THE WEIGHT OF LEPTIN IN IMMUNITY

Antonio La Cava and Giuseppe Matarese‡*

Leptin is an adipocyte-derived hormone/cytokine that links nutritional status with neuroendocrine and immune functions. As a hormone, leptin regulates food intake and basal metabolism, and is sexually dimorphic — that is, its serum concentration is higher in females than in males with a similar body fat mass. As a cytokine, leptin can affect thymic homeostasis and the secretion of acute-phase reactants such as interleukin-1 and tumour-necrosis factor. Similar to other pro-inflammatory cytokines, leptin promotes T helper 1 (T_H1)-cell differentiation and can modulate the onset and progression of autoimmune responses in several animal models of disease. Here, we review the advances and controversy for a role of leptin in the pathophysiology of immune responses.

**Autoimmunity and Tolerance Laboratory, Department of Medicine, University of California Los Angeles, 1000 Veteran Avenue 32-59, Los Angeles, California 90095-1670, USA.*
‡Gruppo di Immuno Endocrinologia, Istituto di Endocrinologia ed Oncologia Sperimentale, Consiglio Nazionale delle Ricerche (IEOS-CNR) c/o Cattedra di Immunologia, Dipartimento di Biologia e Patologia Cellulare e Molecolare, Università di Napoli 'Federico II', via S. Pansini, 5 – 80131, Napoli, Italy.
Correspondence to A.L.C. or G.M. e-mail: alacava@mednet.ucla.edu, gmatarese@napoli.com
doi:10.1038/nri1350

The past few years of research on leptin — the product of the *obese* (*ob*) gene — have provided important insights into the intricate network that links nutrition, metabolism and immune homeostasis[1]. Leptin is mainly produced by the adipose tissue in proportion to the body fat mass and, at lower levels, by tissues such as the stomach, skeletal muscle and placenta[1] (FIG. 1). Although an important role of leptin is to regulate body weight through the inhibition of food intake and stimulation of energy expenditure by increased thermogenesis, recent evidence has indicated that leptin is much more than a 'fat-o-stat' sensor[2]. Indeed, leptin-deficient (*ob/ob*) mice and leptin-receptor-deficient (*db/db*) mice are not only severely obese, but also have a series of marked abnormalities that are secondary to the effects of leptin on reproduction[3], haematopoiesis[4], angiogenesis[5,6], insulin secretion[1], metabolism of bone[7], lipids and glucose[1] and, last but not least, innate and adaptive immunity[8,9] (FIGS 1,2). This review analyses the role of leptin in immune homeostasis, and the direct and indirect influences of leptin on inflammation and autoimmunity.

Leptin as a neuroendocrine and immune mediator

Many studies have linked the immune and neuroendocrine systems[10,11]. Physiological responses to stress usually involve finely integrated interactions between the autonomic nervous system and the HYPOTHALAMO–PITUITARY–ADRENAL (HPA) AXIS, and the immune system and metabolism[10,11]. For example, peripheral inflammation stimulates the central release of corticotrophin-releasing hormone (CRH), which in turn regulates the stress response through the production of adrenocorticotrophic hormone (ACTH) — a hormone that promotes the synthesis and release of GLUCOCORTICOIDS from the adrenal glands. The glucocorticoids — hormones that get their name from their ability to raise levels of blood glucose — have potent anti-inflammatory effects and dampen humoral and cell-mediated immune responses.

Interestingly, mediators that are common to the neuroendocrine and immune systems, such as the cytokines interleukin-1 (IL-1), IL-6 and tumour-necrosis factor (TNF), can all modulate inflammation through the HPA axis[10,11]. Indeed, these peripherally derived cytokines can cross the blood–brain barrier and act on the hypothalamus and pituitary gland to regulate the secretion of ACTH in response to inflammation. These cytokines also mediate a negative feedback on their own peripheral pro-inflammatory activity and are counter-regulated by endogenous glucocorticoids produced by the HPA axis.

Leptin is one of the mediators that are common to the neuroendocrine and immune systems[12]. In the immune system, leptin, together with C-REACTIVE PROTEIN

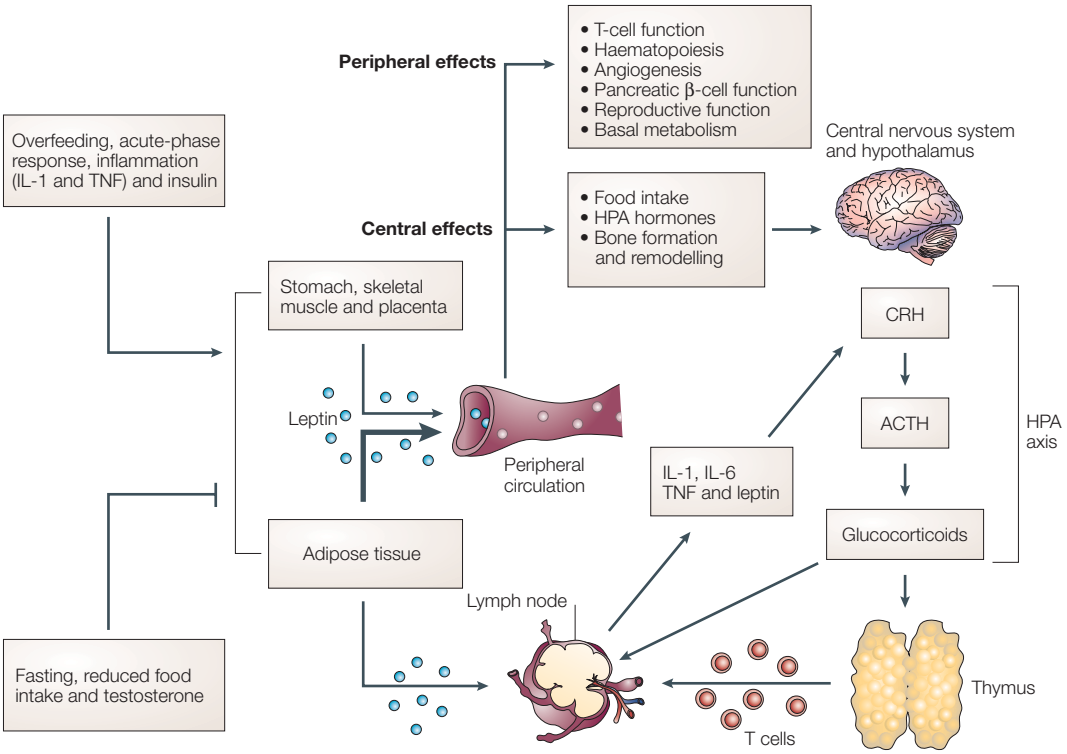

Figure 1 | **Central and peripheral neuroendocrine effects of leptin.** The neuroendocrine and immune systems communicate bidirectionally through common ligands and receptors. The hypothalamo–pituitary–adrenal (HPA) axis is one of the main structures that is responsible for this communication, and HPA hormones (corticotrophin-releasing hormone, CRH, adrenocorticotrophic hormone, ACTH, and glucocorticoids) secreted during stress responses and inflammation control immune responses. Acute-phase reactants — interleukin-1 (IL-1), IL-6 and tumour-necrosis factor (TNF) can influence the secretion of HPA hormones. Leptin is a cytokine/hormone that can also influence the HPA axis. It is mainly produced by adipose tissue and, to a lesser extent, by the stomach, skeletal muscle and placenta[1]. Leptin is secreted into the bloodstream with a circadian rhythm that is opposite to that of glucocorticoid secretion and is proportional to the body mass index (a reliable marker of body fat mass). Once released into the peripheral circulation, leptin has central and peripheral effects. In the hypothalamus, leptin regulates appetite, autonomic nervous system outflow, bone mass and the secretion of HPA hormones[1]. In the periphery, leptin increases basal metabolism, influences reproductive function, regulates pancreatic β-cell function and insulin secretion, is pro-angiogenic for endothelial cells, regulates bone-marrow haematopoiesis, and affects thymic generation of T cells and the differentiation of T helper 1 (T_H1) cells in the lymph nodes[1,3–9]. Leptin secretion is sexually dimorphic, being higher in females than in males for any given age and body fat mass, and is reduced by testosterone[1]. Insulin increases the secretion of leptin and *vice versa*[1]. Endotoxin, IL-1 and TNF also increase the secretion of leptin[1,13–15]. Reduction of leptin secretion occurs after fasting or can be mediated by hormones such as testosterone.

