derived leptin is likely sufficient to modulate immune and inflammatory responses.

What am I doing, or What are leptin's effects on immune and inflammatory responses?

The role of leptin as a modulator of immune and inflammatory responses has been investigated in several experimental models of autoimmunity and inflammation, with results that sometimes appear contradictory. Although *in vitro* data on the effect of leptin in modulating activation and function of rodent and human immune cells are consistent (Lam and Lu, 2007), *in vivo* data are less clear-cut, in part as a result of the experimental models used. In fact, most of the investigations have been performed using *ob/ob* and *db/db* mice or *fa/fa* rats, which have profound metabolic abnormalities associated with congenital deficiency of leptin or its receptor. Interpretation of these results presents several challenges, since it is almost impossible to dissociate the direct effects of leptin or OBR deficiency from those of obesity, diabetes, hepatic steatosis and the other alterations present in these animals. Administration of leptin to *ob/ob* mice using schedules aimed at minimizing its weight-reducing effects has been a commonly used strategy to try to circumvent these issues. However, even short-term administration of leptin profoundly alters the metabolism of *ob/ob* mice and therefore does not represent an optimal solution. The use of tissue-specific or inducible leptin or OBR deficient models, which has already been applied to the study of leptin's effects on metabolic responses (Cohen et al., 2001; Guo et al., 2007), will likely help overcome the above-mentioned problems.

In humans, the role of leptin in modulating the immune system *in vivo* mostly derives from evidence gathered from the extremely rare conditions of massive obesity associated with leptin or OBR deficiency, in which reduced lymphocyte proliferation and cytokine production has been observed (Farooqi et al., 2002; Farooqi et al., 2007). Studies aimed at evaluating the effect of leptin on immunity through modulation of leptin levels by short-term fasting and administration of exogenous leptin have generated less conclusive results, possibly due to the difficulty in reducing leptin below a critical threshold level (Chan et al., 2006). Although not discussed in this review, leptin's effects in regulation of immune responses likely have consequences on susceptibility to infections, both in experimental animals and humans (Lam and Lu, 2007). Children with leptin or OBR mutations appear to be more sensitive to infections, although the extreme rarity of these mutations only allows for circumstantial evidence (Farooqi et al., 2002; Farooqi et al., 2007). Low leptin is also likely involved in the immunosuppression of malnutrition and starvation (Schaible and Kaufmann, 2007).

This section will discuss two open issues on the role of leptin as a modulator of immunity, inflammation and sickness behavior.

Does leptin mediate the anorexia of inflammation?—Anorexia is one of the components of sickness behavior that accompanies inflammatory responses (Konsman et al., 2002). One of the questions investigated shortly after the discovery of leptin and its effect on appetite was the potential involvement of this adipokine in mediating the anorexia of infection and inflammation. In fact, early reports indicated that administration of inflammatory stimuli

to rodents or humans acutely increased leptin gene expression in adipose tissue, resulting in elevated circulating leptin levels (Anderson et al., 2007; Grunfeld et al., 1996). It was thus tempting to speculate that increased leptin levels would act in the hypothalamus to induce the typical anorectic responses of inflammatory diseases. However, different experimental models generated conflicting results. Thus, experiments in which LPS was administered to *ob/ob* mice demonstrated a profound susceptibility of these animals to the anorectic effects of inflammation, even more pronounced than what observed in their lean littermates (Faggioni et al., 1997). In contrast, *db/db* mice developed less severe anorexia compared to their lean controls (Faggioni et al., 1997), while LPS-induced anorexia in *fa/fa* rats was not dramatically different compared to lean rats (Lugarini et al., 2005). Interestingly, aspects of sickness behavior other than anorexia, such as reduced social exploration after administration of LPS, IL-1β or exposure to hypoxic conditions, were exacerbated in *db/db* mice, suggesting a differential involvemt of leptin in regulation of various aspects of the sickness response (Johnson et al., 2007; O'Connor et al., 2005). In lean mice and rats, neutralization of leptin's bioactivity reversed LPS-induced anorexia (Harden et al., 2006; Sachot et al., 2004). In humans, leptin may be involved in mediating anorexia and cachexia in chronic kidney disease, in which elevated circulating leptin levels have been reported (Mak and Cheung, 2007). More controversial remains the link between leptin and the anorexia of cancer, since cancer patients do not consistently show elevated leptin levels, and actually often have low serum leptin (Sato et al., 2002). In conclusion, leptin may participate in the network of mediators involved in the anorectic response to inflammation, but it most likely acts in concert with various cytokines and other factors.

