The intricate interface between immune and metabolic regulation: a role for leptin in the pathogenesis of multiple sclerosis?

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Abstract: Over the last few years, a series of molecules known to play a function in metabolism has also been shown to play an important role in the regulation of the immune response. In this context, the adipocyte-derived hormone leptin has been shown to regulate the immune response in normal as well as in pathological conditions. More specifically, it has been shown that conditions of reduced leptin production (i.e., genetic leptin deficiency, anorexia nervosa, malnutrition) are associated with increased susceptibility to infections. Conversely, immune-mediated disorders such as autoimmune disorders are associated with increased secretion of leptin and production of proinflammatory, pathogenic cytokines. Leptin could represent the “missing link” among immune response, metabolic function, and nutritional status. Indeed, more recently, leptin-deficient mice have been shown to be resistant to a series of experimentally induced autoimmune disorders including experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis. Normal wild-type mice show increased secretion of leptin in serum upon EAE induction, and brain inflammatory infiltrates stain positive for leptin. Finally, leptin neutralization with leptin antagonists improves the EAE course by profoundly altering intracellular signaling of myelin-reactive T cells and increasing the number of regulatory forkhead/winged helix transcription factor 3/FOXP3+CD4+ T cells. These data suggest that leptin can be considered as a link among immune tolerance, metabolic state, and autoimmunity and that strategies aimed at interfering with the leptin axis could represent innovative, therapeutic tools for autoimmune disorders. J. Leukoc. Biol. 84: 893–899; 2008.

Key Words: autoimmunity · multiple sclerosis · Treg · Th1

INTRODUCTION

Organisms require a sufficient energy supply to sustain biological functions. Energy reserves serve to a series of physiological needs and must also be wisely allocated to a wide variety of often-competing, physiological functions. Also, immunity requires adequate and balanced energy supply for optimal function. Although the risk of infection and death is highest when energy reserves are not sufficient, obesity, a state of energy excess, has also been associated with increased susceptibility to infections and poor wound-healing [1]. 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 proven to be fundamental to our understanding of the concept of energy availability influencing several physiological systems. The study of leptin has shown the intricate network that links nutrition, metabolism, and immune homeostasis [2]. 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. 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 [3]. Indeed, leptin-deficient [obese (ob/ob)] mice and leptin receptor-deficient [diabetes mellitus (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 [4], hematopoiesis [5], angiogenesis [6], insulin secretion [2], metabolism of bone [7], lipids and glucose, and last but not least, innate and adaptive immunity.

LEPTIN AS AN IMMUNOENDOCRINE MEDIATOR

Leptin is a 16-kDa nonglycosylated protein encoded by the ob gene, which is located on human chromosome 7 and on mouse chromosome 6. In humans and mice, mutations of the ob gene are associated with hyperphagia and obesity, reduced energy expenditure, and other reproductive, neuroendocrine, and metabolic dysfunctions. Serum leptin is usually higher in obese individuals with increased fat mass and lower in individuals with lower fat mass and higher fat-free mass.
individuals and has a strong sexual dimorphism—higher in females than males matched by age and body weight [2]. Leptin is classically considered a hormone, as it regulates the balance between food intake and energy expenditure, signaling to the brain the changes in stored energy. Serum leptin is correlated directly with the body-fat stores, increasing with fat accumulation and decreasing during fasting. Leptin gene expression is regulated by several factors, including other hormones such as insulin, glucocorticoids, and sex hormones. Insulin stimulates leptin secretion during feeding, and a decrease in insulin levels anticipates a fall in leptin during starvation. Glucocorticoids also operate synergistically with insulin in the secretion of leptin from cultured adipocytes, although an inverse relationship between leptin and glucocorticoids is generally observed [2]. Finally, leptin expression is inhibited by testosterone, increased by ovarian sex steroids, and directly influences the hypothalamic-pituitary-adrenal axis, the reproductive system, hematopoiesis, and angiogenesis. A series of studies has linked the immune and neuroendocrine systems. Leptin is one of the mediators that is common to the neuroendocrine and immune systems [8]. In the immune system, leptin, together with C-reactive protein (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 [2, 9, 10]. 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, and HIV infection and during anti-inflammatory therapy [11–13]. 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 estrogens increase its production). 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 [2]. The fact that leptin has effects on neuroendocrine and immune systems should not come as a surprise, given the functional connection and anatomical contiguity between adipocytes and lymphoid cells [3]. Morphologically, aggregations of lymphoid tissue, including the lymph nodes, omentum, thymus, and bone marrow, are associated with adipose tissue [3]. Fat deposits do not simply have a structural, metabolic, and heat-insulating function but also provide a microenvironment that helps the immune system to sustain immune responses. In particular, lymphoid and adipose tissues interact locally through common mediators known as adipokines, adipocyte-derived molecules that bridge metabolism, and immune homeostasis (these molecules include leptin, adiponectin, chemokines, and other proinflammatory cytokines).