(CRP), IL-1 and IL-6, can act as an early acute-phase reactant, produced at high levels during inflammation, sepsis and fever, and it can be induced by other inflammatory mediators such as TNF and IL-1 (REFS 1,13–19) (FIG. 1). However, although these findings have been demonstrated in several systems, other studies have not found increased leptin in inflammatory conditions in humans, including acute experimental endotoxaemia, newborn sepsis, HIV infection and during anti-inflammatory therapy[20–22]. So, although leptin has well documented pro-inflammatory properties, it seems that it might act as an acute-phase reactant in some conditions and not in others.

The neuroendocrine role of leptin is most evident in conditions such as fasting — during which the production of leptin by adipose tissue is markedly reduced — or in relation to the effects of sex hormones on its production (testosterone reduces the secretion of leptin, whereas oestrogens increase its production)[1] (FIG. 1). The link between leptin and sex hormones is also indicated by the marked gender dimorphism, manifested by a higher serum concentration in females than in males with similar body fat mass[1].

The fact that leptin has effects on both the neuroendocrine and immune systems should not come as a surprise, given the functional connection and anatomical contiguity between adipocytes and lymphoid cells[2]. Morphologically, aggregations of lymphoid tissue, including the lymph nodes, OMENTUM, thymus and bone marrow, are associated with adipose tissue[2]. Fat deposits do not simply have a structural, metabolic and heat-insulating function, but provide a microenvironment that helps the immune system to sustain immune responses[2] (FIG. 2). In particular, lymphoid and adipose tissue interact locally through common mediators known as adipokines — adipocyte-derived molecules

HYPOTHALAMO–PITUITARY–ADRENAL (HPA) AXIS
The neuroendocrine and immune systems communicate bidirectionally through shared ligands and receptors. Factors secreted by the hypothalamus, the pituitary and adrenal glands, such as corticotrophin-releasing hormone, adrenocorticotropic hormone and glucocorticoids, can influence both immune and neuroendocrine responses. Cytokines secreted by immune cells, such as interleukin-1 (IL-1), IL-6, tumour-necrosis factor and interferon-γ, also influence the HPA axis.

GLUCOCORTICOIDS
A series of steroids that influence glucose metabolism, lipolysis and protein synthesis. In humans, the most abundant glucocorticoid is cortisol (also known as hydrocortisone). Secreted with circadian rhythm by the adrenal-gland cortex, glucocorticoids mediate their effects by binding to specific cytosolic receptors. Immunologically, glucocorticoids inhibit the mobilization and function of T and B cells, as well as the secretion of inflammatory mediators. Also, glucocorticoids can induce the apoptosis of developing thymocytes. Natural and synthetic glucocorticoids (that is, prednisolone and dexamethasone) are often used in therapy as anti-inflammatory and immunosuppressive agents.

C-REACTIVE PROTEIN
(CRP). An important acute-phase reactant secreted during inflammation and sepsis. It is part of the collectin family — a group of soluble proteins with an amino terminus similar to collagen. CRP can activate both the classical and alternative pathways of complement activation after binding one of its ligands — Fc-γ receptor I on immune cells or carbohydrates of *Streptococcus pneumoniae*.

OMENTUM
A fold of the peritoneum that extends downwards from the greater curvature of the stomach to lie anteriorly in the peritoneal cavity. It folds back on itself and is adherent to the transverse colon as it crosses the pancreas. The anterior and posterior leaves usually fuse. It often contains an abundant accumulation of adipose tissue and lymph nodes in strict anatomical contiguity.

that bridge metabolism and immune homeostasis (these molecules include leptin, adiponectin, chemokines and other pro-inflammatory cytokines). For example, TNF and chemokines promote the differentiation of adipose tissue and leptin secretion, which in turn sustains the differentiation of T helper 1 (T_H1) cells (see later)[23,24].

Cytokine signalling pathways of leptin

Leptin belongs to the family of long-chain helical cytokines[25] (characterized by a four α-helix bundle) and has structural similarity to IL-6, IL-12, IL-15, granulocyte colony-stimulating factor (G-CSF), oncostatin M (OSM), prolactin and growth hormone (FIG. 3). The leptin receptor, OBR, is a member of the class I cytokine receptor family[1,26] (which includes receptors for IL-6, IL-12, OSM and prolactin), and exists in at least six alternatively spliced forms with cytoplasmic domains of different length, known as OBRa, OBRb, OBRc, OBRd, OBRe and OBRf[26,27]. These receptors are membrane-spanning glycoproteins with fibronectin type III domains in the extracellular region and with a shared 200-amino-acid module containing four conserved cysteine residues and two membrane proximal cytokine-like binding motifs, Trp-Ser-Xaa-Trp-Ser[26,27] (FIG. 4). The short forms of the leptin receptor are expressed by several non-immune tissues and seem to mediate the transport and degradation of leptin. The long form of OBR, known as OBRb, is expressed by the hypothalamus in areas that are responsible for the