What is the effect of leptin on inflammation?—The role of leptin in mediating inflammation and tissue damage has been investigated in a variety of experimental models of acute and chronic inflammation as well as autoimmunity. The results indicate a complex role for this molecule and an even more complex interrelation between the direct effects of leptin and those associated with its deficiency, such as obesity and diabetes.

Initial observations that leptin favors a Th1 pattern of cytokine responses (Lord et al., 1998) lead to the hypothesis that leptin deficiency or reduced leptin levels would be protective in models of autoimmune diseases in which Th1 responses play a major role, such as experimental allergic encephalomyelitis (EAE) – a model for multiple sclerosis – and collagen-induced arthritis (CIA) – a model for rheumatoid arthritis. This indeed turned out to be the case, with *ob/ob* and *db/db* mice showing protection from inflammation and tissue damage in both models (Lam and Lu, 2007; Matarese et al., 2008). Calorie restriction, with associated reduction in serum leptin levels, was also associated with reduced severity in the EAE model, thus confirming the results obtained using leptin- or OBR-deficient mice (Piccio et al., 2008). The important and complex role of leptin in modulating inflammation in patients with multiple sclerosis is discussed in (Matarese et al., 2008). The selective effect of leptin on Th1-mediated conditions was later challenged by the observation that supplementation of lean mice with leptin increased responses to an ovalbumin challenge, a prototypical Th2-mediated model (Shore et al., 2005). Each of the three models mentioned above is mediated by T lymphocytes and requires separate sensitization and challenge steps for disease to develop. Leptin, with its ability to influence both dendritic cell and lymphocyte function (Lam and Lu, 2007) can potentially modulate disease severity at both levels. Leptin- and OBR-deficient mice were also protected from fulminant hepatitis induced by administration of Concanavalin A, a T lymphocyte-mediated model in which pre-sensitization is not necessary (Siegmund et al., 2002a). Thus, leptin appears to favor inflammation in models in which pathology is mediated by T lymphocytes. Interestingly, non-genetically-induced obesity, which is associated with increased leptin levels, does not appear to increase severity in these models (Piccio et al., 2008; Siegmund et al., 2002a), possibly due to development of leptin resistance in obese mice (Myers et al., 2008). Leptin resistance is a condition in which high levels of leptin secondary

to obesity are associated with alterations in leptin signaling, likely due to increased expression of suppressor of cytokine synthesis (SOCS)-3, an inhibitor of STAT-3 signaling (Myers et al., 2008). Recent evidence indicates that chronic activation of the pro-inflammatory transcription factor NFκB leads to overexpression of SOCS-3 and, consequently, to development of leptin resistance in states of overnutrition (Zhang et al., 2008).

In contrast with the above-mentioned lymphocyte-mediated models, leptin deficiency is generally associated with a more severe outcome in pathologies induced by activation of the innate immune system. These models include, among others, administration of LPS, zymosan, IL-1β or TNFα, exposure to ozone to induce airway inflammation as well as induction of acute pancreatitis (Faggioni et al., 1999; Pini et al., 2008; Rivera-Sanchez et al., 2004; Sennello et al., 2008; Zyromski et al., 2008). Furthermore, in contrast with lymphocyte-mediated conditions, diet-induced obesity increases disease severity in this second group of models, at least where this has been tested. Therefore, whereas leptin appears to be play a direct role in promoting inflammation in experimental models mediated by T lymphocytes, leptin deficiency increases disease severity in innate immunity-mediated models, possibly secondary to obesity. However, exceptions to this apparent lymphocyte *versus* innate immunity dichotomy have been reported: for example, *ob/ob* mice are protected from colitis induced by administration of dextran sulfate sodium - a model mediated by activation of innate immunity (Siegmund et al., 2002b) -, but they are susceptible to colitis induced by IL-10 deficiency, a condition dependent on $CD4^+$ T lymphocytes (Siegmund et al., 2004b). Therefore, the role of leptin in modulating inflammation and autoimmunity appears to be highly context-dependent and may be influenced by the network of cells and mediators involved in the specific pathological response.

