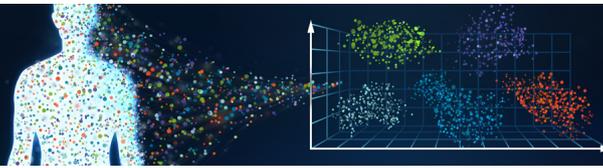


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BRIEF REVIEWS

Leptin in Immunology¹Giuseppe Matarese,^{2,3*} Stergios Moschos,^{2†} and Christos S. Mantzoros^{3‡}

Leptin is an adipokine which conveys information on energy availability. In humans, leptin influences energy homeostasis and regulates neuroendocrine function primarily in states of energy deficiency. As a cytokine, leptin also affects thymic homeostasis and, similar to other proinflammatory cytokines, leptin promotes Th1 cell differentiation and cytokine production. We review herein recent advances on the role of leptin in the pathophysiology of immune responses. The Journal of Immunology, 2005, 173: 3137–3142.

Living organisms require a relatively steady energy supply to sustain biological functions. Moreover, energy reserves must not only be sufficient to serve all physiological needs, but must also be wisely allocated to a wide variety of often competing physiological functions (1). Energy intake and energy expenditure undergo substantial daily and seasonal fluctuations, however.

Immunity requires adequate and balanced energy supply for optimal function (2). Although the risk of infection and death is highest when energy reserves are not sufficient (3), obesity, a state of energy excess, has also been associated with increased susceptibility to infection, bacteremia, and poor wound healing (4).

The discovery of the adipocyte-derived hormone leptin, the levels of which reflect the amount of energy stored in the adipose tissue and are altered by conditions such as fasting and overfeeding, has proved to be fundamental to our understanding of the concept of energy availability influencing several physiological systems. More specifically, leptin has been shown to play an important role in the regulation of neuroendocrine function and energy homeostasis (5) and other energy-demanding physiological processes, such as reproduction (6), hemopoiesis (7), and angiogenesis (8). We review herein accumulating evidence that leptin may also be playing an important role in the regulation of the immune system in energy- or leptin-deficient states.

Leptin and leptin signaling in immune cells

Leptin is mainly secreted by the adipose tissue, which is also present within both primary and secondary lymphoid organs and has a significant metabolic and immunomodulatory role (9, 10). Leptin's three-dimensional structure is similar to that of a cytokine consisting of a four α helix bundle motif which is common to the IL-6 family of cytokines (11). Leptin receptor (ObR), is also a member of the class I cytokine receptor superfamily and has at least six isoforms as a result of alternative splicing. All isoforms share an identical extracellular ligand-binding domain (12). Leptin's functional receptor (ObR_b) is expressed not only in the hypothalamus where it regulates energy homeostasis and neuroendocrine function, but also in all cell types of innate and adaptive immunity (13–16). The full-length b isoform (ObR_b) lacks intrinsic tyrosine kinase activity, is involved in several downstream signal transduction pathways, and has been identified in immune cells of both animals and humans (13) (Fig. 1). Leptin binding to its functional receptor recruits Janus tyrosine kinases and activates the receptor, which then serves as a docking site for cytoplasmic adaptors such as STAT (17). STATs translocate to the nucleus and induce expression of other genes, including negative regulators, such as the suppressor of cytokine signaling 3 (18) and the protein tyrosine phosphatase 1B (19). A number of studies in human PBMCs have shown that, in addition to the JAK-2-STAT-3 pathway, which is an important pathway mediating leptin's effect on immune cells, other pathways are also involved. The MAPK, the insulin receptor substrate 1, and the phosphatidylinositol 3'-kinase (PI3'K)⁴ pathways (20) are also important pathways that mediate leptin's action on immune T cells (21). Moreover, in PBMCs the MAPK pathway seems to mediate antiapoptotic effects (22), whereas the PI3'K pathway may be important in regulating glucose uptake (23). Src associated in mitosis protein (Sam68), an RNA-binding protein, regulator of RNA metabolism and effector of the PI3'K is currently thought to function as an adaptor protein by binding to activated STAT-3 and to the p85 subunit of PI3'K (20) (Fig. 1).