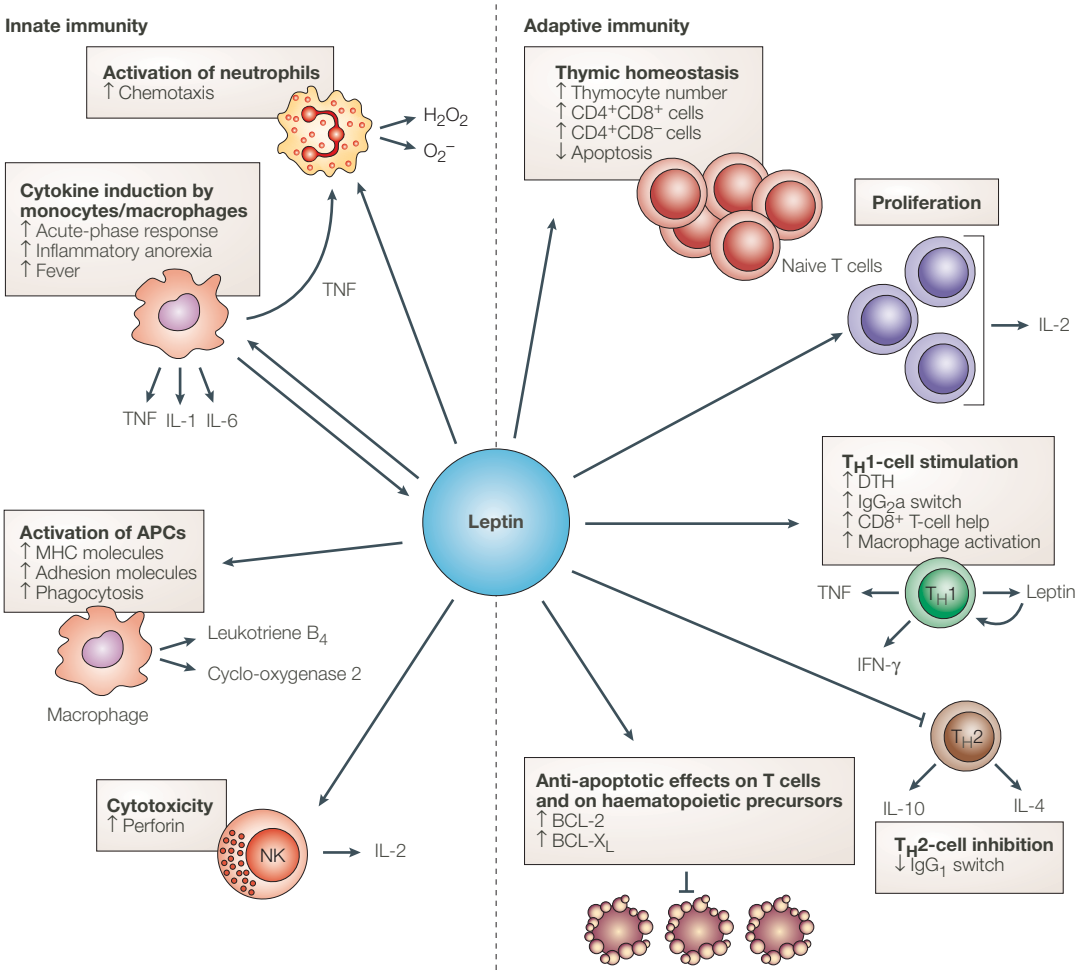

Figure 2 | **Effects of leptin on innate and adaptive immune responses.** Leptin affects both innate and adaptive immunity. In innate immunity, leptin modulates the activity and function of neutrophils by increasing chemotaxis and the secretion of oxygen radicals (such as hydrogen peroxide, H_2O_2, and superoxide, O_2^-)[31,34,35] through direct and indirect mechanisms. In mice, leptin seems to activate neutrophils directly. In humans, the action of leptin seems to be mediated by tumour-necrosis factor (TNF) secreted by monocytes[36]. Leptin increases phagocytosis by monocytes/macrophages and enhances the secretion of pro-inflammatory mediators of the acute-phase response and the expression of adhesion molecules[8,9,13–19]. On natural killer (NK) cells, leptin increases cytotoxic ability and the secretion of perforin and interleukin-2 (IL-2)[37–39]. In adaptive immunity, leptin affects the generation, maturation and survival of thymic T cells by reducing their rate of apoptosis[40]. On naive T-cell responses, leptin increases proliferation and IL-2 secretion through the activation of mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways[87]. On memory T cells, leptin promotes the switch towards T helper 1 (T_H1)-cell immune responses by increasing interferon-γ (IFN-γ) and TNF secretion, the production of IgG2a by B cells and delayed-type hypersensitivity (DTH) responses[8]. This process is then sustained by an autocrine loop of leptin secretion by T_H1 cells[53]. Finally, leptin has anti-apoptotic effects on mature T cells and on haematopoietic precursors[46,48]. APC, antigen-presenting cell.

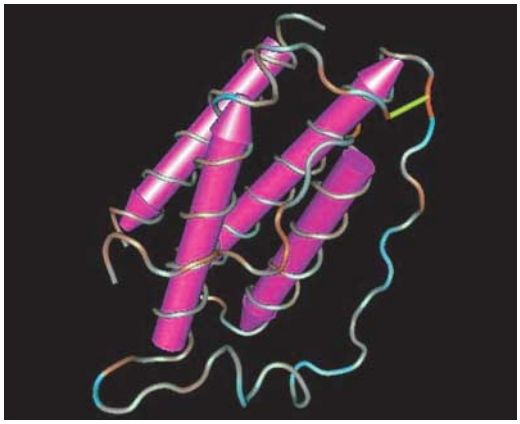

Figure 3 | **Three-dimensional structure of leptin.** Three-dimensional structure of mouse leptin[25] — note the four α-helices that are typical of the long-chain helical cytokines such as interleukin-6 (IL-6), IL-12 and IL-15. Reproduced with permission from REF. 25 © (1997) Macmillan Magazines Ltd.

secretion of neuropeptides and neurotransmitters that regulate appetite, body weight[1,26,27] and bone mass[7]. Interestingly, OBRb is also expressed by endothelial cells, pancreatic β-cells, the ovary, $CD34^+$ haematopoietic bone-marrow precursors, monocytes/macrophages, and T and B cells[1,5–9,26,27]. The expression of OBRb by T and B cells is of interest as it indicates a possible role for leptin in immune-cell activation and signal transduction, and might unveil new effects of leptin on as-yet-unexplored immune-cell functions[2,9,28–30]

Leptin and innate immune responses

In many studies, conditions that are characterized by the release of acute-phase reactants, such as TNF, IL-1 and IL-6, also cause the secretion of leptin[13–15] (FIGS 1,2). For example, increased production of leptin is observed during bacterial infection[18,19], and *ob/ob* mice have impaired immunity to infection with *Klebsiella pneumoniae*[31].

In innate immunity, leptin seems to promote activation of and phagocytosis by monocytes/macrophages and their secretion of leukotriene B_4 (LTB_4), cyclooxygenase 2 (COX2), nitric oxide and pro-inflammatory cytokines[31–33]. The products of the inducible form of COX2 — prostaglandins and leukotrienes (also known as eicosanoids) — as well as nitric oxide, are all involved in the regulation of inflammation, chemotaxis and cytokine production, and therefore markedly impact the immune response[31–33].

Moreover, leptin can induce chemotaxis of neutrophils and the release of oxygen radicals (such as superoxide anion and hydrogen peroxide)[34,35]. These mediators can be particularly harmful to cells, as they can denature proteins and damage membrane lipids (by peroxidation of unsaturated fatty acids), carbohydrates and nucleic acids. At least in human neutrophils, leptin seems to mediate its effects through an indirect mechanism, probably involving the release of TNF from monocytes[36].

Leptin also affects natural killer (NK)-cell development and activation both *in vitro* and *in vivo*[37–39]. As NK cells express OBRb and *db/db* mice have a deficit of NK cells resulting from abnormal NK-cell development, it is possible that leptin might influence the development/maintenance of a normal peripheral NK-cell pool. Indeed, an important role of OBRb in NK-cell physiology is indicated by the ability of OBRb to influence NK-cell cytotoxicity through direct activation of signal transducer and activator of transcription 3 (STAT3) and the transcription of genes encoding IL-2 and perforin[37–39] (FIG. 4).

Last but not least, it has recently been shown that leptin can stimulate the production of growth hormone by peripheral-blood mononuclear cells (PBMCs) through protein kinase C (PKC)- and nitric oxide-dependent pathways[33]. This effect of leptin on the production of growth hormone might be important in immune homeostasis, given the fact that this cytokine-like hormone has marked influences on immune responses by controlling the survival and proliferation of immune cells[33].

Leptin and adaptive immune responses

The effects of leptin on adaptive immune responses have been extensively investigated on human $CD4^+$ T cells. Addition of physiological concentrations of leptin to a MIXED LYMPHOCYTE REACTION (MLR) induces a dose-dependent increase in $CD4^+$ T-cell proliferation[8]. However, leptin has different effects on proliferation and cytokine production by human naive ($CD45RA^+$) and memory ($CD45RO^+$) $CD4^+$ T cells (both of which express OBRb). Leptin promotes proliferation and IL-2 secretion by naive T cells, whereas it minimally affects the proliferation of memory cells (on which it promotes a bias towards T_H1-cell responses) (FIG. 2). Furthermore, leptin increases the expression of adhesion molecules, such as intercellular adhesion molecule 1 (ICAM1, CD54) and very late antigen 2 (VLA2, CD49B), by $CD4^+$ T cells, possibly through the induction of pro-inflammatory cytokines such as interferon-γ (IFN-γ). Increased expression of adhesion molecules could then be responsible for the induction of clustering, activation and migration of immune cells to sites of inflammation[8].

Another important role of leptin in adaptive immunity is highlighted by the observation that leptin deficiency in *ob/ob* mice is associated with immunosuppression and thymic atrophy — a finding similar to that observed in acute starvation[8]. Acute caloric deprivation causes a rapid decrease of serum leptin concentration accompanied by reduced DELAYED-TYPE HYPERSENSITIVITY (DTH) responses and thymic atrophy, which are reversible with administration of leptin[8,40,41]. The thymic atrophy in *ob/ob* mice (or wild-type starved animals) affects the cortex of the thymus, in which most $CD4^+CD8^+$ T cells are found, and leptin replacement reduces the rate of apoptosis of such cells[40].

Despite the evidence of direct effects of leptin on immune responses *in vitro*, a major problem remains in ascertaining whether leptin can influence immune responses *in vivo*. This task is particularly difficult because of the complexity of the network of interactions that link leptin to several endocrine pathways. For example, the immune abnormalities associated with

MIXED LYMPHOCYTE REACTION (MLR). When lymphocytes from two unrelated individuals are cultured together, the T cells of one donor proliferate in response to the allogeneic MHC molecules on the cells of the other donor. The MLR is used to test for histocompatibility.

