Review

The role of leptin in innate and adaptive immune responses

Eiva Bernotiene[1], Gaby Palmer[2,3] and Cem Gabay[2,3]

[1]Department of Experimental Research, Institute of Experimental and Clinical Medicine, Vilnius University, Vilnius, Lithuania
[2]Division of Rheumatology, Department of Internal Medicine, University Hospital, Geneva, Switzerland
[3]Department of Pathology and Immunology, University of Geneva School of Medicine, Geneva, Switzerland

Corresponding author: Cem Gabay, Cem.Gabay@hcuge.ch

Published: 28 July 2006
This article is online at http://arthritis-research.com/content/8/5/217

Arthritis Research & Therapy 2006, **8:**217 (doi:10.1186/ar2004)

Abstract

Leptin is produced primarily by adipocytes and functions in a feedback loop regulating body weight. Leptin deficiency results in severe obesity and a variety of endocrine abnormalities in animals and humans. Several studies indicated that leptin plays an important role in immune responses. It exerts protective anti-inflammatory effects in models of acute inflammation and during activation of innate immune responses. In contrast, leptin stimulates T lymphocyte responses, thus having rather a proinflammatory role in experimental models of autoimmune diseases. Clinical studies have so far yielded inconsistent results, suggesting a rather complex role for leptin in immune-mediated inflammatory conditions in humans.

Introduction

Leptin is a 16 kDa peptide hormone with the tertiary structure of a cytokine that is highly conserved among mammalian species [1]. It is structurally and functionally related to the IL-6 cytokine family. Leptin functions as a signal in a feedback loop regulating food intake and body weight [2]. The leptin receptor Ob-R (or Lepr), is a member of the class I cytokine receptor family, which includes gp-130, the common signal transducing receptor for the IL-6 related family of cytokines [3]. Alternative splicing of the leptin receptor gene produces at least six transcripts designated Ob-Ra through Ob-Rf (Figure 1) [4]. Two of the isoforms have been described in only one species each, Ob-Rd in mice and Ob-Rf in rats [5]. In humans, only expression of Ob-Ra, Ob-Rb and Ob-Rc mRNA has been reported [5]. Ob-Re is a secreted isoform of the receptor, lacking transmembrane and cytoplasmic domains. In humans, transcripts corresponding to Ob-Re have not been described, but soluble leptin receptor protein can be generated by proteolytic cleavage of the Ob-Rb and Ob-Ra isoforms [6].

Ob-Rb is abundantly expressed in the hypothalamus, an area in the brain involved in the control of food intake. The anorexigenic effect of leptin is dependent on binding to the long form of its receptor, Ob-Rb [7]. Both leptin-deficient (*ob/ob*) and leptin receptor (Ob-Rb)-deficient (*db/db*) mice display a severe hereditary obesity phenotype, characterized by increased food intake and body weight, associated with decreased energy expenditure [8]. Administration of leptin reverses the obese phenotype in *ob/ob* mice, but not in *db/db* mice, and decreases food intake in normal mice. Lack of response to leptin is also well described in obese Zucker rats, which bear a mutation (fa) in the leptin receptor gene [9]. Mutations in leptin and Ob-R genes associated with obesity have also been described in humans [10,11]. Leptin is produced predominantly by adipocytes, although low levels have been detected in the hypothalamus, pituitary [12], stomach [13], skeletal muscle [14], mammary epithelia [15], chondrocytes [16] and a variety of other tissues [17]. Plasma leptin concentrations correlate with the amount of fat tissue and, thus, obese individuals produce higher levels of leptin than do lean ones [18]. The correlation between serum leptin concentrations and the percentage of body fat suggests that most obese people are insensitive to endogenously produced leptin [18].

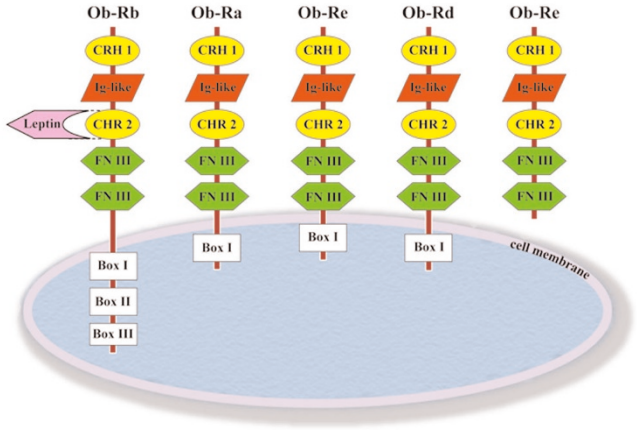
In addition to the regulation of appetite and energy expenditure, leptin exhibits a variety of other effects [19-22]. Consistently, *ob/ob* and *db/db* mice are not only severely obese, but display also several hormonal imbalances, abnormalities in thermoregulation, increased bone mass, infertility, and evidence of immune and hematopoietic defects [17,19, 20,22-25]. In humans, congenital leptin deficiency is associated with hypogonadotropic hypogonadism, morbid obesity and frequent deaths due to infections [11,26].

The role of leptin in immunity and inflammation

In addition to the central role of lipid storage, adipose tissue has major endocrine functions and releases a variety of pro-

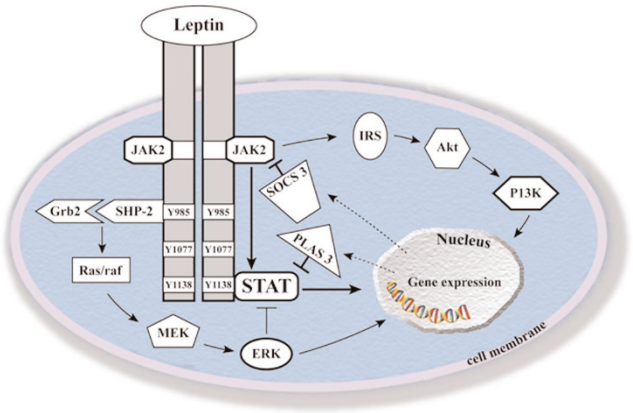
AIA = antigen-induced arthritis; BMI = body mass index; BSA = bovine serum albumin; CRP = C-reactive protein; EAE = experimental autoimmune encephalomyelitis; IFN = interferon; IL = interleukin; JAK/STAT = Janus kinase/signal transducer and activator of transcription; LPS = lipopolysaccharide; MAPK = mitogen-activated protein kinase; PI3K = phosphatidylinositol 3-kinase; PMN = polymorphonuclear leukocyte; RA = rheumatoid arthritis; SOCS = suppressor-of-cytokine signaling; Th = T helper; TNF = tumor necrosis factor.

Figure 1



Structure and isoforms of mouse leptin receptor. Ob-Rb contains the longest intracellular domain, which is crucial for leptin signaling. Ob-Ra, Ob-Rc and Ob-Rd contain only short cytoplasmic domains. Ob-Re is a secreted isoform of the leptin receptor, lacking transmembrane and cytoplasmic parts. Cytokine receptor homology module (CRH)2 is the main binding site for leptin on the Ob-R. The Ig-like and the FN-III domains are critically involved in Ob-R activation. The role of CRH1 remains to be determined [111,112]. FNIII, fibronectin type III domain; Ig-like, immunoglobulin-like fold.