MOLECULAR SIGNALING OF LEPTIN IN IMMUNE CELLS

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-3 and IL-6 family of cytokines [14]. Leptin receptor (OBR) is also a member of the class I cytokine receptor superfamily and has at least six splice forms as a result of alternative splicing with cytoplasmatic domains of different lengths, known as OBRa, OBRb, OBRc, OBRd, OBRe, and OBRf [15, 16]. The short forms of the leptin receptor are expressed by several nonimmune 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 secretion of neuropeptides and neurotransmitters that regulate appetite, body weight [2, 15, 16], and bone mass. Interestingly, OBRb is also expressed by endothelial cells, pancreatic β cells, the ovary, CD34+ hematopoietic bone marrow precursors, monocytes/macrophages, and T and B cells [2, 6, 7, 15–19]. After binding leptin, OBRb-associated JAK2 becomes activated by auto- or cross-phosphorylation, and tyrosine phosphorylates the cytoplasmic domain of the receptor. Four of the phosphorylated tyrosines residues function as docking sites for cytoplasmic adaptors such as STAT factors, particularly STAT3 (in some cases, also STAT1 and STAT5) [20–22]. 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 signaling 3 (SOCS3) and other genes. SOCS3 takes part in a feedback loop that inhibits leptin signaling by binding to phosphorylated tyrosines. SRC homology 2 domain-containing phosphatase 2 is recruited to Tyr985 and Tyr974 and activates ERK1/2 and p38 MAPK pathways through the adaptor protein growth factor receptor-bound protein 2, ultimately inducing the expression of FOS and JUN. After leptin binding, JAK2 can induce phosphorylation of the insulin receptor substrate 1/2 proteins, which are responsible for the activation of PI-3K [15, 16, 20–24]. Moreover, Src associated in mitosis 68 kDa, an RNA-binding protein, regulator of RNA metabolism, and effector of the PI-3K, is currently thought to function as an adaptor protein by binding to activated STAT3 and to the p85 subunit of PI-3K. Phosphotyrosine phosphatase 1B, which is localized on the surface of the endoplasmic reticulum, is involved in negative regulation of OBR signaling through the dephosphorylation of JAK2 after internalization of the OBRb complex.

LEPTIN IN IMMUNITY

Humans with congenital leptin deficiency have a much higher incidence of infection-related death during childhood [25], whereas recombinant human leptin administration in children with congenital leptin deficiency normalized absolute numbers of naive CD4CD45RA T cells and nearly restored the proliferation response and the cytokine release profile from their lymphocytes [26]. Studies in mice have shown that the effect of leptin on the immune system is direct and indirect, i.e., via modulation of central or peripheral pathways. The effects of leptin on adaptive immune responses have been investigated extensively on human CD4+ T cells. Addition of physiological concentrations of leptin to a MLR induces a dose-dependent increase in CD4+ T cell proliferation [18] (Fig. 1). However,
leptin has different effects on proliferation and cytokine production by human naive (CD45RA+/H11001) and memory (CD45RO+/H11001) CD4+/H11001 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 toward Th1 cell responses). 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 [18]. 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 [18, 27, 28]. The thymic atrophy in ob/ob mice (or wild-type, starved animals) affects the cortex of the thymus, in which most CD4+/H11001CD8+/H11001 T cells are found, and leptin replacement reduces the rate of apoptosis of such cells [27].