Conclusions

The evidence presented in this article indicates that leptin is an important factor in modulating immune and inflammatory reactions, both in humans and experimental animals. However, several issues, including those discussed above, need to be clarified in order to obtain a better understanding of the mechanisms through which leptin participates in the complex network of immune and inflammatory mediators.

References

Adeyemi EO, Bastaki SA, Chandranath IS, Hasan MY, Fahim M, Adem A. Mechanisms of action of leptin in preventing gastric ulcer. World J Gastroenterol 2005;11:4154–4160. [PubMed: 16015682]

Ahima RS. Revisiting leptin's role in obesity and weight loss. J Clin Invest 2008;118:2380–2383. [PubMed: 18568083]

Anderson PD, Mehta NN, Wolfe ML, Hinkle CC, Pruscino L, Comiskey LL, Tabita-Martinez J, Sellers KF, Rickels MR, Ahima RS, Reilly MP. Innate immunity modulates adipokines in humans. J Clin Endocrinol Metab 2007;92:2272–2279. [PubMed: 17374708]

Bozkurt A, Cakir B, Ercan F, Yeğen BC. Anti-inflammatory effects of leptin and cholecystokinin on acetic acid-induced colitis in rats: role of capsaicin-sensitive vagal afferent fibers. Regul Pept 2003;116:109–118. [PubMed: 14599722]

Buettner C, Pocai A, Muse ED, Etgen AM, Myers MGJ, Rossetti L. Critical role of STAT3 in leptin's metabolic actions. Cell Metab 2006;4:49–60. [PubMed: 16814732]

Chan JL, Matarese G, Shetty GK, Raciti P, Kelesidis I, Aufiero D, De Rosa V, Perna F, Fontana S, Mantzoros CS. Differential regulation of metabolic, neuroendocrine, and immune function by leptin in humans. Proc Nat Acad Sci USA 2006;103:8481–8486. [PubMed: 16714386]

Cohen P, Zhao C, Cai X, Montez JM, Rohani SC, Feinstein P, Mombaerts P, Friedman JM. Selective deletion of leptin receptor in neurons leads to obesity. J Clin Invest 2001;108:1113–1121. [PubMed: 11602618]

De Rosa V, Procaccini C, Cali' G, Pirozzi G, Fontana S, Zappacosta S, La Cava A, Matarese G. A key role of leptin in the control of regulatory T cell proliferation. Immunity 2007;26:241–255. [PubMed: 17307705]

Dixit VD, Yang H, Sun Y, Weeraratna AT, Youm YH, Smith RG, Taub DD. Ghrelin promotes thymopoiesis during aging. J Clin Invest 2007;117:2778–2790. [PubMed: 17823656]

Faggioni R, Fantuzzi G, Gabay C, Moser A, Dinarello CA, Feingold KR, Grunfeld C. Leptin deficiency enhances sensitivity to endotoxin-induced lethality. Am J Physiol 1999;276:R136–R142. [PubMed: 9887187]

Faggioni R, Fuller J, Moser A, Feingold KR, Grunfeld C. LPS-induced anorexia in leptin deficient (*ob/ob*) and leptin receptor deficient (*db/db*) mice. Am J Physiol 1997;273:R181–R186. [PubMed: 9249548]

Fantuzzi G, Sennello JA, Batra A, Fedke I, Lehr AH, Zeitz M, Siegmund B. Defining the role of T cell-derived leptin in the modulation of hepatic or intestinal inflammation in mice. Clin Exp Immunol 2005;142:31–38. [PubMed: 16178853]

Farooqi IS, Matarese G, Lord GM, Keogh JM, Lawrence E, Agwu C, Sanna V, Jebb SA, Perna F, Fontana S, Lechler RI, DePaoli AM, O'Rahilly S. Beneficial effects of leptin on obesity, T cell hyporesponsivenss and neuroendorcine/metabolic dysfunction of human congenital leptin deficiency. J Clin Invest 2002;110:1093–1103. [PubMed: 12393845]