DELAYED-TYPE HYPERSENSITIVITY (DTH). A form of cell-mediated immunity elicited by antigen in the skin and mediated by $CD4^+$ T helper 1 cells. It is called 'delayed-type' because the reaction appears hours to days after antigen is injected.

high cortisol levels and hyperglycaemia in obese *ob/ob* or *db/db* mice could simply be a consequence of obesity rather than direct effects of leptin[8,40]. To help clarify this issue, studies of food restriction, which can reduce cortisol and glucose levels in *ob/ob* mice, have shown that only leptin replacement can fully restore normal immune responses in *ob/ob* mice, whereas experimentally induced reduction of serum levels of cortisol and glucose cannot reverse immune abnormalities[8,37,40]. Although still controversial, these observations seem to indicate that the immune abnormalities in *ob/ob* mice cannot be simply ascribed to high circulating levels of cortisol and glucose, and that leptin might instead have direct effects on the immune system that are independent of the metabolic abnormalities associated with leptin deficiency[8,37,40].

Another important issue is whether the effects of leptin during acute starvation can be ascribed to its central or peripheral actions. Recent experiments have shown that peripheral leptin has a dominant role in maintaining T-cell-mediated immune responses in rodents. Direct injection of leptin into the central nervous system (CNS) cannot compensate for the immunosuppression that is associated with starvation-induced hypoleptinaemia[42]. These findings might have therapeutic implications, as they indicate a lack of direct action of leptin on the CNS for reversal of starvation-induced immunosuppression, despite the beneficial effects of leptin on hormonal stress associated with starvation (reduced secretion of ACTH and glucocorticoids). In this regard, it is notable that T cells are sensitive to the supply of cellular nutrients, such as glucose[43], because they do not have glycogen stores and, therefore, depend on the import of extracellular glucose to meet their metabolic needs[44]. By stimulating glucose uptake through extracellular signal-regulated kinase 1 (ERK1)/ERK2- and phosphatidylinositol 3-kinase (PI3K)-dependent pathways, leptin might help to restore the impaired T-cell function caused by starvation[8,45]. In this context, it is worth mentioning that other long-chain helical cytokines similar to leptin (such as IL-3, IL-7 and IL-15) are important in promoting the uptake and metabolism of glucose[44]. In the case of IL-3, withdrawal of this cytokine from the culture medium leads to decreased lymphocyte uptake of glucose through reduced cell-surface expression of glucose transporter proteins[44]. It can be hypothesized that similar effects might occur in the case of leptin, given the fact that leptin can also regulate cellular expression of the same transporters[45]. The effects on lymphocyte metabolism are also important because they are linked in part to pro-survival effects in both physiological and pathological conditions (such as in autoreactivity)[44]. For example, leptin might help to promote lymphocyte survival by upregulating lymphocyte surface expression of glucose transporters, such as GLUT1 and GLUT4 (REF. 45). Other pro-survival effects of leptin could result from the ability of leptin to upregulate expression of the anti-apoptotic proteins BCL-2 and BCL-X_L[46–48] (which protect T cells from apoptosis and thymocytes from glucocorticoid-induced apoptosis) (FIG. 2).

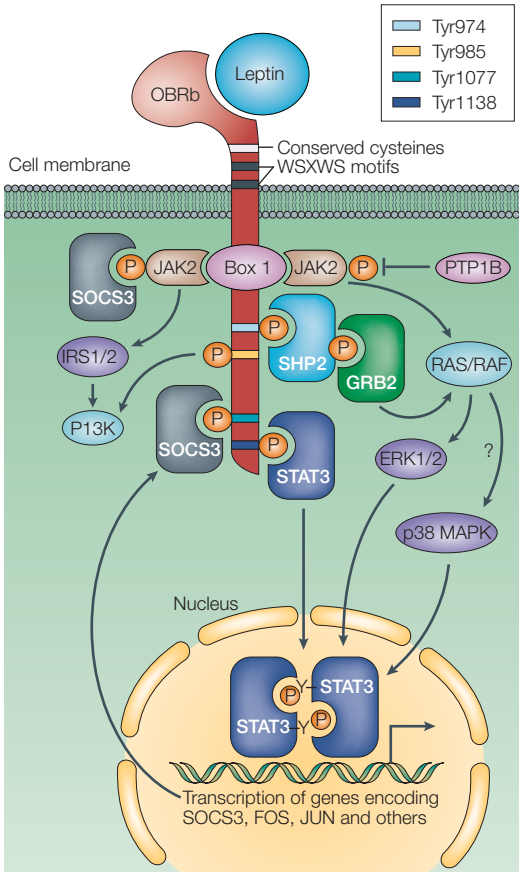

Figure 4 | **Signalling pathways activated by the leptin receptor.** Only the long form of the leptin receptor (OBRb) can signal intracellularly, whereas the short forms of the leptin receptor do not (see text for details)[26–30]. The total length of OBRb is 1162 amino acids; the extracellular domain consists of 816 amino acids and is a class I cytokine receptor that contains two cytokine-like binding motifs, Trp-Ser-Xaa-Trp-Ser (WSXWS), and a fibronectin type III domain[26–30]. After binding leptin, OBRb-associated Janus-family tyrosine kinase 2 (JAK2) becomes activated by auto- or cross-phosphorylation and tyrosine phosphorylates the cytoplasmic domain of the receptor. Four of the phosphorylated tyrosine residues function as docking sites for cytoplasmic adaptors such as signal transducer and activator of transcription (STAT) factors, particularly STAT3 (in some cases, also STAT1 and STAT5)[26–30]. The membrane distal tyrosine (position 1138) functions as a docking site for STAT3, which is a substrate of JAK2. After subsequent dimerization, STAT3 translocates to the nucleus and induces the expression of suppressor of cytokine signalling 3 (*SOCS3*) and other genes. SOCS3 takes part in a feedback loop that inhibits leptin signalling by binding to phosphorylated tyrosines. SRC homology 2 (SH2) domain-containing phosphatase 2 (SHP2) is recruited to Tyr985 and Tyr974, and activates extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 mitogen-activated protein kinase (MAPK) pathways through the adaptor protein growth factor receptor-bound protein 2 (GRB2), ultimately inducing the expression of FOS and JUN[26–30,87–89]. After leptin binding, JAK2 can induce phosphorylation of the insulin receptor substrate 1/2 (IRS1/2) proteins that are responsible for the activation of phosphatidylinositol 3-kinase (PI3K)[26–30,87–89]. Phosphotyrosine phosphatase 1B (PTP1B), which is localized on the surface of the endoplasmic reticulum, is involved in negative regulation of OBRb signalling through the dephosphorylation of JAK2 after internalization of the OBRb complex.

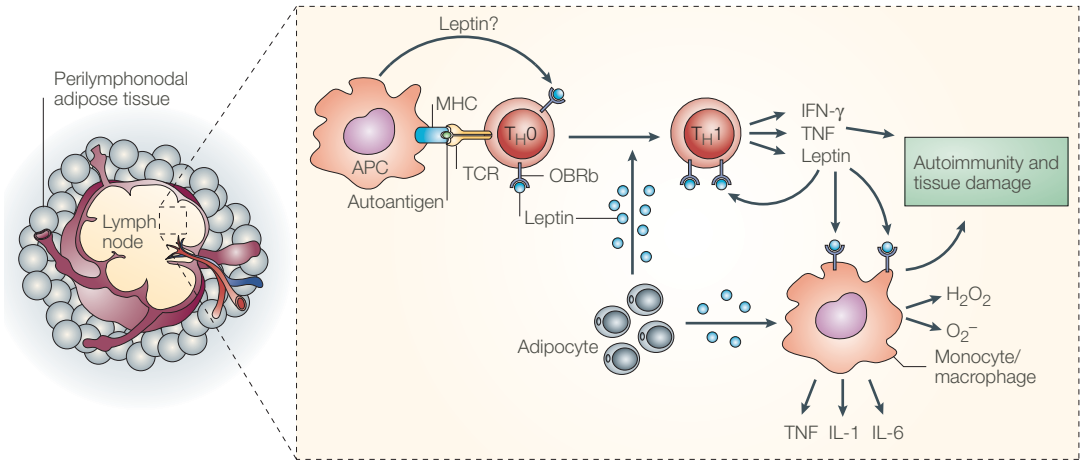

Figure 5 | **Schematic model for a role of leptin in autoimmunity.** Leptin is produced by adipocytes that are present in the perilymphonodal adipose tissue and the lymph node itself[2]. In the lymph node, leptin promotes the differentiation of T helper 1 (T_H1) cells, the activation of monocytes/macrophages and the secretion of cytokines of the acute-phase response and oxygen radicals. Autoantigens could be presented to T_H0 cells that express the long form of the leptin receptor (OBRb)[8]. Leptin could then affect the priming of autoreactive T cells towards T_H1-type pro-inflammatory responses — for example, in experimentally induced autoimmune diseases that affect the central nervous system (CNS)[52,53,62], the gastrointestinal mucosa[56], hepatocytes[37,50], pancreatic β-cells[60], synovial cells and cartilage[51]. Paracrine effects of T_H1 cells that produce leptin after activation with antigen could then sustain an autocrine loop of proliferation and T-cell survival[52]. APC, antigen-presenting cell; H_2O_2, hydrogen peroxide; IFN-γ, interferon-γ; IL, interleukin; TCR, T-cell receptor; TNF, tumour-necrosis factor.