Figure 2



Mechanisms of leptin signaling. Upon leptin binding to Ob-Rb, the Janus kinase/signal transducer and activator of transcription (JAK/STAT), mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) and phosphatidylinositol 3-kinase (PI3K) pathways are activated. Akt, protein kinase B; Grb-2, growth receptor-bound-2; IRS, insulin receptor substrate; MEK, mitogen-activated protein kinase kinase; PIAS 3, protein inhibitor of activated STAT3; Raf, MEK-kinase; Ras, G-protein; SHP-2, SH2-domain containing protein tyrosine phosphatase; SOCS3, suppressor of cytokine signalling-3.

inflammatory and anti-inflammatory factors, including adipocytokines, such as leptin, adiponectin and resistin, as well as cytokines and chemokines. Altered levels of different adipocytokines have been observed in a variety of inflammatory conditions (reviewed in [27]) and, in particular, the role of leptin in immune responses and inflammation has lately become increasingly evident. Altered leptin production during infection and inflammation strongly suggests that leptin is a part of the cytokine cascade, which orchestrates the innate immune response and host defense mechanisms [28,29]. Like other members of the IL-6 family, leptin was shown to activate the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway (Figure 2) [3]. Leptin also induces the expression of the suppressor-of-cytokine signaling (SOCS)-3, which inhibits STAT signaling [30]. In addition, stimulation of leptin receptor triggers activation of phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) [31]. Activation of these pathways is also characteristic for the signaling of other cytokines belonging to the IL-6 family [32]. Physiological levels of leptin can modulate the response to an inflammatory challenge by altering production of proinflammatory and anti-inflammatory cytokines and may also affect cytokine signaling by a variety of mechanisms, including induction of SOCS-3 [33].

In vitro studies revealed that Ob-Rb is expressed in T and B cells, macrophages and hematopoietic cells and direct effects of leptin on those cells have been demonstrated [34-41]. Moreover, activated T cells themselves have been shown to express and secrete leptin, which sustained their proliferation in an autocrine loop [42]. However, a recent study indicated that T cell-derived leptin does not play a major role in the regulation of the inflammatory process in experimental models of hepatitis and colitis in mice, emphasizing the critical role of adipose tissue-derived leptin in immune modulation [43].

Regulation of leptin production during inflammatory conditions

Some studies report increased levels of leptin during infectious and inflammatory processes. Leptin expression in adipose tissue and circulating leptin levels are increased after administration of inflammatory stimuli such as lipopolysaccharide (LPS) or turpentine to hamsters [44,45]. Endotoxin has also been shown to stimulate the release of leptin into peripheral blood in human and nonhuman primates [46]. LPS, as well as proinflammatory mediators such as tumor necrosis factor (TNF)-α and IL-1, increase the expression of leptin mRNA in adipose tissue [45] and a statistically significant elevation of plasma leptin concentrations has been demonstrated in adult septic patients compared with healthy subjects [47-50]. However, other studies have not found increased leptin levels in inflammatory conditions, including acute experimental endotoxemia in humans, HIV infection and newborn sepsis [51-53]. Moreover, in tuberculosis patients, plasma leptin concentrations were significantly reduced [54]. Similarly, decreased circulating levels of leptin were observed in mice following intravenous injection of *Staphylococcus*

Table 1

Effects of leptin or leptin receptor deficiency and leptin administration in experimental models of innate immune response in rodents

Model	WT mice/rats	*ob/ob* mice	Ob-R-deficient mice/rats	Leptin administration	References
LPS-induced lethality	Fasted mice: ↑ Susceptibility ↑ TNF-α ↓ Interferon-γ	↑ Susceptibility ↓ IL-10 ↓ IL-1Ra		Fasted WT mice: effect reversed *ob/ob* mice: effect partly reversed	[57]
LPS ip		↓ TNF-α ↓ IL-6	*fa/fa* rats: ↓ TNF-α ↓ IL-6		[64]
LPS-induced hepatotoxicity		↑ Sensitivity ↓ Hepatic CD4+NK T cells ↑ Serum IL-18 ↑ Hepatic IL-18 and IL-12 ↓ Hepatic IL-10 ↑ IFN-γ	*fa/fa* rats: ↑ Sensitivity ↑ IFN-γ mRNA ↓ IL-12 mRNA		[60]
TNF-α-induced lethality	Fasted mice: ↑ Susceptibility Leptin antagonist: ↑ Susceptibility	↑ Susceptibility	↑ Susceptibility	Fasted WT mice: effect not reversed Leptin antagonist: effect partly reversed *ob/ob* mice: effect reversed	[58]
Pancreatitis				WT rats: protective effects ↑ IL-4 ↓ TNF-α and IL-1β	[62]
Escherichia coli iv infusion		↓ Clearance Smaller fraction of *E. coli* killed			[64]
Klebsiella pneumoniae intratracheal challenge	↑ Leptin after infection	↑ Mortality ↑ Bacterial counts in lungs and blood			[65]
Candida albicans iv infusion			*fa/fa* rats: ↑ Yeast/g organ		[66]
Staphylococcus aureus-induced arthritis	↓ Leptin production			WT mice: ↓ Severity ↓ IL-6	[55]
Zymosan-induced arthritis		↑ Joint inflammation ↑ SAA and IL-6	↑ Joint inflammation ↑ SAA and IL-6		[90]

Up and down arrows indicate increase and decrease, respectively. ip, intraperitoneal; iv, intravenous; LPS, lipopolysaccharide; *ob/ob*, leptin deficient mice; Ob-R, leptin receptor; SAA, serum amyloid A; TNF, tumor necrosis factor; WT, wild-type.

aureus [55]. Increased leptin production is thus observed in inflammatory conditions in many, although not all, animal models and diseases examined.

Effects of leptin on innate immune responses

The increased sensitivity of leptin-deficient rodents to pro-inflammatory, monocyte/macrophage-activating stimuli, suggests a role for leptin in the regulation of inflammatory responses (Table 1) [56]. *Ob/ob*, as well as fasted wild-type mice, which display decreased leptin levels, are significantly more susceptible to LPS-induced lethality, and this phenotype was partly reversed by the administration of leptin [57,58]. Similarly, *ob/ob*, *db/db* and fasted wild-type mice are more likely to succumb after the administration of TNF-α. This phenotype was again reversed by leptin treatment in *ob/ob* and wild-type, but not in *db/db*, mice [58,59]. The protective role of leptin against TNF-α-induced toxicity was further supported by the deleterious effect of neutralizing anti-leptin antibodies administered to TNF-α-injected mice [59]. Ob-R-deficient *fa/fa* rats also displayed enhanced sensitivity to LPS-induced hepatotoxicity [60]. Dysregulation in cytokine induction after LPS stimulation may contribute to the

increased susceptibility to LPS toxicity, as demonstrated in a number of experimental studies in transgenic and gene knockout animals. Lower levels of anti-inflammatory cytokines, such as IL-10, and IL-1Ra, and higher levels of the proinflammatory cytokines IL-12, IL-18 and interferon (IFN)-γ have been detected after LPS injection in *ob/ob* mice [57,60,61]. Consistently, protective effects of leptin demonstrated in a model of experimental pancreatitis were attributed to increased IL-4 production and to reduced serum TNF-α or IL-1β [62,63]. Anti-inflammatory effects of leptin were further demonstrated by reduced TNF-α and IL-6 responses in endotoxin treated primates [33]. Taken together, these different observations are mostly consistent with the notion that leptin deficiency constitutes a proinflammatory state.