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⁴ Abbreviations used in this paper: PI3'K, phosphatidylinositol 3'-kinase; EAE, experimental autoimmune encephalomyelitis; rmetHuLeptin, recombinant human leptin.

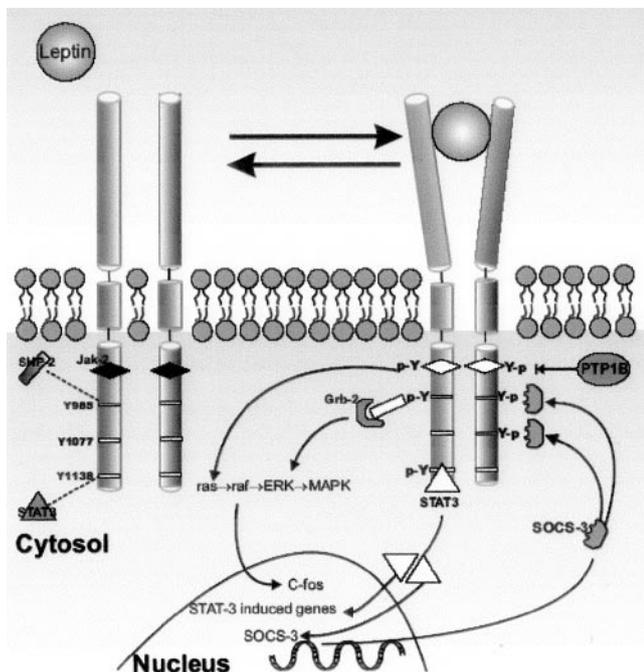


FIGURE 1. Leptin receptor signaling (long isoform). The leptin receptor has three conserved tyrosines in its cytoplasmic domain, which, in the murine receptor, correspond to positions Y985, Y1077, and Y1138. Leptin signaling occurs typically through the JAK-STAT pathway. After ligand-induced clustering, leptin receptor predominantly activates JAK-2 (white rhombus), although JAK-1 has also been demonstrated to be activated in some settings. JAK-2 phosphorylates these three conserved tyrosines, including the Y1138, which serves as a docking site for STAT-3. STAT-3 becomes activated (white triangle), homodimerizes, and translocates to the nucleus, resulting in induction of specific genes. It is unclear whether STAT-3 is the only STAT that is activated upon stimulation. Src homology 2-containing phosphatase is recruited to the Y985 position, becomes activated (white triangle), and activates the MAPK pathway through the adapter protein Grb-2, ultimately inducing *c-fos* expression. One of the STAT-3-induced genes is suppressor of cytokine signaling 3 which, through the proximal Y985 and Y1077, is involved in regulation and attenuation of leptin signaling. Phosphotyrosine phosphatase 1B is localized on the surface of the endoplasmic reticulum and is also involved in negative regulation of leptin receptor signaling through dephosphorylation of JAK-2.

The role of leptin in innate and adaptive immunity

Mice lacking leptin or its functional receptor have a number of defects in both cell-mediated and humoral immunity (24, 25). Similarly, humans with congenital leptin deficiency have a much higher incidence of infection-related death during childhood (26), whereas recombinant human leptin (rmetHuLeptin) administration in two children with congenital leptin deficiency normalized absolute numbers of naive CD4⁺CD45RA⁺ T cells and nearly restored the proliferation response and the cytokine release profile from their lymphocytes (27). A number of studies in mice have shown that the effect of leptin on the immune system is both direct and indirect, i.e., via modulation of central or peripheral pathways (28, 29).