Farooqi IS, Wangensteen T, Collins S, Kimber W, Matarese G, Keogh JM, Lank E, Bottomley B, Lopez-Fernandez J, Ferraz-Amaro I, Dattani MT, Ercan O, Myhre AG, Retterstol L, Stanhope R, Edge JA, McKenzie S, Lessan N, Ghodsi M, De Rosa V, Perna F, Fontana S, Barroso I, Undlien DE, O'Rahilly S. Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. N Engl J Med 2007;356:237–247. [PubMed: 17229951]

Friedman JM. The function of leptin in nutrition, weight, and physiology. Nutr Rev 2002;60:S1–S14. [PubMed: 12403078]

Grunfeld C. Leptin and the immunosuppression of malnutrition. J Clin Endocrinol Metab 2002;87

Grunfeld C, Zhao C, Fuller J, Pollock A, Moser A, Friedman J, Feingold KR. Endotoxin and cytokines induce expression of leptin, the *ob* gene product, in hamsters. A role for leptin in the anorexia of infection. J Clin Invest 1996;97:2152–2157. [PubMed: 8621806]

Gruver AL, Sempowski GD. Cytokines, leptin, and stress-induced thymic atrophy. J Leukoc Biol 2008;84:915–923. [PubMed: 18495786]

Guo K, McMinn JE, Ludwig T, Yu YH, Yang G, Chen L, Loh D, Li C, Chua SJ, Zhang Y. Disruption of peripheral leptin signaling in mice results in hyperleptinemia without associated metabolic abnormalities. Endocrinology 2007;148:3987–3997. [PubMed: 17495001]

Harden LM, du Plessis I, Poole S, Laburn HP. Interleukin-6 and leptin mediate lipopolysaccharide-induced fever and sickness behavior. Physiol Behav 2006;89

Hardwick JC, Van Den Brink GR, Offerhaus GJ, Van Deventer SJ, Peppelenbosch MP. Leptin is a growth factor for colonic epithelial cells. Gastroenterology 2001;121:79–90. [PubMed: 11438496]

Hick RW, Gruver AL, Ventevogel MS, Haynes BF, Sempowski GD. Leptin selectively augments thymopoiesis in leptin deficiency and lipopolysaccharide-induced thymic atrophy. J Immunol 2006;177:169–176. [PubMed: 16785512]

Hosoi T, Okuma Y, Ono A, Nomura Y. Subdiaphragmatic vagotomy fails to inhibit intravenous leptin-induced IL-1beta expression in the hypothalamus. Am J Physiol Regul Integr Comp Physiol 2002;282:R627–631. [PubMed: 11792675]

Howard JK, Lord GM, Matarese G, Vendetti S, Ghatei MA, Ritter MA, Lechler RI, Bloom SR. Leptin protects mice from starvation-induced lymphoid atrophy and increases thymic cellularity in *ob/ob* mice. J Clin Invest 1999;104:1051–1059. [PubMed: 10525043]

Hummel KP, Dickie MM, Coleman DL. Diabetes, a new mutation in the mouse. Science 1966;153:1127–1128. [PubMed: 5918576]

Ingalls AM, Dickie MM, Snell GD. Obese, a new mutation in the house mouse. J Hered 1950;41:317–318. [PubMed: 14824537]

Izcue A, Coombes JL, Powrie F. Regulatory T cells suppress systemic and mucosal immune activation to control intestinal inflammation. Immunol Rev 2006;212:256–271. [PubMed: 16903919]

Johnson DR, O'Connor JC, Dantzer R, Freund GG. Inhibition of vagally mediated immune-to-brain signaling by vanadyl sulfate speeds recovery from sickness. Proc Natl Acad Sci U S A 2005;102:15184–15189. [PubMed: 16217019]

Johnson DR, O'Connor JC, Hartman ME, Tapping RI, Freund GG. Acute hypoxia activates the neuroimmune system, which diabetes exacerbates. J Neurosci 2007;27:1161–1166. [PubMed: 17267571]