Effects of leptin on phagocytes

The role of leptin in the regulation of important macrophage functions is further emphasized by alterations in the phenotype of those cells during chronic leptin deficiency. Impaired phagocytic functions resulting in reduced bacterial elimination have been described for macrophages from leptin-deficient mice during infections with *Escherichia coli*, *Candida albicans and Klebsiella pneumoniae* (Table 1) [64-66]. In addition to modulating phagocytosis and cytokine production by macrophages, leptin has recently been shown to regulate other aspects of the innate immune response. Leptin was indeed reported to enhance oxidative species production by stimulated polymorphonuclear leukocytes (PMNs) [36], whereas another study provides evidence that leptin inhibits neutrophil migration in response to classical chemoattractants [67]. These findings, as well as an increased rate of death due to infections among leptin-deficient individuals [26], suggest that leptin contributes to host defense against microorganisms. Several recent studies demonstrated that PMNs express the short (Ob-Ra), but not the long isoform Ob-Rb. Whether Ob-Ra can deliver intracellular signals or not remains a matter of debate [67-69]. For instance, the effect of leptin on CD11b expression in neutrophils is likely to be indirect and mediated by the induction of TNF-α production by monocytes [69]. In contrast, it was reported that leptin directly activates neutrophils and delays spontaneous apoptosis of these cells by inhibiting proapoptotic events proximal to mitochondria, the effect being mediated via PI3K and p38 MAPK signaling pathways [68]. In general, leptin thus appears to increase the activity of phagocytes and may thereby contribute to efficient host defense.

Effects of leptin on adaptive immune responses

Leptin was reported to stimulate the proliferation of T cells *in vitro*, to promote T helper (Th)1 responses and to protect T cells from corticosteroid-induced apoptosis [38,39]. *Ob/ob* mice display a higher level of thymocyte apoptosis and reduced thymic cellularity compared to control mice and these effects were reversed by peripheral administration of recombinant leptin [38]. In the same study, wild-type mice treated with leptin during a 48 hour fast were completely protected against the profound thymic atrophy observed in non-treated fasted mice [38]. *Ob/ob* mice also exhibit defective cellular and humoral immune responses and are protected from immune-mediated inflammation in various models, such as experimental colitis, T-cell mediated hepatitis, glomerulonephritis and experimental autoimmune encephalomyelitis (EAE), an experimental model for multiple sclerosis (Table 2) [19,28,70-74]. Leptin replacement in *ob/ob* mice converted resistance to EAE into susceptibility and this effect was accompanied by a switch from a Th2 to a Th1 pattern of cytokine release and consequent reversal of Ig subclass production [72]. Likewise, administration of leptin to EAE susceptible mice after disease onset increased the severity of the symptoms and leptin administration accelerated type 1 diabetes development in NOD mice [73,75]. Conversely, blockade of leptin with anti-leptin antibodies or with a soluble mouse leptin receptor chimera, either before or after onset of EAE, ameliorated the clinical symptoms, inhibited antigen-specific T cell proliferation, and switched cytokine secretion toward a Th2 and T regulatory profile [76].

Starvation and malnutrition are associated with reduced leptin levels and alterations of the immune response, which can be reversed by leptin administration [39,40,77]. Acute starvation, which is able to prevent increases in serum leptin, delayed EAE onset and attenuated clinical symptoms [42]. Furthermore, in humans, leptin deficiency was associated with reduced numbers of circulating CD4+ T cells and impaired T cell proliferation and cytokine release, all of which were reversed by recombinant human leptin administration [78]. *In vitro*, leptin dose-dependently enhances proliferation and activation of human circulating T lymphocytes when they are costimulated by phytohemagglutinin or concanavalin A and modulates CD4(+) T lymphocyte activation toward a Th1 phenotype by stimulating the synthesis of IL-2 and IFN-γ [79]. Finally, human dendritic cells express leptin receptors and leptin down-regulates their IL-10 production and drives naive T cell polarization towards a Th1 phenotype [80]. In view of these different observations, leptin thus seems to display a stimulatory effect on adaptive immune responses and to favor Th1 polarization.

Taken together, the experimental data collected suggest that chronic leptin deficiency differently affects adaptive versus innate immune responses: adaptive immune-mediated responses are attenuated whereas, in experimental models involving the innate immune response, leptin deficiency causes inadequate control of the inflammatory response. As already mentioned, leptin and its receptor share some homologies with the IL-6 and IL-6 receptor families, respectively [3]. Interestingly, many similarities can be observed also in the pattern of leptin and IL-6 effects during adaptive or innate immune response-mediated inflammation. IL-6 exerts deleterious actions in many models of chronic immune

Table 2

Effects of leptin or leptin receptor deficiency and leptin administration in disease models mediated by adaptive immune responses in mice

Models	WT mice	*ob/ob* mice	*db/db* mice	Leptin injection	References
Non-obese diabetic mice	↑ Serum leptin before onset of diabetes			↑ Destruction of insulin-producing β-cells ↑ IFN-γ production by T lymphocytes	[75]
AIA		↓ Arthritis severity ↓ Anti-mBSA Abs ↓ *Ex vivo* T-cell proliferation ↓ IFN-γ and ↑ IL-10 production	↓ Arthritis severity ↓ Anti-mBSA Abs ↓ *Ex vivo* T-cell proliferation ↓ IFN-γ and ↑ IL-10 production		[35]
EAE	↑ Serum leptin before onset of EAE Serum leptin correlated with EAE susceptibility Administration of anti-leptin Abs or soluble leptin receptors: ↓ Disease severity	↓ Susceptibility		↑ Severity in SJL females SJL males: become susceptible Restored susceptibility in *ob/ob* mice associated to Th2 to Th1 switch	[42]
T-cell mediated hepatitis		Protected from liver damage ↓ TNF-α and IL-18		*ob/ob* mice: restored susceptibility	[70,110]
Colitis		↓ Severity ↓ Local release of proinflammatory cytokines			[71]
Immune-mediated glomerulonephritis		Protected			[74]

Up and down arrows indicate increase and decrease, respectively. Abs, antibodies; AIA, antigen-induced arthritis; *db/db*, leptin receptor deficient mice; EAE, autoimmune encephalomyelitis; *ob/ob*, leptin deficient mice; Th, T helper; TNF, tumor necrosis factor; WT, wild-type.

mediated inflammation, whereas it has been shown to possess protective effects in some models of innate immune response-mediated inflammation [81].

Direct and indirect effects of leptin during immune response and inflammation

As mentioned above, leptin exerts various direct effects on cells involved in the immune and inflammatory responses. However, the connection between leptin, immune responses and inflammation *in vivo* is complex. Indeed, leptin/leptin receptor deficiency causes multiple neuroendocrine and metabolic modifications in *ob/ob* or *db/db* mice, including the activation of the hypothalamic-pituitary-adrenal axis and hypercorticosteronemia, hyperglycemia and diabetes, which may also indirectly affect the immune system. Similarly, leptin deficiency after starvation in rodents is linked to increased glucocorticoid levels, and decreased levels of thyroid and growth hormone, each of which may mediate immune suppression [77,82-84]. Numerous neuroendocrine defects have been also reported in human leptin-deficient patients. These include decreased symphathetic tone, elevated thyroid stimulating hormone, parathyroid hormone, cortisol and adrenocorticotropic hormone (ACTH) levels, abnormal growth hormone stimulation, thyroid function, and others [26], which could indirectly contribute to the development of immune system dysfunction in those patients. All these data underscore the potential importance of both direct and indirect effects of leptin or leptin deficiency during immune response and inflammation. In addition, leptin deficiency results in morbid obesity and multiple immunomodulatory functions have been recently described for adipose tissue [85-87]. In fact, obesity itself may represent a low grade systemic inflammatory state and could thus favor different immune and inflammatory responses.