Leptin has a well-established role in all cells involved in innate immunity, which “inflexibly” senses either specific pathogen-associated molecular patterns, formally not expressed by host tissues, or endogenous molecules released from “stressed” cells. In macrophages/monocytes, leptin up-regulates phagocytic function (30) via phospholipase activation (31) as well as proinflammatory cytokine secretion, such as TNF- α (early), IL-6 (late), and IL-12 (32, 33). Leptin stimulates the prolifera-

tion of human circulating monocytes in vitro and up-regulates expression of activation markers, such as CD25 (α -chain of IL-2 receptor), CD71 (transferring receptor), CD69, and CD38, while it further increases the expression of other activation markers already present at high levels on the surface of resting monocytes, such as HLA-DR, CD11b, and CD11c (28). In polymorphonuclear cells of healthy subjects, leptin stimulates reactive oxygen species production (16) and chemotaxis (34) via a mechanism that may involve interaction with monocytes (35). In NK cells, leptin is involved in all processes of cell development, differentiation, proliferation, activation, and cytotoxicity (36). The effect is mediated at least via STAT-3 activation and up-regulated expression of perforin and IL-2 genes (14).

The effect of leptin in adaptive immunity, which is mediated by lymphocytes that predominantly recognize peptide-MHC complexes and provides a broad range of immune responses against molecular structures other than carbohydrates in mice, is also well studied. Leptin may induce lymphopoiesis in mice (7), and leptin also provides a survival signal for the double-positive CD4⁺CD8⁺ and the single-positive CD4⁺CD8⁻ thymocytes during T lymphocyte maturation (37).

Studies in humans have further delineated the role of leptin in activation of lymphocytes. In contrast to macrophages/monocytes, leptin alone is unable to induce proliferation and activation of mature human peripheral blood lymphocytes unless it is coadministered with other nonspecific immunostimulants, in which case leptin results in induction of early (CD69) and late activation markers (CD25, CD71) in both CD4⁺ and CD8⁺ lymphocytes (38). The proliferative effect of leptin seems to be specific only for distinct lymphocyte subpopulations, however. More specifically, leptin induces proliferation of the naive CD4⁺CD45RA⁺ T cells, but inhibits proliferation of the CD4⁺CD45RO⁺ T cells (39). At the functional level, leptin polarizes Th cytokine production toward a proinflammatory (Th1, IFN- γ \pm IL-2) rather than anti-inflammatory phenotype (Th2, IL-4) (13, 38). These effects may be mediated by promoting T lymphocyte survival by up-regulating expression of antiapoptotic proteins, such as Bcl-x_L (40) and T-bet (39), and synergize with other cytokines in lymphocyte proliferation and activation possibly via STAT3 (41, 42).

Leptin and states of immune dysfunction: energy deficiency and energy excess

The above-described “permissive” or potentiating role of leptin in the function of the immune system could be clinically relevant in several nutrition deficiency states, as well as inflammatory and autoimmune phenomena. Energy restriction results in significant reduction of leptin levels and altered ObR_b mRNA expression in rat splenocytes (43). Exogenous leptin replacement modulates T cell responses in mice and prevents starvation-induced immunosuppression (13) and alters thymic cellularity and lymphoid atrophy (37). In humans, congenital leptin deficiency has been associated with childhood infections and early mortality (26), as well suppressed lymphocyte subpopulations and Th1 immunity, conditions which were reversed with exogenous leptin administration (27). In controlled studies, decreased serum leptin levels have also been associated with suppressed lymphoproliferative responses whereas proinflammatory Th1 cytokine production in malnourished infants were reversed after 10% weight gain (44) which also increased leptin

levels. Finally, leptin was positively correlated with CD4⁺ levels in children infected with HIV (45).

In this context, we have recently shown that leptin administration to women with exercise-induced relative energy and leptin deficiency improves not only neuroendocrine but also immune function in the Th1 direction (46). Whether administration of leptin will be effective in enhancing Th1 responses or morbidity/mortality from other conditions that have long been associated with protein calorie malnutrition, such as tuberculosis, remains to be studied.