Konsman JP, Parnet P, Dantzer R. Cytokine-induced sickness behaviour: mechanisms and implications. Trends Neurosci 2002;25:154–159. [PubMed: 11852148]

Lam QL, Lu L. Role of leptin in immunity. Cell Mol Immunol 2007;4:1–13. [PubMed: 17349207]

Lord GM, Matarese G, Howard JK, Baker RJ, Bloom SR, Lechler RI. Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. Nature 1998;394:897–901. [PubMed: 9732873]

Lord GM, Matarese G, Howard JK, Bloom SR, Lechler RI. Leptin inhibits the anti-CD3-driven proliferation of peripheral blood T cells but enhances the production of proinflammatory cytokines. J Leukoc Biol 2002;72:330–338. [PubMed: 12149424]

Lugarini F, Hrupka BJ, Schwartz GJ, Plata-Salaman CR, Langhans W. Acute and chronic administration of immunomodulators induces anorexia in Zucker rats. Physiol Behav 2005;84:165–173. [PubMed: 15642620]

Mak RH, Cheung W. Cachexia in chronic kidney disease: role of inflammation and neuropeptide signaling. Curr Opin Nephrol Hypertens 2007;16:27–31. [PubMed: 17143068]

Matarese G, Carrieri PB, La Cava A, Perna F, Sanna V, De Rosa V, Aufiero D, Fontana S, Zappacosta S. Leptin increase in multiple sclerosis associates with reduced number of CD4(+)CD25+ regulatory T cells. Proc Natl Acad Sci U S A 2005;102:5150–5155. [PubMed: 15788534]

Matarese G, Leiter EH, La Cava A. Leptin in autoimmunity: many questions, some answers. Tissue Antigens 2007;70:87–95. [PubMed: 17610413]

Matarese G, Procaccini C, De Rosa V. The intricate interface between immune and metabolic regulation: a role for leptin in the pathogenesis of multiple sclerosis. J Leukoc Biol 2008;84

Myers MG, Cowley MA, Münzberg H. Mechanisms of leptin action and leptin resistance. Annu Rev Physiol 2008;70:537–556. [PubMed: 17937601]

O'Connor JC, Satpathy A, Hartman ME, Horvath EM, Kelley KW, Dantzer R, Johnson RW, Freund GG. IL-1beta-mediated innate immunity is amplified in the db/db mouse model of type 2 diabetes. J Immunol 2005;174:4991–4997. [PubMed: 15814729]

Palmer G, Aurrand-Lions M, Contassot E, Talabot-Ayer D, Ducrest-Gay D, Vesin C, Chobaz-Péclat V, Busso N, Gabay C. Indirect effects of leptin receptor deficiency on lymphocyte populations and immune response in db/db mice. J Immunol 2006;177:2899–2907. [PubMed: 16920925]

Phillips MS, Liu Q, Hammond HA, Dugan V, Hey PJ, Caskey CJ, Hess JF. Leptin receptor missense mutation in the fatty Zucker rat. Nat Genet 1996;13:18–19. [PubMed: 8673096]

Piccio L, Stark JL, Cross AH. Chronic calorie restriction attenuates experimental autoimmune encephalomyelitis. J Leukoc Biol. 2008In press

Pini M, Gove ME, Sennello JA, van Baal JW, Chan L, Fantuzzi G. Role and regulation of adipokines during zymosan-induced peritoneal inflammation in mice. Endocrinology 2008;149:4080–4085. [PubMed: 18450950]

Rivera-Sanchez YM, Johnston RA, Schwartzman IN, Valone J, Silverman ES, Fredberg JJ, Shore SA. Differential effects of ozone on airway and tissue mechanics in obese mice. J Appl Physiol 2004;96:2200–2206. [PubMed: 14966019]

Sachot C, Poole S, Luheshi GN. Circulating leptin mediates lipopolysaccharide-induced anorexia and fever in rats. J Physiol 2004;561:263–272. [PubMed: 15388782]

Sanna V, Di Giacomo A, La Cava A, Lechler RI, Fontana S, Zappacosta S, Matarese G. Leptin surge precedes onset of autoimmune encephalomyelitis and correlates with development of pathogenic T cell responses. J Clin Invest 2003;111:241–250. [PubMed: 12531880]