To investigate the relative contributions of direct and indirect effects of leptin on the immune system in a normal environment, we recently generated bone marrow chimeras by transplantation of leptin receptor-deficient *db/db* bone marrow cells into wild-type recipients (GP and CG, manuscript submitted). The size and cellularity of the thymus, as well as cellular and humoral immune responses were normal when

db/db bone marrow was grafted into wild-type mice. Direct effects of leptin on lymphocytes are thus not necessary for T cell maturation and immune response in a normal environment. Conversely, thymus weight and cell number were decreased in the reverse graft setting when wild-type bone marrow was transferred into *db/db* mice, indicating that expression of the leptin receptor in the systemic and/or local environment is mandatory for T cell development. Based on these observations, it appears that in mice major effects of leptin receptor-deficiency on the immune system are indirect.

Interestingly, in contrast to leptin or leptin receptor-deficient rodents, in human patients, gradual compensations of several endocrine functions that were initially impaired due to a mutated leptin molecule were observed, possibly due to the longevity of humans [26]. The authors suggest that, over a time span of several decades, other factors seem to bring back to normal functions that were initially dysregulated in the absence of leptin, such as thyroid axis activity, reproduction, and possibly immunity. These observations further emphasize the complexity of the neuroendocrine regulatory and compensatory mechanisms in leptin-deficiency.

The role of leptin in experimental models of arthritis

A potential role of leptin has been recently investigated in several models of arthritis depending on acquired or innate immune responses. Antigen-induced arthritis (AIA) is an experimental model of rheumatoid arthritis (RA), which is based on the induction of a local Arthus reaction by intra-articular injection of methylated bovine serum albumin (mBSA) into the knee joint of mBSA-immunized mice. *Ob/ob* and *db/db* mice had a milder form of AIA than their lean littermates [35]. In addition, *ex vivo* proliferation and IFN-γ production following the stimulation of lymph node cells by mBSA were significantly reduced in *ob/ob* and *db/db* mice. In contrast, IL-10 production by lymph node cells from *ob/ob* and *db/db* mice was increased [35]. The levels of anti-mBSA antibodies were also decreased in immunized *ob/ob* and *db/db* mice compared to their controls. These results indicate that leptin contributes to joint inflammation in AIA by regulating both humoral and cell-mediated immune responses.

To investigate a potential effect of leptin on inflammatory events in the joint, we explored the role of leptin in zymosan-induced arthritis, a mouse model of arthritis that is not dependent on the adaptive immune response. This model relies on intra-articular injection of zymosan A, which is a ligand for toll-like receptor 2, as well as an activator of the alternative complement pathway, and which triggers a local activation of the innate immune system, causing inflammation of the injected joint [88,89]. We observed that both *ob/ob* and *db/db* mice exhibited a delayed resolution of the inflammatory process and an increased acute-phase response during zymosan-induced arthritis compared to their lean littermates [90]. It is noteworthy that this increased inflammatory response was observed in *ob/ob* and *db/db* mice, despite the presence of elevated glucocorticoid levels. This observation is in agreement with data obtained in another study, where treatment of wild-type mice with leptin caused a significant decrease in the severity of septic arthritis induced by *S. aureus*, which also strongly depends on innate immunity [55].

Overall, the data obtained in experimental models of arthritis suggest that, like in other experimental disease models, chronic leptin deficiency differently affects acquired versus innate immune responses: adaptive immune-mediated responses are attenuated, whereas in models involving the innate immune response, leptin deficiency causes inadequate control of inflammation.

Role of leptin in rheumatoid arthritis

As described above, leptin contributes to adaptive immunity-mediated inflammation in different models in rodents (Table 2). However, studies in humans show more controversial results. A potential role of leptin in RA, one of the most frequent immune-mediated inflammatory diseases in humans, has been investigated in several studies (Table 3). Only a couple of studies so far demonstrated elevated leptin concentrations in RA patients [91]. One of those studies showed increased plasma levels of leptin in RA patients compared to healthy controls, associated with significantly lower leptin levels in matched synovial fluid samples [91]. However, the lack of data concerning the body mass index (BMI) limits interpretation of the results of this study [56]. In another study, gender distribution differs between the groups (male:female ratio in RA patient group is 9:22, whereas in healthy controls 8:10) [92]. Plasma leptin levels are more than twice as high in healthy females than in males of corresponding weight status [93]; therefore, interpretation of these data is also limited. In addition, the only indication regarding disease activity in both these studies is measurement of C-reactive protein (CRP) levels, which either correlates [92] or not [91] with serum leptin levels.

Moreover, two other studies showed that serum levels of leptin were not increased in RA patients compared with controls and the only correlations observed were between leptin and BMI or the percentage of body fat [94,95]. Yet another study showed even lower plasma leptin levels in RA patients than in controls and leptin did not correlate with BMI, CRP, total fat mass or disease activity score [96]. Finally, a significant inverse correlation was found between inflammation and leptin concentrations in one study on patients with active RA, although plasma leptin concentrations did not significantly differ from those in healthy controls [97]. Short course anti-TNF-α treatment did not modify leptin concentrations, despite significant reductions of CRP and IL-6. It was reported that fasting leads to an improvement of RA activity associated with a marked decrease in serum leptin and a shift toward Th2 cytokine production [98],

Table 3

Circulating leptin levels in patients with immune-mediated inflammatory diseases

Diseases	Leptin levels: patients versus healthy controls	Correlation of leptin levels with disease activity	Comments	References
RA	Elevated	No correlation with CRP	No data on BMI	[91]
RA	Elevated	Correlation with CRP	Different gender distribution in the groups	[92]
RA	Similar	No correlation	Correlated with BMI and percentage of body fat	[94]
RA	Similar	No correlation	Correlated with BMI	[95]
RA	Similar	Negative correlation with CRP and IL-6	No effect of short course anti-TNF-α therapy on leptin levels	[97]
RA	Reduced	No correlation	No correlation with BMI, CRP or total fat mass	[96]
SLE	Elevated	No correlation	Correlated with BMI	[102]
Systemic sclerosis	Reduced	No correlation	Correlated with BMI	[103]
Behçet's disease	Elevated	Positive correlation	Gender ratio, age and BMI similar in patient and control groups	[104]
Multiple sclerosis	Similar	Positive correlation	Leptin levels increased before exacerbation and decreased after treatment with IFN-β	[100]
Multiple sclerosis	Similar	No correlation	Leptin levels increased in IFN-β treated patients during active disease and remission	[101]

BMI, body mass index; CRP, C-reactive protein; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor.

reminiscent of the features observed during antigen-induced arthritis in *ob/ob* mice (Table 2). However, after a seven day ketogenic diet in RA patients, there were no significant changes in any clinical or biological measurements of disease activity, despite a significant decrease in serum leptin concentrations [99]. In conclusion, in the light of the present controversial data, it seems difficult to make an unambiguous conclusion about a potential role of leptin in RA.