Despite the evidence of direct effects of leptin on immune responses in vitro, a major problem remains 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. It is notable that T cells are sensitive to the supply of cellular nutrients, such as glucose [29], as they do not have glycogen stores and therefore, depend on the import of extracellular glucose to meet their metabolic needs [30]. By stimulating glucose uptake through ERK1/ERK2- and PI-3K-dependent pathways, leptin might help to restore the impaired T cell function caused by starvation [18]. 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 [30].

In innate immunity, leptin seems to promote activation of and phagocytosis by monocytes/macrophages and their secretion of leukotriene B4 (LTB4), cyclooxygenase 2 (COX2), NO, and proinflammatory cytokines [31]. The products of the inducible form of COX2—PGs and LTs (also known as eicosanoids)—as well as NO are involved in the regulation of inflammation, chemotaxis, and cytokine production and therefore, markedly impact the immune response. Moreover, leptin can induce chemotaxis of neutrophils and the release of oxygen radicals (such as superoxide anion and hydrogen peroxide) [31]. 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 [32, 33]. Leptin also affects NK cell development and activation in vitro and in vivo [34–36]. 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 STAT3 and the transcription of genes encoding IL-2 and perforin. Last but not least, it has recently been shown that leptin can stimulate the production of the growth hormone by PBMCs through protein kinase C- and NO-dependent pathways [37]. This effect of leptin on the production of the 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.

LEPTIN IN AUTOIMMUNITY: A POSSIBLE ROLE IN THE PATHOGENESIS OF MULTIPLE SCLEROSIS (MS)?

MS is a chronic, immune-mediated, inflammatory disorder of the CNS [38]. The most-studied model of MS in animals is experimental autoimmune encephalomyelitis (EAE), in which autoimmunity to CNS components is induced in susceptible strains of mice through immunization with self-antigens derived from basic myelin protein. The disease is characterized by autoreactive T cells that traffic to the brain and to the spinal cord and injure the myelin sheaths of the CNS, with the result of chronic or relapsing-remitting paralysis (depending on the antigen and the strain of mice used). It has long been known that myelin-reactive Th1 CD4+ cells can induce and/or transfer disease, and Th1 cytokines are elevated in the CNS inflammatory lesions of EAE. In contrast, Th2 cytokines typically associate with recovery from EAE and/or protection from the disease [38]. It has been shown that leptin is involved in the induction and in the progression of EAE [39, 40]. Leptin-deficient mice are resistant to induction of active and adoptively transferred EAE. This protection is reversed by leptin administration and associates with a switch from Th2- to Th1-type responses and a IgG1-to-IgG2a isotype switch. Similarly, in susceptible wild-type C57BL/6J mice, leptin worsens disease by increasing IFN-γ release and IgG2a production [39]. Importantly, a surge of serum leptin anticipates the onset of clinical manifestations of EAE. The peak of serum leptin correlates with inflammatory anorexia, weight loss, and the development of pathogenic T cell responses against myelin. Lymphomononuclear infiltrates in the CNS of EAE mice indicate in situ production of leptin in active, inflammatory lesions, thus representing a significant local source of leptin [40]. Systemic and/or in situ leptin secretion were instead lacking in EAE-resistant mice. Taken together, these data suggest an involvement of leptin in CNS inflammation in the EAE model of MS (Fig. 1). Indeed, recent evidence by De Rosa et al. [41] showed that leptin neutralization (with antileptin mAb) was able to improve clinical onset, progression, and clinical relapses of actively induced and passively transferred EAE. This effect was associated with marked inhibition of DTH reaction against proteolipid protein139–151 peptide, CD4+ T cell hyporesponsiveness, and increased IL-4 and IL-10 production against myelin antigens. Forkhead/winged helix transcription factor 3 (Foxp3; a selective marker for Treg cells, a cellular subpopulation known to be involved in the control of immune tolerance) expression was also induced on CD4+ T cells in leptin-neutralized mice, suggesting the induction of a regulatory phenotype. At the biochemical level, T cell hyporesponsiveness, induced by leptin neutralization, might be explained by the failure to down-modulate the anergy factor kinase inhibitor p27 (p27kip1) and by the increase in the tyrosine phosphorylation levels of ERK1/2 and STAT6 (a factor well known to be able to induce the transcription of IL-4 and associated with a classical Th2/regulatory-type cytokine response during EAE) [41].