The role of leptin in regulating the immune system of obese subjects who have a higher incidence of infections remains less well defined. Leptin levels are increased and mRNA expression of the ObR_b receptor isoform may be decreased in diet-induced obese vs control rats, indicating a state of leptin resistance (43). In rodent models of diet-induced obesity, thymic lymphopenia, lower mitogenic response of splenocytes, and suppressed NK cytotoxic activity have been observed (47). Similarly, in obese subjects, T lymphocyte subpopulations (CD3⁺, CD4⁺ CD45RO⁺, CD8⁺) and their proliferative response to polyclonal mitogens are also suppressed (48). These immune abnormalities are reversed with energy restriction (which decreases leptin levels) in both humans and animals (43). Although the exact mechanism for these immune defects in obesity remains largely unknown, leptin levels are correlated not only with the organism's energy status but also with serum TNF- α levels which are also elevated in obesity and have a suppressive effect on lymphocyte function (48, 49). We have recently completed the first interventional studies involving leptin administration to subjects with leptin sufficiency or excess (obesity). Our data indicate that although STAT-3 (but not MAPK) was activated after exogenous leptin administration in obese subjects (46), no direct link between leptin and any alterations of the immune system associated with obesity could be established (50). More work is thus needed to fully elucidate the role of leptin in the immune system of the obese and to further delineate the signaling pathways activated by leptin in lean and obese subjects in health and disease.

Leptin, inflammation, and enhanced anti-self-immune responses

The role of leptin in inflammation remains incompletely understood. Animal models of leptin deficiency are protected from the toxic effects of innate immunity-mediated inflammation (i.e., monocytes/macrophages, polymorphonuclear cells, NK cells, LPS (51, 52), TNF- α (53), zymosan-induced arthritis (54)). The mechanism for this presumed anti-inflammatory effect of leptin deficiency is unknown, but an imbalance between proinflammatory (unchanged) and anti-inflammatory cytokines (IL-10 and IL-1R antagonist are reduced) has been noted (51), raising the hypothesis that leptin may alter the production of anti-inflammatory cytokines by monocytes/macrophages via STAT-3 activation (55). In animals with adaptive immunity-mediated inflammation (lymphocytes) (Con A-induced hepatitis (56, 57), *Clostridium difficile* toxin A-induced enteritis (58), Ag-induced arthritis (59), or other autoimmune disease, see below), leptin deficiency has a protective effect by resulting in reduced production of proinflammatory Th1 cytokines (57) and a shift toward a Th2 response (59). Importantly, inflammatory cells may themselves express and secrete leptin which may further foster the inflammatory process (60, 61).

Several groups have investigated the susceptibility of *ob/ob* and *db/db* mice to experimentally induced autoimmune diseases (56–59, 61–65). *Ob/ob* mice are resistant to both actively and passively induced experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis but, consistent with leptin's Th1-promoting activities, these mice become susceptible to the disease after leptin administration (63). Resistance to EAE in *ob/ob* mice is associated with a reduced proliferative response to myelin Ags and with an increased IL-4 response, whereas leptin replacement converted the Th2 toward a Th1-type cytokine response, leading to secretion of IFN- α and to an IgG1-to-IgG2a isotype shift switch. Leptin administration to susceptible wild-type mice also worsened the disease by increasing both proinflammatory cytokine levels and IgG2a production. Furthermore, infiltrating T cells and macrophages in the CNS lesions stain positive for production of immunoreactive leptin, suggesting that leptin is also produced by immune cells during acute EAE (Fig. 2A).

In an animal model of intestinal autoimmune inflammation in which common confounding factors of altered immune response were controlled for (66), it was demonstrated that T cells from leptin-resistant *db/db* mice display reduced capacity to induce colitis upon passive transfer in T cell-deficient mice (*scid* mice). Transfer of T cells from *db/db* mice induced only delayed disease compared with transfer of wild-type cells. Histological examination of the colon, early after the induction of disease, revealed marked inflammation in mice injected with wild-type cells, whereas no inflammation was observed in mice receiving *db/db* cells (66). These data suggest that leptin may prove to be a pivotal mediator in intestinal inflammation (58).