Role of leptin in other immune-mediated inflammatory conditions

Several studies suggest a potential implication of leptin in the pathogenesis of other autoimmune inflammatory conditions in humans. However, the results of these studies do not consistently show a correlation between leptin levels and activity of immune-mediated diseases (Table 3). In patients with multiple sclerosis, serum levels of leptin were comparable to those of healthy controls [100,101]. Nonetheless, variable effects of IFN-β treatment on leptin levels were reported in two studies. In the first study, circulating leptin levels were increased before clinical exacerbation in relapsing patients and significantly decreased after IFN-β treatment [100]. In another study, leptin levels were increased in IFN-β treated patients compared to untreated controls during both active disease and remission [101]. Moreover, leptin induced secretion of IL-10, an anti-inflammatory cytokine, by peripheral blood mononuclear cells from multiple sclerosis patients in culture.

Elevated serum levels of leptin were found in women with systemic lupus erythematosus [102]. However, leptin levels correlated with BMI, but not with disease activity, as assessed by the Mexican SLE disease activity index. In contrast, in systemic sclerosis patients, decreased serum leptin levels were found [103]. There was no correlation between serum leptin levels and the duration of the symptoms of systemic sclerosis, while serum leptin levels correlated with BMI. In 35 patients with Behçet's syndrome, leptin levels were significantly higher than in healthy controls and correlated positively with disease activity [104]. Finally, some investigations suggest an association of leptin levels with several inflammatory markers, such as soluble TNF receptors [105,106] or CRP in healthy humans [107]. However, several recent clinical studies failed to demonstrate an effect of leptin administration on proinflammatory markers in healthy lean or obese humans [105,108,109].

Taken together, the results of these different studies do not consistently show a correlation between leptin levels and activity of immune-mediated disease. In addition, although circulating leptin levels correlated with inflammatory markers in some studies, there is no evidence for pro-inflammatory effects induced by leptin administration.

Conclusions

Taken together, results of *in vitro* and experimental animal studies suggest that leptin acts mostly as a proinflammatory

agent during adaptive immune responses, whereas in processes involving innate immunity, anti-inflammatory effects of leptin are prevalent. However, it is difficult to elucidate the role, if any, of leptin during inflammatory conditions in human patients as different clinical studies have so far yielded inconsistent results, suggesting that leptin has a rather complex role in immune response and inflammation in humans. In particular, indirect effects of leptin or leptin deficiency are likely to considerably influence immune responses and inflammatory processes, and potentially opposite direct and indirect effects of leptin might thus partly account for some controversies observed in different investigations.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

EB drafted the manuscript. GP and CG participated in discussions and manuscript revisions.

Acknowledgements

CG is supported by a Swiss National Science Foundation grant (320000-107592) and GP is supported by grants from the De Reuter and the Academic Society Foundations (Geneva, Switzerland).

References

1. Gaucher EA, Miyamoto MM, Benner SA: **Evolutionary, structural and biochemical evidence for a new interaction site of the leptin obesity protein.** *Genetics* 2003, **163:**1549-1553.
2. Friedman JM, Halaas JL: **Leptin and the regulation of body weight in mammals.** *Nature* 1998, **395:**763-770.
3. Baumann H, Morella KK, White DW, Dembski M, Bailon PS, Kim H, Lai CF, Tartaglia LA: **The full-length leptin receptor has signaling capabilities of interleukin 6-type cytokine receptors.** *Proc Natl Acad Sci USA* 1996, **93:**8374-8378.
4. Fei H, Okano HJ, Li C, Lee GH, Zhao C, Darnell R, Friedman JM: **Anatomic localization of alternatively spliced leptin receptors (Ob-R) in mouse brain and other tissues.** *Proc Natl Acad Sci USA* 1997, **94:**7001-7005.
5. Chua SC, Jr, Koutras IK, Han L, Liu SM, Kay J, Young SJ, Chung WK, Leibel RL: **Fine structure of the murine leptin receptor gene: splice site suppression is required to form two alternatively spliced transcripts.** *Genomics* 1997, **45:**264-270.
6. Ge H, Huang L, Pourbahrami T, Li C: **Generation of soluble leptin receptor by ectodomain shedding of membrane-spanning receptors in vitro and in vivo.** *J Biol Chem* 2002, **277:** 45898-45903.
7. Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, Lallone RL, Burley SK, Friedman JM: **Weight-reducing effects of the plasma protein encoded by the obese gene.** *Science* 1995, **269:**543-546.
8. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM: **Positional cloning of the mouse obese gene and its human homologue.** *Nature* 1994, **372:**425-432.
9. 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.
10. Clement K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, Cassuto D, Gourmelen M, Dina C, Chambaz J, Lacorte JM, *et al.*: **A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction.** *Nature* 1998, **392:**398-401.
11. Strobel A, Issad T, Camoin L, Ozata M, Strosberg AD: **A leptin missense mutation associated with hypogonadism and morbid obesity.** *Nat Genet* 1998, **18:**213-215.
12. Jin L, Burguera BG, Couce ME, Scheithauer BW, Lamsan J, Eberhardt NL, Kulig E, Lloyd RV: **Leptin and leptin receptor expression in normal and neoplastic human pituitary: evidence of a regulatory role for leptin on pituitary cell proliferation.** *J Clin Endocrinol Metab* 1999, **84:**2903-2911.
13. Bado A, Levasseur S, Attoub S, Kermorgant S, Laigneau JP, Bortoluzzi MN, Moizo L, Lehy T, Guerre-Millo M, Le Marchand-Brustel Y, *et al.*: **The stomach is a source of leptin.** *Nature* 1998, **394:** 790-793.
14. Wang J, Liu R, Hawkins M, Barzilai N, Rossetti L: **A nutrient-sensing pathway regulates leptin gene expression in muscle and fat.** *Nature* 1998, **393:**684-688.
15. Bonnet M, Delavaud C, Laud K, Gourdou I, Leroux C, Djiane J, Chilliard Y: **Mammary leptin synthesis, milk leptin and their putative physiological roles.** *Reprod Nutr Dev* 2002, **42:**399-413.
16. Dumond H, Presle N, Terlain B, Mainard D, Loeuille D, Netter P, Pottie P: **Evidence for a key role of leptin in osteoarthritis.** *Arthritis Rheum* 2003, **48:**3118-3129.
17. Margetic S, Gazzola C, Pegg GG, Hill RA: **Leptin: a review of its peripheral actions and interactions.** *Int J Obes Relat Metab Disord* 2002, **26:**1407-1433.
18. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohannesian JP, Marco CC, McKee LJ, Bauer TL, *et al.*: **Serum immunoreactive-leptin concentrations in normal-weight and obese humans.** *N Engl J Med* 1996, **334:**292-295.
19. Ahima RS, Flier JS: **Leptin.** *Annu Rev Physiol* 2000, **62:**413-437.
20. Fantuzzi G, Faggioni R: **Leptin in the regulation of immunity, inflammation, and hematopoiesis.** *J Leukoc Biol* 2000, **68:**437-446.
21. Konstantinides S, Schafer K, Koschnick S, Loskutoff DJ: **Leptin-dependent platelet aggregation and arterial thrombosis suggests a mechanism for atherothrombotic disease in obesity.** *J Clin Invest* 2001, **108:**1533-1540.
22. Takeda S, Elefteriou F, Levasseur R, Liu X, Zhao L, Parker KL, Armstrong D, Ducy P, Karsenty G: **Leptin regulates bone formation via the sympathetic nervous system.** *Cell* 2002, **111:**305-317.
23. Holness MJ, Munns MJ, Sugden MC: **Current concepts concerning the role of leptin in reproductive function.** *Mol Cell Endocrinol* 1999, **157:**11-20.
24. Moschos S, Chan JL, Mantzoros CS: **Leptin and reproduction: a review.** *Fertil Steril* 2002, **77:**433-444.
25. Trayhurn P: **Thermoregulation in the diabetic-obese (db/db) mouse. The role of non-shivering thermogenesis in energy balance.** *Pflugers Arch* 1979, **380:**227-232.
26. Ozata M, Ozdemir IC, Licinio J: **Human leptin deficiency caused by a missense mutation: multiple endocrine defects, decreased sympathetic tone, and immune system dysfunction indicate new targets for leptin action, greater central than peripheral resistance to the effects of leptin, and spontaneous correction of leptin-mediated defects.** *J Clin Endocrinol Metab* 1999, **84:**3686-3695.
27. Fantuzzi G: **Adipose tissue, adipokines, and inflammation.** *J Allergy Clin Immunol* 2005, **115:**911-919.
28. Faggioni R, Feingold KR, Grunfeld C: **Leptin regulation of the immune response and the immunodeficiency of malnutrition.** *Faseb J* 2001, **15:**2565-2571.
29. Pecoits-Filho R, Nordfors L, Heimburger O, Lindholm B, Anderstam B, Marchlewska A, Stenvinkel P: **Soluble leptin receptors and serum leptin in end-stage renal disease: relationship with inflammation and body composition.** *Eur J Clin Invest* 2002, **32:**811-817.
30. Bjorbaek C, Elmquist JK, Frantz JD, Shoelson SE, Flier JS: **Identification of SOCS-3 as a potential mediator of central leptin resistance.** *Mol Cell* 1998, **1:**619-625.
31. Martin-Romero C, Sanchez-Margalet V: **Human leptin activates PI3K and MAPK pathways in human peripheral blood mononuclear cells: possible role of Sam68.** *Cell Immunol* 2001, **212:**83-91.
32. Heinrich PC, Behrmann I, Haan S, Hermanns HM, Muller-Newen G, Schaper F: **Principles of interleukin (IL)-6-type cytokine signalling and its regulation.** *Biochem J* 2003, **374:**1-20.
33. Xiao E, Xia-Zhang L, Vulliemoz NR, Ferin M, Wardlaw SL: **Leptin modulates inflammatory cytokine and neuroendocrine responses to endotoxin in the primate.** *Endocrinology* 2003, **144:**4350-4353.
34. Bennett BD, Solar GP, Yuan JQ, Mathias J, Thomas GR, Matthews W: **A role for leptin and its cognate receptor in hematopoiesis.** *Curr Biol* 1996, **6:**1170-1180.