Sato T, Meguid MM, Miyata G, Chen C, Hatakeyama K. Does leptin really influence cancer anorexia? Nutrition 2002;18:82–83. [PubMed: 11827771]

Schaible UE, Kaufmann SH. Malnutrition and infection: complex mechanisms and global impacts. PLoS Med 2007;4:e115. [PubMed: 17472433]

Sennello JA, Fayad R, Pini M, Gove ME, Fantuzzi G. Transplantation of wild-type white adipose tissue normalizes metabolic, immune and inflammatory alterations in leptin-deficient ob/ob mice. Cytokine 2006;36:261–266. [PubMed: 17368040]

Sennello JA, Fayad R, Pini M, Gove ME, Ponemone V, Cabay RJ, Siegmund B, Dinarello CA, Fantuzzi G. Interleukin-18 together with interleukin-12 induces severe acute pancreatitis in obese but not in non-obese leptin-deficient mice. Proc Natl Acad Sci USA. 2008In press

Shore SA, Schwartzman IN, Mellema MS, Flynt L, Imrich A, Johnston RA. Effect of leptin on allergic airway responses in mice. J Allergy Clin Immunol 2005;115:103–109. [PubMed: 15637554]

Siegmund B, Lear-Kaul KC, Faggioni R, Fantuzzi G. Leptin deficiency, not obesity, protects mice from ConA-induced hepatitis. Eur J Immunol 2002a;32:552–560. [PubMed: 11828372]

Siegmund B, Lehr HA, Fantuzzi G. Leptin: a pivotal mediator of intestinal inflammation in mice. Gastroenterology 2002b;122:2011–2025. [PubMed: 12055606]

Siegmund B, Sennello JA, Jones-Carson J, Gamboni-Robertson F, Lehr HA, Batra A, Fedke I, Zeitz M, Fantuzzi G. Leptin receptor expression on T lymphocytes modulates chronic intestinal inflammation in mice. Gut 2004a;53:965–969. [PubMed: 15194645]

Siegmund B, Sennello JA, Lehr HA, Batra A, Fedke I, Zeitz M, Fantuzzi G. Development of intestinal inflammation in double IL-10- and leptin-deficient mice. J Leukoc Biol 2004b;76:782–786. [PubMed: 15240754]

Taleb S, Herbin O, Ait-Oufella H, Verreth W, Gourdy P, Barateau V, Merval R, Esposito B, Clement K, Holvoet P, Tedgui A, Mallat Z. Defective leptin/leptin receptor signaling improves regulatory T cell immune responses and protects mice from atherosclerosis. Arterioscler Thromb Vasc Biol 2007;27:2691–2698. [PubMed: 17690315]

Tartaglia LA. The leptin receptor. J Biol Chem 1997;272:6093–6096. [PubMed: 9102398]

Trotter-Mayo RN, Roberts MR. Leptin Acts in the Periphery to Protect Thymocytes from Glucocorticoid-mediated Apoptosis in the Absence of Weight Loss. Endocrinology. 2008In press

Wang YH, Taché Y, Sheibel AB, Go VLW, Wei JY. Two types of leptin-responsive gastric vagal afferent terminals: an in vitro single-unit study in rats. Am J Physiol Regulatory Integrative Comp Physiol 1997;273:R833–R837.

Zhang X, Zhang G, Zhang H, Karin M, Bai H, Cai D. Hypothalamic IKKbeta/NFkappaB and ER stress link overnutrition to energy imbalance and obesity. Cell 2008;135:61–73. [PubMed: 18854155]

Zyromski NJ, Mathur A, Pitt HA, Lu D, Gripe JT, Walker JJ, Yancey K, Wade TE, Swartz-Basile DA. A murine model of obesity implicates the adipokine milieu in the pathogenesis of severe acute pancreatitis. Am J Physiol Gastrointest Liver Physiol. 2008In press