The role of leptin has also been investigated in spontaneous models of autoimmunity, such as type 1 diabetes, and NOD

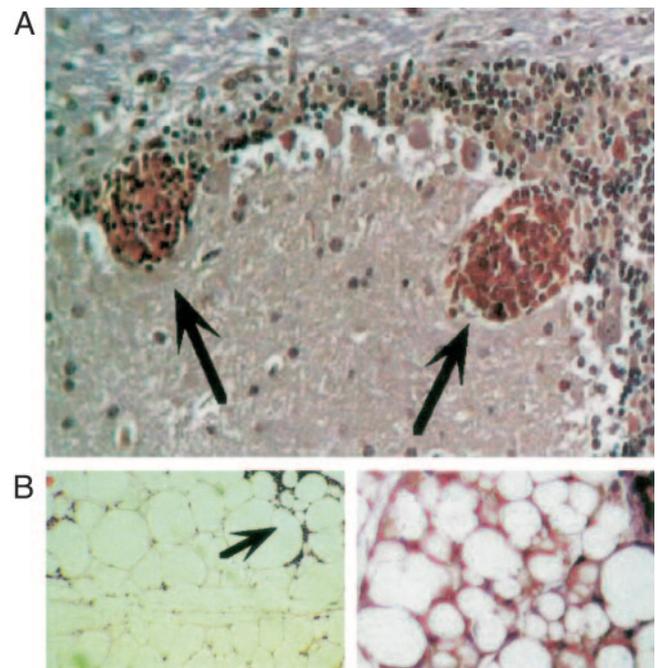


FIGURE 2. *A*, Section of brain (cerebellum) showing two infiltrates staining positive for leptin secretion by inflammatory T cells (arrows) during EAE, indicating leptin secretion by inflammatory cells during the acute phase of CNS autoimmunity. *B*, Section of mouse adipose tissue showing the presence of mononuclear immune cells (arrow). The same adipose tissue is also stained with an anti-leptin Ab (brown), consistent with massive leptin secretion by adipocytes (right).

(NOD/LtJ) mice as well as in relation to the gender-related difference in susceptibility to autoimmune diseases. More specifically, leptin administration significantly increases inflammatory infiltrates in pancreatic islets, increases IFN- γ production by T cells, anticipates the onset of type 1 diabetes, increases mortality, and increases inflammatory infiltrates in pancreatic islets (65). Mouse strains spontaneously developing autoimmune diseases, such as the NOD/LtJ and the IL-2-deficient mice, have increased basal serum leptin before the development of disease onset (45, 65, 67) and reduced numbers of circulating regulatory T cells (68). In humans, the prevalence of autoimmune diseases (i.e., multiple sclerosis, rheumatoid arthritis, thyroiditis, and systemic lupus erythematosus) is increased in females (69), as are serum leptin levels. Recent clinical reports on patients with autoimmune diseases demonstrate that high serum leptin levels may be either a contributing factor (70–72) or a marker of disease activity (73–75), and hypocaloric diets, which decrease serum leptin levels, may have a beneficial role in the control of autoimmunity in humans (70), but whether these associations are causal has not yet been tested.