In human MS, it has been reported that the secretion of leptin is increased in serum and cerebrospinal fluid (CSF) of naive-to-treatment patients with MS, an aspect that positively correlates with the secretion of IFN-γ in the CSF and inversely correlates with the percentage of circulating Treg cells, a subset of lymphocytes that is known to dampen the autoimmune response mediated by Teff cells and that is reduced in patients with MS as compared with healthy, matched controls. Of note, the number of peripheral Treg cells in patients with MS inversely correlates with the serum levels of leptin, suggesting a link between the number of Treg cells and leptin secretion [42]. Considering that Treg cells are generated in the thymus, it is not known whether peripheral leptin or that produced in the perithymic adipose tissue could affect Treg cell generation/function in autoimmunity-prone subjects. This aspect is not defined yet and is the object of current, extensive investigation. In any case, the fact that increased leptin secretion occurs in acute phases of MS and correlates with CSF production of IFN-γ is of possible interest for the pathogenesis and clinical follow-up of patients with MS. As mentioned before, increased leptin secretion is present in the serum and in the CSF of patients with MS and does not correlate with body mass index (BMI) [42]. The increase of leptin in the CSF is higher than in the serum, suggesting possible secondary in situ synthesis of leptin in the CNS and/or an increased transport across the blood-brain-barrier following enhanced systemic production. A recent gene microarray analysis of Th1 lymphocytes from active MS lesions has shown elevated transcripts of many genes of the neuroimmunoendocrine axis, including leptin [43], and leptin transcripts were also abundant in gene expression profiles of human Th1 clones, confirming that leptin gene transcription is induced concomitantly with the polarization toward Th1 responses, which are often involved in T cell-mediated autoimmune diseases, including MS. Moreover, in situ secretion of leptin near inflammatory T cells and macrophages was observed in active EAE lesions [40]. A possible explanation for the in situ, elevated levels of leptin in the CSF of patients with MS could be the inflammatory cell itself, as suggested by studies with autoreactive human myelin basic protein (hMBP)-specific T cells from patients with MS that produced leptin and up-regulated the expression of the leptin receptor after activation [40, 42]. Antileptin and antileptin receptor-blocking antibodies reduced the proliferative responses of the hMBP-specific T cell lines to antigen stimulation, underlying a possibility of leptin-based intervention on this autocrine loop to block autoreactivity. Finally, recent reports have shown increased secretion of serum leptin before relapses in patients with MS during treatment with IFN-β and a capacity of leptin to enhance in vitro secretion of TNF-α, IL-6, and IL-10 from PBMCs of patients with MS in acute
phase of the disease but not in patients with stable disease [44]. Moreover, ObR was up-regulated on T cells of MS patients during relapse and was associated with increased phosphor-STAT3 levels [44]. In view of all of these considerations, we suggest that leptin could be one of the many proinflammatory factors that act in concert to promote the pathogenic (autoactive) Th1 responses targeting neuroantigens in MS (Fig. 1).