35. Busso N, So A, Chobaz-Peclat V, Morard C, Martinez-Soria E, Talabot-Ayer D, Gabay C: **Leptin signaling deficiency impairs humoral and cellular immune responses and attenuates experimental arthritis.** *J Immunol* 2002, **168:**875-882.
36. Caldefie-Chezet F, Poulin A, Tridon A, Sion B, Vasson MP: **Leptin: a potential regulator of polymorphonuclear neutrophil bactericidal action?** *J Leukoc Biol* 2001, **69:**414-418.
37. Gainsford T, Willson TA, Metcalf D, Handman E, McFarlane C, Ng A, Nicola NA, Alexander WS, Hilton DJ: **Leptin can induce proliferation, differentiation, and functional activation of hemopoietic cells.** *Proc Natl Acad Sci USA* 1996, **93:**14564-14568.
38. 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.
39. 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.
40. Matarese G: **Leptin and the immune system: how nutritional status influences the immune response.** *Eur Cytokine Netw* 2000, **11:**7-14.
41. Mikhail AA, Beck EX, Shafer A, Barut B, Gbur JS, Zupancic TJ, Schweitzer AC, Cioffi JA, Lacaud G, Ouyang B, *et al.*: **Leptin stimulates fetal and adult erythroid and myeloid development.** *Blood* 1997, **89:**1507-1512.
42. 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.
43. Fantuzzi G, Sennello JA, Batra A, Fedke I, Lehr HA, 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.
44. Faggioni R, Fantuzzi G, Fuller J, Dinarello CA, Feingold KR, Grunfeld C: **IL-1 beta mediates leptin induction during inflammation.** *Am J Physiol* 1998, **274:**R204-208.
45. Grunfeld C, Zhao C, Fuller J, Pollack A, Moser A, Friedman J, Feingold KR: **Endotoxin and cytokines induce expression of leptin, the ob gene product, in hamsters.** *J Clin Invest* 1996, **97:**2152-2157.
46. Landman RE, Puder JJ, Xiao E, Freda PU, Ferin M, Wardlaw SL: **Endotoxin stimulates leptin in the human and nonhuman primate.** *J Clin Endocrinol Metab* 2003, **88:**1285-1291.
47. Arnalich F, Lopez J, Codoceo R, Jim nez M, Madero R, Montiel C: **Relationship of plasma leptin to plasma cytokines and human survivalin sepsis and septic shock.** *J Infect Dis* 1999, **180:**908-911.
48. Bornstein SR, Licinio J, Tauchnitz R, Engelmann L, Negrao AB, Gold P, Chrousos GP: **Plasma leptin levels are increased in survivors of acute sepsis: associated loss of diurnal rhythm, in cortisol and leptin secretion.** *J Clin Endocrinol Metab* 1998, **83:**280-283.
49. Maruna P, Gurlich R, Frasko R, Haluzik M: **Serum leptin levels in septic men correlate well with C-reactive protein (CRP) and TNF-alpha but not with BMI.** *Physiol Res* 2001, **50:**589-594.
50. Torpy DJ, Bornstein SR, Chrousos GP: **Leptin and interleukin-6 in sepsis.** *Horm Metab Res* 1998, **30:**726-729.
51. Bornstein SR, Preas HL, Chrousos GP, Suffredini AF: **Circulating leptin levels during acute experimental endotoxemia and anti-inflammatory therapy in humans.** *J Infect Dis* 1998, **178:**887-890.
52. Koc E, Ustundag G, Aliefendioglu D, Ergenekon E, Bideci A, Atalay Y: **Serum leptin levels and their relationship to tumor necrosis factor-alpha and interleukin-6 in neonatal sepsis.** *J Pediatr Endocrinol Metab* 2003, **16:**1283-1287.
53. Yarasheski KE, Zachwieja JJ, Horgan MM, Powderly WG, Santiago JV, Landt M: **Serum leptin concentrations in human immunodeficiency virus-infected men with low adiposity.** *Metabolism* 1997, **46:**303-305.
54. van Crevel R, Karyadi E, Netea MG, Verhoef H, Nelwan RH, West CE, van der Meer JW: **Decreased plasma leptin concentrations in tuberculosis patients are associated with wasting and inflammation.** *J Clin Endocrinol Metab* 2002, **87:**758-763.
55. Hultgren OH, Tarkowski A: **Leptin in septic arthritis: decreased levels during infection and amelioration of disease activity upon its administration.** *Arthritis Res* 2001, **3:**389-394.
56. Palmer G, Gabay C: **A role for leptin in rheumatic diseases?** *Ann Rheum Dis* 2003, **62:**913-915.
57. 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:**R136-142.
58. Faggioni R, Moser A, Feingold KR, Grunfeld C: **Reduced leptin levels in starvation increase susceptibility to endotoxic shock.** *Am J Pathol* 2000, **156:**1781-1787.
59. Takahashi N, Waelput W, Guisez Y: **Leptin is an endogenous protective protein against the toxicity exerted by tumor necrosis factor.** *J Exp Med* 1999, **189:**207-212.
60. Yang SQ, Lin HZ, Lane MD, Clemens M, Diehl AM: **Obesity increases sensitivity to endotoxin liver injury: implications for the pathogenesis of steatohepatitis.** *Proc Natl Acad Sci USA* 1997, **94:**2557-2562.
61. Guebre-Xabier M, Yang S, Lin HZ, Schwenk R, Krzych U, Diehl AM: **Altered hepatic lymphocyte subpopulations in obesity-related murine fatty livers: potential mechanism for sensitization to liver damage.** *Hepatology* 2000, **31:**633-640.
62. Jaworek J, Bonior J, Pierzchalski P, Tomaszewska R, Stachura J, Sendur R, Leja A, Jachimczak B, Konturek PC, Bielanski W, *et al.*: **Leptin protects the pancreas from damage induced by caerulein overstimulation by modulating cytokine production.** *Pancreatology* 2002, **2:**89-99.
63. Warzecha Z, Dembinski A, Ceranowicz P, Jaworek J, Konturek PC, Dembinski M, Bilskl J, Konturek SJ: **Influence of leptin administration on the course of acute ischemic pancreatitis.** *J Physiol Pharmacol* 2002, **53:**775-790.
64. Loffreda S, Yang SQ, Lin HZ, Karp CL, Brengman ML, Wang DJ, Klein AS, Bulkley GB, Bao C, Noble PW, *et al.*: **Leptin regulates proinflammatory immune responses.** *Faseb J* 1998, **12:**57-65.
65. Mancuso P, Gottschalk A, Phare SM, Peters-Golden M, Lukacs NW, Huffnagle GB: **Leptin-deficient mice exhibit impaired host defense in Gram-negative pneumonia.** *J Immunol* 2002, **168:**4018-4024.
66. Plotkin BJ, Paulson D, Chelich A, Jurak D, Cole J, Kasimos J, Burdick JR, Casteel N: **Immune responsiveness in a rat model for type II diabetes (Zucker rat, fa/fa): susceptibility to Candida albicans infection and leucocyte function.** *J Med Microbiol* 1996, **44:**277-283.
67. Ottonello L, Gnerre P, Bertolotto M, Mancini M, Dapino P, Russo R, Garibotto G, Barreca T, Dallegri F: **Leptin as a uremic toxin interferes with neutrophil chemotaxis.** *J Am Soc Nephrol* 2004, **15:**2366-2372.
68. Bruno A, Conus S, Schmid I, Simon HU: **Apoptotic pathways are inhibited by leptin receptor activation in neutrophils.** *J Immunol* 2005, **174:**8090-8096.
69. Zarkesh-Esfahani H, Pockley AG, Wu Z, Hellewell PG, Weetman AP, Ross RJ: **Leptin indirectly activates human neutrophils via induction of TNF-alpha.** *J Immunol* 2004, **172:**1809-1814.
70. Siegmund B, Lear-Kaul KC, Faggioni R, Fantuzzi G: **Leptin deficiency, not obesity, protects mice from Con A-induced hepatitis.** *Eur J Immunol* 2002, **32:**552-560.
71. Siegmund B, Lehr HA, Fantuzzi G: **Leptin: a pivotal mediator of intestinal inflammation in mice.** *Gastroenterology* 2002, **122:**2011-2025.
72. Matarese G, Di Giacomo A, Sanna V, Lord GM, Howard JK, Di Tuoro A, Bloom SR, Lechler RI, Zappacosta S, Fontana S: **Requirement for leptin in the induction and progression of autoimmune encephalomyelitis.** *J Immunol* 2001, **166:**5909-5916.
73. Matarese G, Sanna V, Di Giacomo A, Lord GM, Howard JK, Bloom SR, Lechler RI, Fontana S, Zappacosta S: **Leptin potentiates experimental autoimmune encephalomyelitis in SJL female mice and confers susceptibility to males.** *Eur J Immunol* 2001, **31:**1324-1332.
74. Tarzi RM, Cook HT, Jackson I, Pusey CD, Lord GM: **Leptin-deficient mice are protected from accelerated nephrotoxic nephritis.** *Am J Pathol* 2004, **164:**385-390.
75. Matarese G, Sanna V, Lechler RI, Sarvetnick N, Fontana S, Zappacosta S, La Cava A: **Leptin accelerates autoimmune diabetes in female NOD mice.** *Diabetes* 2002, **51:**1356-1361.
76. De Rosa V, Procaccini C, La Cava A, Chieffi P, Nicoletti GF, Fontana S, Zappacosta S, Matarese G: **Leptin neutralization interferes with pathogenic T cell autoreactivity in autoimmune encephalomyelitis.** *J Clin Invest* 2006, **116:**447-455.
77. Flier JS: **Lowered leptin slims immune response.** *Nat Med* 1998, **4:**1124-1125.