Obesity, a hyperleptinemic state, is increasingly being considered a chronic proinflammatory state associated with progressive adipose tissue infiltration by macrophages (60, 76) (Fig. 2B and Fig. 3) that secrete proinflammatory cytokines (TNF- α , IL-1 β , and IL-6), which in turn stimulate adipocytes to further secrete leptin and proinflammatory cytokines such as TNF- α ; leptin levels are thus associated with several proinflammatory cytokines (77–79). To prove or disprove whether the above associations reflect a causal role for leptin, we have re-

cently performed interventional studies involving rmetHuLeptin administration to normal and obese humans. We demonstrated that rmetHuLeptin administration to increase circulating leptin levels to high physiological or pharmacological levels does not materially alter proinflammatory cytokine levels or immune function in subjects with leptin sufficiency or excess (obesity) (50). Thus, similar to neuroendocrine function, the main role of leptin may be to regulate immune function in leptin-deficient and not leptin-sufficient states in humans.

Future directions

In summary, although a growing body of evidence indicates that leptin may play an important role as the link between energy homeostasis and the immune system accounting for several of the neuroimmunoendocrine abnormalities during nutrition deficiency states, a number of questions remain unanswered.

What is the effect of leptin on the function of the immune system in obesity or other leptin-resistant states? In vitro studies in diet-induced obese mice have shown that LPS stimulates proliferation of cultured splenocytes and that PHA stimulated production of certain cytokines (IFN- γ and IL-10), but not all (IL-2) (80). In vivo studies in fasting diet-induced obese mice showed that leptin administration prevents pre- and poststarvation reduction in spleen weight compared with lean controls, but does not affect cytokine production (IL-2, IL-10, IFN- γ) in these mice, implying that the effect of leptin on immune cells in the obese state may be insignificant (81). Although our initial studies in humans (see above) are consistent with these findings in mice, it remains to be fully examined to which extent leptin