It has been hypothesized that low serum leptin might contribute to increased susceptibility to infection by reducing Th cell priming and by affecting thymic function [18, 27]. On the contrary, the Th1-promoting effects of leptin have been linked to an enhanced susceptibility to develop experimentally induced autoimmune diseases including EAE, type 1 diabetes (T1D), and antigen-induced arthritis [25]. Although more experimental evidence is needed to unequivocally define the role of leptin in several autoimmune conditions, it is nonetheless exciting that new developments in the field are leading to several new lines of inquiry. In this context, it is worth mentioning that leptin may only represent one of the many factors derived from the adipose tissue and neuroendocrine system, which in addition to playing an important function in the regulation of food intake and metabolism, also significantly affects the immune response. These mediators include adiponectin, visfatin, neuropeptide Y, and ghrelin [45]. Of particular interest is the anti-inflammatory effect of ghrelin toward the leptin-induced secretion of inflammatory cytokines as well as its powerful action for thymic homeostasis [46].

**Treg CELLS AND LEPTIN**

Over the past decade, a population of so-called Treg cells has been linked to the prevention of autoimmunity. Treg cells act in a dominant, transacting way to actively suppress immune activation, thereby functioning as critical mediators of self-tolerance and immune homeostasis. Efforts to better define the subset of cells mediating suppression of autoimmunity culminated in the identification of CD4+ T cells constitutively expressing the IL-2Rα chain (CD25) as being highly “enriched” in suppressor activity [47]. These “naturally arising” CD4+CD25+ Treg cells became the best candidates for the T cell population-mediating, dominant tolerance to self. After TCR cross-linking in vitro, Treg cells are unable to proliferate or produce IL-2 but are able to inhibit proliferative responses and cytokine production by Teff cells. However, this in vitro anergy belies a more complex activity in vivo. Adoptive-transfer experiments suggest that Treg cells are capable of self-renewal, as transfer of relatively small numbers of Treg cells afforded a long-lasting protection against autoimmunity. In addition, Treg cells are capable of robust MHC class II–dependent proliferation in lymphopenic conditions after specific TCR stimulation or after transfer into mice genetically deficient in Treg cells [48–51]. An in vitro protocol has been developed for the expansion of Treg cell populations after TCR and CD28 engagement in the presence of high concentrations of IL-2, which could allow for isolation and cloning of antigen-specific Treg cells. Thus, despite their apparent in vitro anergy, the Treg cell population is capable of robust expansion in vivo, and its early description as anergic cells is misleading.

The Foxp3 was shown to be expressed specifically by CD25+ Treg cells, as well as by CD25– T cells with regulatory activity. This transcription factor is thought to program the development and function of this subset and so far, is the most unambiguous marker available to identify naturally occurring Treg cells [49].

The identification of mutations in the gene encoding Foxp3 as the cause of the fatal human autoimmune disorder “immune dysregulation, polyendocrinopathy, enteropathy, X-linked” and the analogous disease in a spontaneous mutant mouse, scurfy, was a breakthrough in the field and led to subsequent studies that argue for the idea of Treg cells as a dedicated, functional lineage [52–54]. Recent reports [55] have shown that leptin can act as a negative signal for the proliferation of human naturally occurring Foxp3+CD4+CD25+ Treg cells (Fig. 1). Freshly isolated Treg cells produce leptin and express high amounts of ObR. In vitro neutralization with leptin mAb, during anti-CD3 and anti-CD28 stimulation, results in Treg cell proliferation that is IL-2-dependent. Treg cells that proliferated in the presence of leptin mAb had increased expression of Foxp3 and remained suppressive over time. The phenomena appeared secondary to leptin signaling via ObR, and importantly, leptin neutralization reversed the anergic state of the Treg cells, as indicated by down-modulation of the cyclin-dependent p27kip-1 and the phosphorylation of ERK1 and ERK2. Taken together, these findings suggest a potential role for leptin neutralization as a novel protocol to expand Treg cells in vitro.