Leptin in inflammation and autoimmunity

As mentioned earlier, *ob/ob* mice have several abnormalities that are common to starved animals[1]. However, *ob/ob* (and *db/db*) mice also have additional endocrine and metabolic disturbances that could affect the immune system indirectly, such as hypercorticosteronaemia and diabetes[1]. Similarly, starvation not only associates with hypoleptinaemia, but also with an increased concentration of glucocorticoids and decreased levels of thyroid and growth hormones (which can result in immune suppression)[1]. So, the effects of leptin on the immune system should take into account both the direct and indirect effects of this molecule on other hormones. Although the influence of thyroid and growth hormones on the effects of leptin remains elusive, it seems that leptin can affect thymic output and T-cell function independently of glucocorticoids, as congenitally leptin-deficient individuals have glucocorticoid levels within a normal range, but markedly reduced numbers of naive T cells[49].

More importantly, *ob/ob* mice have reduced secretion of IL-2, IFN-γ, TNF and IL-18, and increased production of T_H2-type cytokines, such as IL-4 and IL-10, after mitogenic stimulation[8,50,51]. As a result, *ob/ob* mice are resistant to the induction of several experimentally induced autoimmune diseases (FIG. 5). For example, in ANTIGEN-INDUCED ARTHRITIS (AIA), *ob/ob* mice have less severe joint inflammation, reduced T-cell proliferation, lower concentrations of antibodies specific for the inducing antigen methylated bovine serum albumin, reduced expression of T_H1-type cytokines and a bias towards the production of T_H2-type cytokines[51] (TABLE 1).

Ob/ob mice are also protected from EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS (EAE)[52,53], whereas administration of leptin to susceptible wild-type mice worsens EAE by increasing the secretion of pro-inflammatory cytokines and directly correlates with pathogenic T-cell autoreactivity[52,53] (TABLE 1). Notably, leptin is expressed by T cells and macrophages in both the lymph nodes and active inflammatory lesions of the CNS during acute and relapsing EAE, but not during remission[53]. Finally, increased leptin expression has recently been described in active inflammatory lesions of the CNS in patients with multiple sclerosis[54] (MS) and in the serum of patients with MS before relapses after treatment with IFN-β[55].

Protection of *ob/ob* mice from autoimmune damage is also observed in experimentally induced hepatitis (EIH), in which leptin deficiency protects against the T-cell-mediated liver damage induced by administration of concanavalin A (ConA) or *Pseudomonas aeruginosa* exotoxin A[37,50]. Also in this case, leptin administration restores responsiveness of *ob/ob* mice to ConA (TABLE 1). Of note, the liver of *ob/ob* mice with EIH shows reduced production of TNF, IFN-γ and IL-18 (REF. 50).

Finally, *ob/ob* mice are resistant to acute and chronic intestinal inflammation induced by dextran sodium sulphate and to colitis induced by trinitrobenzene sulphonic acid (experimentally induced colitis, EIC)[56] (TABLE 1). In acute EIC, *ob/ob* mice do not develop intestinal inflammation and show decreased secretion of pro-inflammatory cytokines and chemokines. As expected, leptin replacement increases cytokine production to the levels observed in control mice[56]. Similarly, in chronic colitis, *ob/ob* mice have decreased secretion of pro-inflammatory cytokines, such as TNF, IFN-γ, IL-1β, IL-6 and IL-18, and reduced production of chemokines, such as CXC-chemokine ligand 2 (CXCL2; macrophage inflammatory protein 2, MIP2) and CC-chemokine ligand 3 (CCL3; macrophage

ANTIGEN-INDUCED ARTHRITIS (AIA). An inflammatory disease of the joints that develops in susceptible mice immunized with methylated bovine serum albumin into the knees in immunogenic adjuvant. It is considered to be a model of inflammatory arthritis.

EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS (EAE). An inflammatory disease of the central nervous system that develops in susceptible mice immunized with neural antigens in immunogenic adjuvant. It is considered to be a model of human multiple sclerosis.

HYPERPHAGIA
A condition of excessive eating beyond normal hunger.

HYPOTHALAMIC HYPOGONADISM
A condition of decreased functional activity of the gonads, resulting in retardation of puberty and/or reproductive insufficiency. It is due to disorders of the hypothalamus or of the pituitary gland.

inflammatory protein 1α, MIP1α)[56] (TABLE 1). Of interest, recent reports have shown that leptin secreted by the gastric mucosa is not completely degraded by proteolysis and can therefore reach the intestine in an active form, where it can control the expression of sodium/glucose and peptide transporters on intestinal epithelial cells[57,58]. As a result, leptin might have a dual nature: on the one hand, leptin could function as a growth factor for the intestine, because of its involvement in the absorption of carbohydrates and proteins; on the other hand, leptin could function as a mediator of intestinal inflammation[56–58].

Most recently, protection from autoimmunity in *ob/ob* mice has been observed in experimentally induced glomerulonephritis[59]. In this immune-complex-mediated inflammatory disease induced by the injection of sheep antibodies specific for mouse glomerular basement membrane into mice pre-immunized against sheep IgG, Tarzi *et al.*[59] have observed renal protection of *ob/ob* mice associated with reduced glomerular-crescent formation and reduced macrophage infiltration. These protective effects were associated with concomitant defects of both adaptive and innate immune responses (testified by reduced *in vitro* proliferation of splenic T cells and reduced humoral responses to sheep IgG, respectively) (TABLE 1). In spite of this trend, in one experiment, *ob/ob* mice showed normal humoral responses (compared to wild-type mice) and one out of six mice developed histological injury. Tarzi *et al.* hypothesized that defective innate effector responses were present in *ob/ob* mice, in line with *in vitro* experiments that have indicated defective phagocytosis and cytokine production in *ob/ob* mice[9,16,59].

All these studies concern a role for leptin in experimentally induced autoimmunity. However, leptin is also important in spontaneous autoimmune diabetes in non-obese diabetic (NOD) mice[60]. Female NOD mice have increased levels of serum leptin before the development of disease, and administration of exogenous leptin accelerates the onset and progression of disease by promoting insulitis and local production of IFN-γ[60] (FIG. 2). Of interest, IL-2-deficient mice, which develop spontaneous inflammatory bowel disease (IBD), have increased levels of pro-inflammatory cytokines, including leptin, after food deprivation[61]. Incidentally, in this case, the increase in leptin concentration seems to depend on the secretion of TNF[61]. Taken together, the data in NOD mice and IL-2-deficient mice indicate that the production of leptin can be favoured and/or sustained by ongoing inflammation[60,61].

Another indication that leptin could be involved in autoimmunity is the sexual dimorphism of serum leptin concentration (higher in females than in males matched for age and body mass index). In this sense, leptin could add to the list of hormones, such as oestradiol and prolactin, that have long been known to have a role in favouring the predisposition of females to the development of autoimmunity[2,62]. In particular, only hyperleptinaemic female mice develop autoimmunity, whereas hypoleptinaemic mice are protected, and treatment of EAE-resistant SJL/J males with recombinant leptin renders them susceptible to EAE[62].