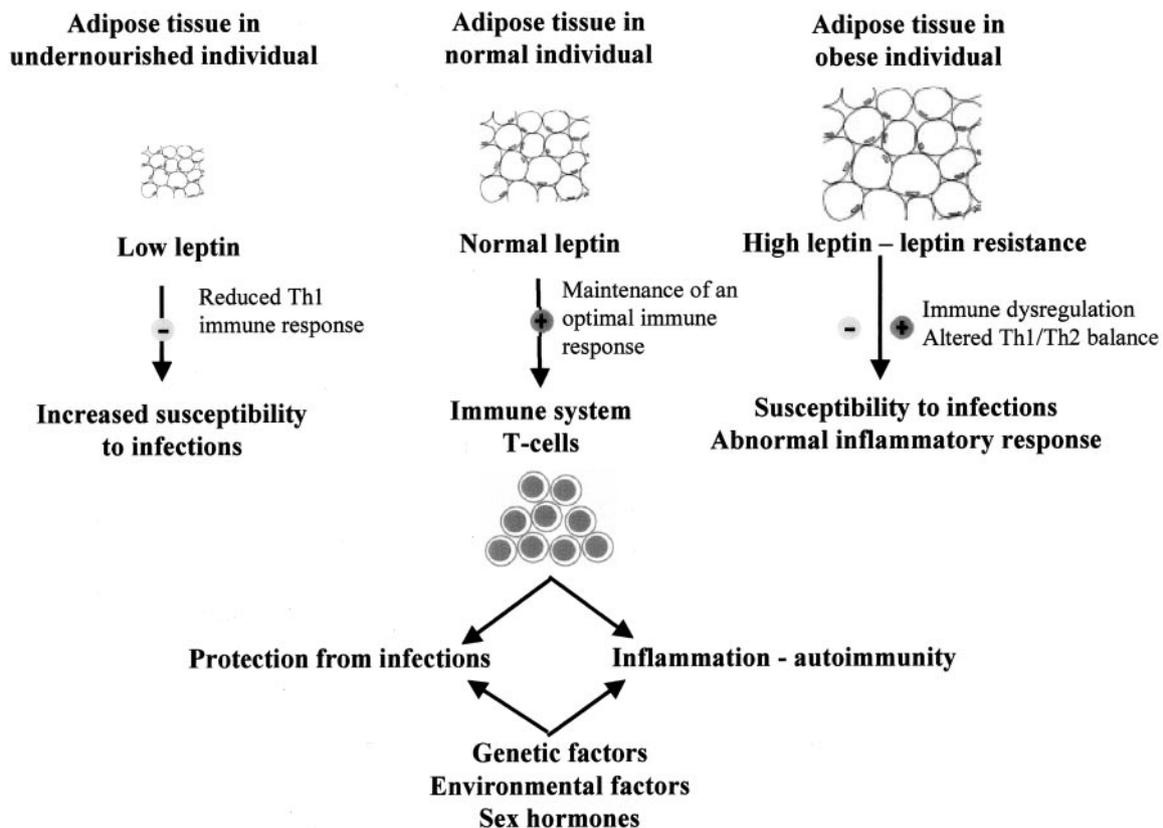


FIGURE 3. Possible model of leptin action on infection susceptibility and autoimmunity that needs to be further investigated. In undernourished individuals (*left*) low adipocyte mass causes a reduction in serum leptin and consequent impairment of the Th1 immune response; in non-leptin-deficient obese individuals (*right*), high leptin levels reflect leptin resistance and ObR down-regulation. This could possibly lead to immune dysregulation and alteration in the Th1/Th2 balance. In normal individuals (*middle*), the presence of leptin sustains and regulates an optimal immune response.

influences the immune system and/or contributes to infections more frequently seen in patients with obesity. Thus, carefully designed studies in obese humans are needed.

Can exogenous leptin administration potentiate the immune system in energy-deficient states and, if yes, under which conditions and in which population of subjects? Exogenous leptin administration in subjects with congenital leptin deficiency restored CD4⁺ counts and proliferative responses, and we have shown that exogenously administered rmetHuLeptin to subjects with acquired leptin deficiency (exercise-induced energy deficiency of several years duration) improves their circulating cytokine levels. Energy and thus leptin deficiency models, such as anorexia nervosa, eating disorders, or exercise-induced energy deficiency, can be useful models to address the impact of chronic caloric deprivation and associated reduction of serum leptin levels on the immune function. Therefore, it would be very interesting to study in detail the immune function of the above groups of subjects and the impact of leptin on their immune system (46). Would exogenous rmetHuLeptin administration improve lymphocyte subpopulations, proliferation, or immune function assessed by other detailed methods in this model of chronic leptin deficiency? Would rmetHuLeptin administration induce or exacerbate inflammation, based on clinical or laboratory grounds, in subjects with normal or low leptin levels at a steady state? Only detailed, interventional studies utilizing rmetHuLeptin administration to humans can answer these questions. Finally, what is the role of leptin in other models of energy/leptin deficiency such as HIV-lipoatrophy or advanced cancer? Such patients exhibit a poorly functioning immune system, a higher percentage of apoptotic PBMCs, and lower levels of leptin and IL-2, probably as a result of cachexia (82) which has been correlated with both severity of disease and poor survival. What would be the effect of rmetHuLeptin administration in the immune system preservation and/or effect in overall survival? Carefully designed studies in humans are expected to answer all of these clinically important questions in the near future.

If leptin's role is fundamental in Th1-mediated autoimmune diseases or inflammatory diseases, such as inflammatory bowel syndrome, would any therapeutic effect be anticipated by blocking peripheral leptin action (83)? Moreover, what would be the effect, immunosuppressive or other, of antileptin therapy in the innate vs the adaptive arms of immunity? Is there a role for anti-leptin blocking Abs in the treatment of disease states such as intestinal inflammation in humans?

Great progress has been achieved in understanding leptin's role in vitro or in studies in animals. Although several observational studies in humans have raised important hypotheses, it is only through well-designed interventional studies in humans that any causal role for leptin in the physiology and pathophysiology of the immune system in humans can be elucidated. Similarly interventional studies in humans are also needed to clearly define whether rmetHuLeptin will eventually find a position in our therapeutic armamentarium for the treatment of immune diseases.

Disclosures

The authors have no financial conflict of interest.

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