78. Farooqi IS, Matarese G, Lord GM, Keogh JM, Lawrence E, Agwu C, Sanna V, Jebb SA, Perna F, Fontana S, *et al.*: **Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency.** *J Clin Invest* 2002, **110:**1093-1103.
79. Martin-Romero C, Santos-Alvarez J, Goberna R, Sanchez-Margalet V: **Human leptin enhances activation and proliferation of human circulating T lymphocytes.** *Cell Immunol* 2000, **199:**15-24.
80. Mattioli B, Straface E, Quaranta MG, Giordani L, Viora M: **Leptin promotes differentiation and survival of human dendritic cells and licenses them for Th1 priming.** *J Immunol* 2005, **174:**6820-6828.
81. de Hooge AS, van De Loo FA, Arntz OJ, van Den Berg WB: **Involvement of IL-6, apart from its role in immunity, in mediating a chronic response during experimental arthritis.** *Am J Pathol* 2000, **157:**2081-2091.
82. Coleman DL, Burkart DL: **Plasma corticosterone concentrations in diabetic (db) mice.** *Diabetologia* 1977, **13:**25-26.
83. Guillaume-Gentil C, Rohner-Jeanrenaud F, Abramo F, Bestetti GE, Rossi GL, Jeanrenaud B: **Abnormal regulation of the hypothalamo-pituitary-adrenal axis in the genetically obese fa/fa rat.** *Endocrinology* 1990, **126:**1873-1879.
84. Takeshita N, Yoshino T, Mutoh S: **Possible involvement of corticosterone in bone loss of genetically diabetic db/db mice.** *Horm Metab Res* 2000, **32:**147-151.
85. Das UN: **Is obesity an inflammatory condition?** *Nutrition* 2001, **17:**953-966.
86. Juge-Aubry CE, Henrichot E, Meier CA: **Adipose tissue: a regulator of inflammation.** *Best Pract Res Clin Endocrinol Metab* 2005, **19:**547-566.
87. Trayhurn P, Wood IS: **Signalling role of adipose tissue: adipokines and inflammation in obesity.** *Biochem Soc Trans* 2005, **33:**1078-1081.
88. Keystone EC, Schorlemmer HU, Pope C, Allison AC: **Zymosan-induced arthritis: a model of chronic proliferative arthritis following activation of the alternative pathway of complement.** *Arthritis Rheum* 1977, **20:**1396-1401.
89. Takeuchi O, Akira S: **Toll-like receptors; their physiological role and signal transduction system.** *Int Immunopharmacol* 2001, **1:**625-635.
90. Bernotiene E, Palmer G, Talabot-Ayer D, Szalay-Quinodoz I, Aubert ML, Gabay C: **Delayed resolution of acute inflammation during zymosan-induced arthritis in leptin-deficient mice.** *Arthritis Res Ther* 2004, **6:**R256-263.
91. Bokarewa M, Bokarew D, Hultgren O, Tarkowski A: **Leptin consumption in the inflamed joints of patients with rheumatoid arthritis.** *Ann Rheum Dis* 2003, **62:**952-956.
92. Otero M, Lago R, Gomez R, Lago F, Dieguez C, Gomez-Reino JJ, Gualillo O: **Changes in fat-derived hormones plasma concentrations: adiponectin, leptin, resistin, and visfatin in rheumatoid arthritis subjects.** *Ann Rheum Dis* 2006. **[AU: please provide the volume and page numbers of ref.92 or state if this is in press]**
93. Chow VT, Phoon MC: **Measurement of serum leptin concentrations in university undergraduates by competitive ELISA reveals correlations with body mass index and sex.** *Adv Physiol Educ* 2003, **27:**70-77.
94. Anders HJ, Rihl M, Heufelder A, Loch O, Schattenkirchner M: **Leptin serum levels are not correlated with disease activity in patients with rheumatoid arthritis.** *Metabolism* 1999, **48:**745-748.
95. Nishiya K, Nishiyama M, Chang A, Shinto A, Hashimoto K: **Serum leptin levels in patients with rheumatoid arthritis are correlated with body mass index.** *Rinsho Byori* 2002, **50:**524-527.
96. Tokarczyk-Knapik A, Nowicki M, Wyroslak J: **The relation between plasma leptin concentration and body fat mass in patients with rheumatoid arthritis.** *Pol Arch Med Wewn* 2002, **108:**761-767.
97. Popa C, Netea MG, Radstake TR, van Riel PL, Barrera P, van der Meer JW: **Markers of inflammation are negatively correlated with serum leptin in rheumatoid arthritis.** *Ann Rheum Dis* 2005, **64:**1195-1198.
98. Fraser DA, Thoen J, Reseland JE, Forre O, Kjeldsen-Kragh J: **Decreased CD4+ lymphocyte activation and increased interleukin-4 production in peripheral blood of rheumatoid arthritis patients after acute starvation.** *Clin Rheumatol* 1999, **18:**394-401.
99. Fraser DA, Thoen J, Bondhus S, Haugen M, Reseland JE, Djoseland O, Forre O, Kjeldsen-Kragh J: **Reduction in serum leptin and IGF-1 but preserved T-lymphocyte numbers and activation after a ketogenic diet in rheumatoid arthritis patients.** *Clin Exp Rheumatol* 2000, **18:**209-214.
100. Batocchi AP, Rotondi M, Caggiula M, Frisullo G, Odoardi F, Nociti V, Carella C, Tonali PA, Mirabella M: **Leptin as a marker of multiple sclerosis activity in patients treated with interferon-beta.** *J Neuroimmunol* 2003, **139:**150-154.
101. Chatzantoni K, Papathanassopoulos P, Gourzoulidou E, Mouzaki A: **Leptin and its soluble receptor in plasma of patients suffering from remitting-relapsing multiple sclerosis (MS) In vitro effects of leptin on type-1 and type-2 cytokine secretion by peripheral blood mononuclear cells, T-cells and monocytes of MS patients.** *J Autoimmun* 2004, **23:**169-177.
102. Garcia-Gonzalez A, Gonzalez-Lopez L, Valera-Gonzalez IC, Cardona-Munoz EG, Salazar-Paramo M, Gonzalez-Ortiz M, Martinez-Abundis E, Gamez-Nava JI: **Serum leptin levels in women with systemic lupus erythematosus.** *Rheumatol Int* 2002, **22:**138-141.
103. Kotulska A, Kucharz EJ, Brzezinska-Wcislo L, Wadas U: **A decreased serum leptin level in patients with systemic sclerosis.** *Clin Rheumatol* 2001, **20:**300-302.
104. Evereklioglu C, Inaloz HS, Kirtak N, Doganay S, Bulbul M, Ozerol E, Er H, Ozbek E: **Serum leptin concentration is increased in patients with Behcet's syndrome and is correlated with disease activity.** *Br J Dermatol* 2002, **147:**331-336.
105. Chan JL, Bullen J, Stoyneva V, Depaoli AM, Addy C, Mantzoros CS: **Recombinant methionyl human leptin administration to achieve high physiologic or pharmacologic leptin levels does not alter circulating inflammatory marker levels in humans with leptin sufficiency or excess.** *J Clin Endocrinol Metab* 2005, **90:**1618-1624.
106. van Dielen FM, van't Veer C, Schols AM, Soeters PB, Buurman WA, Greve JW: **Increased leptin concentrations correlate with increased concentrations of inflammatory markers in morbidly obese individuals.** *Int J Obes Relat Metab Disord* 2001, **25:**1759-1766.
107. Shamsuzzaman AS, Winnicki M, Wolk R, Svatikova A, Phillips BG, Davison DE, Berger PB, Somers VK: **Independent association between plasma leptin and C-reactive protein in healthy humans.** *Circulation* 2004, **109:**2181-2185.
108. Hukshorn CJ, Lindeman JH, Toet KH, Saris WH, Eilers PH, Westerterp-Plantenga MS, Kooistra T: **Leptin and the proinflammatory state associated with human obesity.** *J Clin Endocrinol Metab* 2004, **89:**1773-1778.
109. Gomez-Ambrosi J, Salvador J, Silva C, Rotellar F, Gil MJ, Cienfuegos JA, Fruhbeck G: **Leptin therapy does not affect inflammatory markers.** *J Clin Endocrinol Metab* 2005, **90:**3803; author reply 3803.
110. Faggioni R, Jones-Carson J, Reed DA, Dinarello CA, Feingold KR, Grunfeld C, Fantuzzi G: **Leptin-deficient (ob/ob) mice are protected from T cell-mediated hepatotoxicity: role of tumor necrosis factor alpha and IL-18.** *Proc Natl Acad Sci USA* 2000, **97:**2367-2372.
111. Zabeau L, Defeau D, Iserentant H, Vandekerckhove J, Peelman F, Tavernier J: **Leptin receptor activation depends on critical cysteine residues in its fibronectin type III subdomains.** *J Biol Chem* 2005, **280:**22632-22640.
112. Zabeau L, Defeau D, Van der Heyden J, Iserentant H, Vandekerckhove J, Tavernier J: **Functional analysis of leptin receptor activation using a Janus kinase/signal transducer and activator of transcription complementation assay.** *Mol Endocrinol* 2004, **18:**150-161.