The role of leptin in human immunity

Recent studies on congenitally leptin-deficient humans before and after treatment with recombinant leptin have indicated a key role for leptin in innate and adaptive immunity in humans[49,63]. Human *OB* mutations are rare (estimated frequency of 1 in 250 obese individuals) and are phenotypically characterized by HYPERPHAGIA, obesity, HYPOTHALAMIC HYPOGONADISM, impaired fertility, increased susceptibility to opportunistic infections and

Table 1 | **Susceptibility of leptin-deficient *ob/ob* mice to experimentally induced inflammatory/autoimmune diseases**

Disease model	Susceptibility of *ob/ob* mice	Cytokines and inflammatory factors involved	Antibodies present	Effects of leptin administration	Refs
EAE	Reduced/resistant	Increased IL-4; absent IFN-γ after myelin-specific stimulation of T cells	Increased myelin-specific IgG1; reduced IgG2a	Restores IFN-γ secretion and disease susceptibility is comparable to wild-type mice; promotes myelin-specific antibody switch from IgG1 to IgG2a	52,53
AIA	Reduced/resistant	Increased IL-10; reduced IFN-γ after mBSA stimulation of T cells; reduced synovial IL-1β and TNF	Decreased serum antibody specific for mBSA	N.D.	51
EIC	Reduced/resistant	Reduced IFN-γ, TNF, IL-1β, IL-6, IL-10 and IL-18; reduced chemokines CCL3 and CXCL2; reduced MPO activity; reduced COX2 expression	N.D.	Restores normal secretion of IFN-γ, TNF, IL-1β, IL-6, IL-10 and IL-18; restores disease susceptibility to a level comparable to wild-type mice	56
EIH	Reduced/resistant	Reduced serum TNF and IL-18	N.D.	Restores TNF and IL-18 secretion; restores disease susceptibility to a level comparable to wild-type mice	37,50
EINN	Reduced/resistant	Undetectable *in vitro* proliferative and cytokine T-cell responses against sheep IgG; reduced glomerular IgG deposition	Reduced or no difference in sheep-IgG-specific serum antibodies	N.D.	59

AIA, antigen-induced arthritis; COX2, cyclo-oxygenase 2; EAE, experimental autoimmune encephalomyelitis; EIC, experimentally induced colitis; EIH, experimentally induced hepatitis; EINN, experimentally induced nephrotoxic nephritis; IL, interleukin; IFN-γ, interferon-γ; mBSA, methylated bovine serum albumin; MPO, myeloperoxidase; N.D., not determined; TNF, tumour-necrosis factor.

immune abnormalities, including impaired T-cell proliferation, reduction of the number of circulating $CD4^+$ T cells (especially naive T cells) and impaired cytokine production[49] (increased production of transforming growth factor-β, lack of IFN-γ secretion, and reduction of IL-4 and IL-10 production). Importantly, in leptin-deficient humans, administration of recombinant leptin reverses the immune abnormalities[49]. Human leptin-deficient individuals — in contrast to *ob/ob* mice — do not have hypercortisolaemia and their cortisol levels are not affected by leptin administration. These data indicate that leptin deficiency in humans can probably decrease thymic output of naive T cells independently of circulating glucocorticoid levels. Nonetheless, the question remains as to whether concomitant endocrine abnormalities in humans could contribute to their immune abnormalities.

Increased peripheral secretion of leptin in humans is associated with chronic inflammatory conditions, such as pelvic endometriosis, nonalcoholic hepatitis, chronic pulmonary inflammation, IBD, inflammatory nephritis, Behcet's syndrome, Graves disease, type 1 diabetes and rheumatoid arthritis[64–73]. However, although one group has reported increased plasma levels of leptin in patients with rheumatoid arthritis compared with healthy controls[73], other groups have not confirmed this association[74]. In a similar manner, the concentration of serum leptin has been found to be within the normal and/or physiological range in several inflammatory conditions[75–77]. Sampling and disease staging should be carefully evaluated when interpreting the results of these studies. It is nonetheless common to find an increase in leptin concentration in the early phases of autoimmune diseases and before relapses[53,55,64–73]. Intriguingly, food deprivation ameliorates the symptoms associated with some of these inflammatory conditions. For example, in rheumatoid arthritis, fasting (and subsequent decrease of serum leptin) leads to improvement of disease activity and a shift towards T_H2-cell responses[78]. Fasting and/or caloric deprivation, or dietary changes in controlled trials in humans can ameliorate clinical symptoms of autoimmune diseases such as IBD and MS, and similar changes are also effective in ameliorating disease in animal models of systemic lupus erythematosus and Sjogren's syndrome[67,79–84]. However, it must also be considered that the fall of leptin levels subsequent to fasting is not the only event associated with reduced caloric intake. Other hormonal and stress-response-related changes need to be taken into account to explain the final outcome (often resulting in improvement of chronic inflammation). Once again, the intimate connection between molecules that influence body weight and the network of molecules, cells and pathways that finely tune the immune response makes these studies complex. There is therefore still much to learn about the interaction between metabolic regulation (including energy expenditure) and immune responses. Nonetheless, increasing evidence is starting to reveal the importance of several molecules, including leptin, that operate at the interface between metabolism and immune responses.

Concluding remarks and future perspectives

Despite a series of important studies carried out recently, many cellular and molecular aspects of the role of leptin in immune homeostasis remain elusive. Nonetheless, particularly because of its dual role in nutrition and autoimmunity and its modulation by food intake, leptin could be a new immunotherapeutic target in conditions where leptin is thought to promote disease[85,86]. For example, Steinman and colleagues[85] have suggested that the stress responses of acute starvation could prove beneficial in certain autoimmune conditions in which leptin promotes chronic inflammation. However, acute starvation and subsequent hypoleptinaemia would be detrimental during infection as they might result in suppression of immune responses[2]. Another unresolved issue is whether modulation of leptin might sufficiently impact immune processes alone or whether it would be necessary to complement it with other approaches to attain beneficial effects. Moreover, new studies will need to address the role of leptin in other aspects of the immune response that have not yet been investigated, such as immune regulation and tolerance, survival of autoreactive T cells and antigen-presenting cell function.

1. Friedman, J. M. & Halaas, J. L. Leptin and the regulation of body weight in mammals. *Nature* **395**, 763–770 (1998).
2. Matarese, G. *et al.* Balancing susceptibility to infection and autoimmunity: a role for leptin? *Trends Immunol.* **23**, 182–187 (2002).
3. Chehab, F., Lim, M. & Lu, R. Correction of the sterility defect in homozygous obese female mice by treatment with the human recombinant leptin. *Nature Genet.* **12**, 318–320 (1996).
4. Bennett, B. D. *et al.* A role for leptin and its cognate receptor in hematopoiesis. *Curr. Biol.* **6**, 1170–1180 (1996).
5. Sierra-Honigmann, M. R. *et al.* Biological action of leptin as an angiogenic factor. *Science* **281**, 1683–1686 (1998).
6. Park, H. Y. *et al.* Potential role of leptin in angiogenesis: leptin induces endothelial cell proliferation and expression of matrix metalloproteinases *in vivo* and *in vitro*. *Exp. Mol. Med.* **33**, 95–102 (2001).
7. Ducy, P. *et al.* Leptin inhibits bone formation through a hypothalamic relay: a central control of bone mass. *Cell* **100**, 197–207 (2000).
8. Lord, G. M. *et al.* Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. *Nature* **394**, 897–901 (1998).
   The first demonstration that leptin modulates $CD4^+$ T-cell responses and is involved in starvation-induced immunosuppression.
9. Sanchez-Margalet, V. *et al.* Role of leptin as an immunomodulator of blood mononuclear cells: mechanisms of action. *Clin. Exp. Immunol.* **133**, 11–19 (2003).
10. Turnbull, A. V. & Rivier, C. L. Regulation of the hypothalamic–pituitary–adrenal axis by cytokines: actions and mechanisms of action. *Physiol. Rev.* **79**, 1–71 (1999).
11. Haddad, J. J. *et al.* Cytokines and neuro-immune-endocrine interactions: a role for the hypothalamic–pituitary–adrenal revolving axis. *J. Neuroimmunol.* **133**, 1–19 (2002).
12. Zhang, Y. *et al.* Positional cloning of the mouse *obese* gene and its human homologue. *Nature* **372**, 425–432 (1994).
    This study reports the cloning of the gene encoding leptin in mice and humans.
13. Landman, R. E. *et al.* Endotoxin stimulates leptin in the human and nonhuman primate. *J. Clin. Endocrinol. Metab.* **88**, 1285–1291 (2003).
14. Grunfeld, C. *et al.* 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.* **97**, 2152–2160 (1996).
15. Sarraf, P. *et al.* Multiple cytokines and acute inflammation raise mouse leptin levels: potential role in inflammatory anorexia. *J. Exp. Med.* **185**, 171–180 (1997).
16. Fantuzzi, G. & Faggioni, R. Leptin in the regulation of immunity, inflammation, and hematopoiesis. *J. Leukoc. Biol.* **68**, 437–446 (2000).
17. Bullo, M., Garcia-Lorda, P., Megias, I. & Salas-Salvado, J. Systemic inflammation, adipose tissue tumor necrosis factor, and leptin expression. *Obes. Res.* **11**, 525–531 (2003).
18. Arnalich, F. *et al.* Relationship of plasma leptin to plasma cytokines and human survivalin sepsis and septic shock. *J. Infect. Dis.* **180**, 908–911 (1999).
19. Orbak, Z., Ertekin, V., Akay, F., Ozkan, B. & Ors, R. Serum leptin levels in neonatal septicemia. *J. Pediatr. Endocrinol. Metab.* **16**, 727–731 (2003).
20. Bornstein, S. R., Preas, H. L., Chrousos, G. P. & Suffredini, A. F. Circulating leptin levels during acute experimental endotoxiemia and antiinflammatory therapy in humans. *J. Infect. Dis.* **178**, 887–890 (1998).