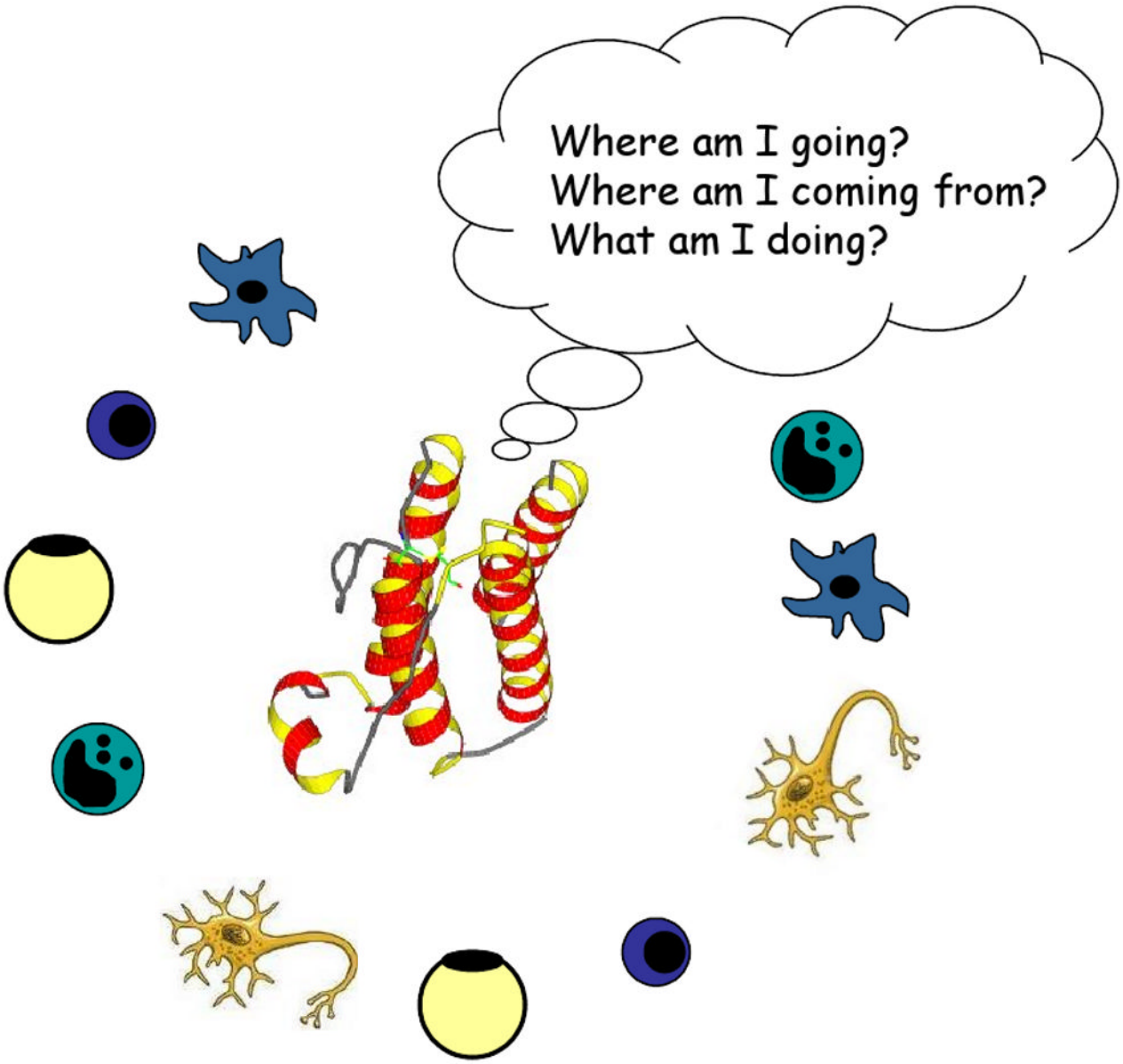

Figure.

Leptin, produced by adipocytes but also by other cell types, exerts a variety of complex modulating effects on the immune system. Immune cells, neurons and other cell types express functional leptin receptors and are therefore potential targets of leptin's effects. Despite clear *in vitro* evidence of direct activities of leptin of immune cells, *in vivo* data are more controversial. In this article, leptin asks three fundamental questions about its own origin, destination and function.