**OBESITY AND LEPTIN: BRIDGING THE GAP BETWEEN INFLAMMATION AND ADIPOSE TISSUE**

The genetic evidence for a critical role of leptin and its downstream anorexigenic pathways in the control of food intake is extremely strong and highly suggestive of a system with little redundancy [2]. The severe and continued hyperphagia seen in rodents and humans when the leptin signaling system is disrupted, which persists in the face of extreme expansion of the adipose tissue mass, suggests that other adipocyte-derived signals play, at most, a subsidiary role in adipoostatic control of food intake [2]. Obesity and the associated metabolic pathologies are the most common and detrimental metabolic diseases, affecting over 50% of the adult population [2]. These conditions are associated with a chronic inflammatory response characterized by abnormal cytokine production, increased acute-phase reactants, and activation of inflammatory signaling pathways, classically related to the innate immune response activation [56]. This association is not an inconsequential one, at least in experimental models, and is causally linked to obesity itself or closely linked diseases such as insulin resistance, T2D, and cardiovascular disease [56]. An interesting feature of the inflammatory response that emerges in the presence of obesity is that it appears to be triggered and to reside predominantly in adipose tissue, although other metabolically critical sites may also be involved during the course of the disease. The temporal and spatial properties of the inflammatory response in the context of obesity and its complications,

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the target cell(s) that are critical in metabolic dysregulation, and the underlying molecular mechanisms remain as unanswered but critical questions. Although the role of adipocytes in metabolic pathways is clear, little is understood about their role in inflammation. Following careful examination, it has been shown that adipocytes and diverse types of immune cells such as monocytes and macrophages possess similar roles in pathways such as complement activation and inflammatory cytokine production [56]. Leptin may represent one of the most important common mediator-linking adiposity-to-inflammation observed in obesity.

Linked to a functional but not real leptin deficiency is the most common form of human obesity, associated to central/ peripheral leptin resistance because of high serum leptin levels [2]. Epidemiological studies show increased infection frequency in these patients, mainly affecting the respiratory and urinary tracts [57]. Many factors contribute to this, such as the alteration in the normal dynamics in lungs ventilation and in urinary flow from kidneys as a results of the excess in body fat. Another of these factors can also be the leptin-receptor desensitization expressed on CD4+ T-lymphocytes as a result of the high leptin levels, finally perceived from T cells as a condition of leptin resistance [57]. In summary, obesity associates with chronic, low-degree activation of innate immunity (macrophage system) responsible for pathologic conditions such as T2D, insulin resistance, and atherosclerosis [56]; in addition, this condition is associated with increased frequency of infections. Finally, another important point of discussion is the possibility that obesity and autoimmune disorders are associated. At the moment, it is not possible to draw definitive conclusions about this specific issue as a result of the absence of robust, large-scale epidemiological studies. BMI in MS patients has been shown to be increased; whether this is related to conventional drug treatment (corticosteroids, IFN-β) that may affect food intake and fat mass or to reduced physical activity as a result of neuromuscular impairment is not clear [58]. Future studies are needed to specifically address this issue.

CONCLUSIONS

From the above considerations, it is possible to hypothesize that there is a strong relationship between metabolic state and Treg cell response that controls immunological tolerance (Fig. 1). Leptin acts as a proinflammatory cytokine that promotes Th1 responses on one side and inhibits Treg cell expansion on the other, setting the basis for exaggerated, immunoinflammatory responses to altered self or nonself and leading to autoimmunity in subjects with autoimmunity risk factors (i.e., genetic predisposition, HLA, environment, etc.; Fig. 1). Future studies are needed to identify the precise relationship among leptin, metabolic state, and Treg cells in the context of autoimmune disease susceptibility. In this context, recent studies from Fontana et al. [59] have shown that caloric restriction and consequent lowering of serum leptin are able in humans to reduce immunoinflammatory parameters (such as IL-6 and CRP) significantly, suggesting that nutritional intervention is able to dampen inflammatory responses. Moreover, the evidence that acute starvation or leptin neutralization with mAb in mice is able to significantly improve onset, progression, and neurological signs of EAE by increasing IL-4 and IL-10 secretion [40, 41], as well as that a leptin antagonist can block peritoneal inflammation in mouse endometriosis, suggests that future strategies aimed at interfering with leptin signaling may help to block immune and autoimmune responses.

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