21. Koc, E. *et al.* Serum leptin levels and their relationship to tumor necrosis factor-α and interleukin-6 in neonatal sepsis. *J. Pediatr. Endocrinol. Metab*. **16**, 1283–1287 (2003).
22. Yarasheski, K. E. *et al.* Serum leptin concentrations in human immunodeficiency virus-infected men with low adiposity. *Metabolism* **46**, 303–305 (1997).
23. Bruun, J. M. *et al*. Effects of pro-inflammatory cytokines and chemokines on leptin production in human adipose tissue *in vitro*. *Mol. Cell. Endocrinol*. **190**, 91–99 (2002).
24. Gerhardt, C. C. *et al.* Chemokines control fat accumulation and leptin secretion by cultured human adipocytes. *Mol. Cell. Endocrinol*. **175**, 81–92 (2001).
25. Zhang, F. *et al.* Crystal structure of the obese protein leptin-E100. *Nature* **387**, 206–208 (1997).
This paper describes the crystal structure of leptin.
26. Tartaglia, L. A. *et al.* Identification and expression cloning of a leptin receptor, Ob-R. *Cell* **83**, 1263–1270 (1995).
This study reports the cloning of the gene encoding the leptin receptor.
27. Tartaglia, L. A. The leptin receptor. *J. Biol. Chem.* **272**, 6093–6100 (1997).
28. Banks, A. S., Davis, S. M., Bates, S. H. & Myers, M. G. Activation of downstream signals by the long form of the leptin receptor. *J. Biol. Chem.* **275**, 14563–14572 (2000).
29. Bjorbaek, C. *et al.* Divergent roles of SHP-2 in ERK activation by leptin receptors. *J. Biol. Chem.* **276**, 4747–4755 (2001).
30. Sweeney, G. Leptin signalling. *Cell Signal*. **14**, 655–663 (2002).
31. Mancuso, P. *et al.* Leptin-deficient mice exhibit impaired host defense in Gram-negative pneumonia. *J. Immunol.* **168**, 4018–4024 (2002).
32. Zarkesh-Esfahani, H. *et al.* High-dose leptin activates human leukocytes via receptor expression on monocytes. *J. Immunol*. **167**, 4593–4599 (2001).
33. Dixit, V. D., Mielenz, M., Taub, D. D. & Parvizi, N. Leptin induces growth hormone secretion from peripheral blood mononuclear cells via a protein kinase C- and nitric oxide-dependent mechanism. *Endocrinology* **144**, 5595–5603 (2003).
34. Caldefie-Chezet, F., Poulin, A., Tridon, A., Sion, B. & Vasson, M. P. Leptin: a potential regulator of polymorphonuclear neutrophil bactericidal action? *J. Leukoc. Biol*. **69**, 414–418 (2001).
35. Caldefie-Chezet, F., Poulin, A. & Vasson, M. P. Leptin regulates functional capacities of polymorphonuclear neutrophils. *Free Radic. Res*. **37**, 809–814 (2003).
36. Zarkesh-Esfahani, H. *et al.* Leptin indirectly activates human neutrophils via induction of TNF-α. *J. Immunol*. **172**, 1809–1814 (2004).
37. Siegmund, B., Lear-Kaul, K. C., Faggioni, R. & Fantuzzi, G. Leptin deficiency, not obesity, protects mice from Con A-induced hepatitis. *Eur. J. Immunol*. **32**, 552–560 (2002).
38. Zhao, Y., Sun, R., You, L., Gao, C. & Tian, Z. Expression of leptin receptors and response to leptin stimulation of human natural killer cell lines. *Biochem. Biophys Res. Commun*. **300**, 247–252 (2003).
39. Tian, Z., Sun, R., Wei, H. & Gao, B. Impaired natural killer (NK) cell activity in leptin receptor deficient mice: leptin as a critical regulator in NK cell development and activation. *Biochem. Biophys Res. Commun.* **298**, 297–302 (2002).
40. Howard, J. K. *et al.* Leptin protects mice from starvation-induced lymphoid atrophy and increases thymic cellularity in *ob/ob* mice. *J. Clin. Invest.* **104**, 1051–1059 (1999).
The first study of the effects of leptin on thymic cellularity and function.
41. Lord, G. M., Matarese, G., Howard. J. K. & Lechler, R. I. The bioenergetics of the immune system. *Science* **292**, 855–856 (2001).
42. Zhang, Y. *et al*. Peripheral but not central leptin prevents the immunosuppression associated with hypoleptinaemia in rats. *J. Endocrinol*. **174**, 455–461 (2002).
43. Frauwirth, K. A. *et al.* The CD28 signaling pathway regulates glucose metabolism. *Immunity*. **16**, 769–777 (2002).
44. Khaled, A. R. & Durum, S. K. Lymphocide: cytokines and the control of lymphoid homeostasis. *Nature Rev. Immunol*. **2**, 817–830 (2002).
45. Berti, L., & Gammeltoft, S. Leptin stimulates glucose uptake in C2C12 muscle cells by activation of ERK2. *Mol. Cell. Endocrinol*. **157**, 121–130 (1999).
46. Fujita Y. *et al.* Leptin inhibits stress-induced apoptosis of T lymphocytes. *Clin. Exp. Immunol*. **128**, 21–26 (2002).
47. Shimabukuro, M., Wang, M. Y., Zhou, Y. T., Newgard, C. B. & Unger, R. H. Protection against lipoapoptosis of β-cells through leptin-dependent maintenance of Bcl-2 expression. *Proc. Natl Acad. Sci. USA* **95**, 9558–9561 (1998).
48. Najib, S. & Sanchez-Margalet, W. Human leptin promotes survival of human circulating blood monocytes prone to apoptosis by activation of p42/44 MAPK pathway. *Cell. Immunol*. **220**, 143–149 (2002).
49. Farooqi, I. S. *et al*. Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *J. Clin. Invest*. **110**, 1093–1103 (2002).
The first demonstration that congenitally leptin-deficient individuals have defective CD4+ T-cell function and cytokine abnormalities that can be reversed by leptin replacement.
50. Faggioni, R. *et al.* Leptin-deficient (*ob/ob*) mice are protected from T cell-mediated hepatotoxicity: role of tumor necrosis factor α and IL-18. *Proc. Natl Acad. Sci. USA* **97,** 2367–2372 (2000).
This study (together with references 37, 51–53, 56 and 59) shows that leptin-deficient *ob/ob* mice are resistant to the induction of autoimmunity.
51. Busso, N. *et al.* Leptin signaling deficiency impairs humoral and cellular immune responses and attenuates experimental arthritis. *J. Immunol.* **168**, 875–882 (2002).
52. Matarese, G. *et al.* Requirement for leptin in the induction and progression of autoimmune encephalomyelitis. *J. Immunol.* **166**, 5909–5916 (2001).
53. Sanna, V. *et al.* Leptin surge precedes onset of autoimmune encephalomyelitis and correlates with development of pathogenic T cell responses. *J. Clin. Invest.* **111**, 241–250 (2003).
The first report showing that T helper 1 cells can produce leptin and can be found in inflammatory lesions in experimental autoimmune encephalomyelitis.
54. Lock, C. *et al.* Gene-microarray analysis of multiple sclerosis lesions yields new targets validated in autoimmune encephalomyelitis. *Nature Med*. **8**, 500–508 (2002).
55. Batocchi, A. P. *et al.* Leptin as marker of multiple sclerosis activity in patients treated with interferon-β. *J. Neuroimmunol*. **139**, 150–154 (2003).
56. Siegmund, B., Lehr, H. A. & Fantuzzi, G. Leptin: a pivotal mediator of intestinal inflammation in mice. *Gastroenterology* **122**, 2011–2025 (2002).
57. Buyse, M., Sitaraman, S. V., Liu, X., Bado, A. & Merlin, D. Luminal leptin enhances CD147/MCT-1-mediated uptake of butyrate in the human intestinal cell line Caco2-BBE. *J. Biol. Chem*. **277**, 28182–28190 (2002).
58. Buyse, M. *et al.* PepT1-mediated epithelial transport of dipeptides and cephalexin is enhanced by luminal leptin in the small intestine. *J. Clin. Invest*. **108**, 1483–1494 (2001).
59. Tarzi, R. M., Cook, T. H., Jackson, I., Pusey, C. D. & Lord G. M. Leptin-deficient mice are protected from accelerated nephrotoxic nephritis. *Am. J. Pathol*. **164**, 385–390 (2004).
60. Matarese, G. *et al.* Leptin accelerates autoimmune diabetes in female NOD mice. *Diabetes* **51**, 1356–1361 (2002).
61. Gaetke, L. M., Oz, H. S., Frederich, R. C. & McClain, C. J. Anti-TNF-α antibody normalizes serum leptin in IL-2 deficient mice. *J. Am. Coll. Nutr*. **22**, 415–420 (2003).
62. Matarese, G. *et al.* Leptin potentiates experimental autoimmune encephalomyelitis in SJL female mice and confers susceptibility to males. *Eur. J. Immunol*. **31**, 1324–1332 (2001).
63. Ozata, M., Ozdemir, I. C. & Licinio, J. Human leptin deficiency caused by a missense mutation: multiple endocrine defects, decreased sympathetic tone, and immune system dysfunction indicates 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*. **84**, 3686–3690 (1998).
64. Matarese, G. *et al.* Increased leptin levels in serum and peritoneal fluid of patients with pelvic endometriosis. *J. Clin. Endocrinol. Metab*. **85**, 2483–2487 (2000).
65. Uygun, A. *et al.* Serum leptin levels in patients with nonalcoholic steatohepatitis. *Am. J. Gastroenterol.* **95**, 3584–3589 (2000).
66. Schols, A. M. *et al.* Plasma leptin is related to pro-inflammatory status and dietary intake in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med*. **160**, 1220–1226 (1999).
67. Stein, R. B., Lichtenstein, G. R. & Rombeau, J. L. Nutrition in inflammatory bowel disease. *Curr. Opin. Clin. Nutr. Metab. Care* **2**, 367–371 (1999).
68. Stenvinkel, P. *et al.* Increases in serum leptin levels during peritoneal dialysis are associated with inflammation and a decrease in lean body mass. *J. Am. Soc. Nephrol*. **11**, 1303–1309 (2000).
69. Evereklioglu, C. *et al.* Serum leptin concentration is increased in patients with Behcet's syndrome and is correlated with disease activity. *Br. J. Dermatol*. **147**, 331–336 (2002).
70. Sera, N. *et al.* Thyroid hormones influence serum leptin levels in patients with Graves' diseas during suppression of β-adrenergic receptors. *Thyroid* **10**, 641–646 (2000).
71. Mazziotti, G. *et al.* High leptin levels in women developing post-partum thyroiditis. *Clin. Endocrinol*. **60**, 208–213 (2004)
72. Ahmed, M. L. *et al.* Elevated leptin levels are associated with excess gains in fat mass in girls, but not in boys, with type 1 diabetes: longitudinal study during adolescence. *J. Clin. Endocrinol. Metab*. **86**, 1188–1193 (2001).
73. Bokarewa, M., Bokarew, D., Hultgren, O. & Tarkowski, A. Leptin consumption in the inflamed joints of patients with rheumatoid arthritis. *Ann. Rheum. Dis*. **62**, 952–956 (2003).
74. Anders, H. J., Rihl, M., Heufelder, A., Loch, O. & Schattenkirchner, M. Leptin serum levels are not correlated with disease activity in patients with rheumatoid arthritis. *Metabolism* **48**, 745–748 (1999).
75. Chalasani, N. *et al.* Does leptin play a role in the pathogenesis of human nonalcoholic steatohepatitis? *Am. J. Gastroenterol*. **98**, 2771–2776 (2003).
76. Takabatake, N. *et al.* Circulating leptin in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **159**, 1215–1219 (1999).
77. Hoppin, A. G. *et al.* Serum leptin in children and young adults with inflammatory bowel disease. *J. Pediatr. Gastroenterol. Nutr.* **26**, 500–505 (1998).
78. Fraser, D. A., Thoen, J., Reseland, J. E., 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*. **18**, 394–401 (1999).
79. Kjeldsen-Kragh, J. *et al.* Controlled trial of fasting and one year vegetarian diet in rheumatoid arthritis. *Lancet* **338**, 899–902 (1991).
80. Payne, A. Nutrition and diet in the clinical management of multiple sclerosis. *J. Hum. Nutr. Diet.* **14**, 349–357 (2001).
81. Beach, R. S., Gershwin, M. E. & Hurley, L. S. Nutritional factors and autoimmunity. III. Zinc deprivation versus restricted food intake in MRL/1 mice — the distinction between interacting dietary influences. *J. Immunol*. **129**, 2686–2692 (1982).
82. Johnson, B. C., Gajjar, A., Kubo, C. & Good, R. A. Calories versus protein in onset of renal disease in NZB x NZW mice. *Proc. Natl Acad. Sci. USA* **83**, 5659–5662 (1986).
83. Mizutani, H. *et al.* Calorie restriction prevents the occlusive coronary vascular disease of autoimmune (NZW x BXSB) F, mice. *Proc. Natl Acad. Sci. USA* **91**, 4402–4406 (1994).
84. Chandrasekar, B. *et al.* Effects of calorie restriction of transforming growth factor-β1 and proinflammatory cytokines in murine Sjogren's syndrome. *Clin. Immunol. Immunopathol.* **76**, 291–296 (1995).
85. Steinman, L., Conlon, P., Maki R. & Foster, A. The intricate interplay among body weight, stress, and the immune response to friend or foe. *J. Clin. Invest.* **111**, 183–185 (2003).
86. Kuchroo, V. K. & Nicholson, L. B. Fast and feel good? *Nature* **422**, 27–28 (2003).
87. 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*. **212**, 83–91 (2001).
88. Sanchez-Margalet, V. & Marin-Romero, C. Human leptin signaling in human peripheral blood mononuclear cells: activation of the JAK–STAT pathway. *Cell. Immunol*. **211**, 30–36 (2001).
89. Van den Brink, G. R. *et al*. Leptin signaling in human peripheral blood mononuclear cells, activation of p38 and p42/44 mitogen-activated protein (MAP) kinase and p70 S6 kinase. *Mol. Cell. Biol. Res. Commun*. **4**, 144–150 (2000).

Acknowledgements

This work was supported by the Fondazione Italiana Sclerosi Multipla (FISM) and Comitato Trenta Ore per la Vita (Mediaset), and the Arthritis National Research and Lupus Foundations. This work is dedicated to the memory of A. Di Tuoro.

Competing interests statement

The authors declare that they have no competing financial interests.

Online links

DATABASES

The following terms in this article are linked online to:

LocusLink: http://www.ncbi.nlm.nih.gov/LocusLink/

ACTH | CCL3 | CD49B | COX2 | CRH | CRP | CXCL2 | G-CSF | GLUT1 | GLUT4 | ICAM1 | IFN-γ | IL-1 | IL-6 | IL-18 | *ob* | OBR | OSM | STAT3 | TNF

Access to this interactive links box is free online.