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EDITORIALS

Role of Leptin in Autoimmune Diseases

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ABSTRACT

Leptin represents a link between metabolism, nutritional status, and immune responses. Leptin is important for optimal functioning of the immune system. Leptin is a cytokine-like hormone with pro-inflammatory properties linked to autoimmune diseases. Moreover, there has been increasing evidence that leptin is involved in the pathogenesis of various autoimmune diseases. Leptin has been shown to enhance immune reactions in autoimmune diseases that are commonly associated with inflammatory responses. Both high and low levels of leptin might contribute to autoimmune diseases. Leptin has been explored as a potential target for therapeutic development in treating autoimmune diseases. In this review, we review here the most recent advances on the role of leptin in autoimmunity and in immune-rheumatological diseases.

Keywords: leptin, autoimmunity, pathophysiology, autoimmune diseases

Leptin functions

Leptin is a peptide hormone (16 kDa) secreted mainly by adipocytes, with a variety of physiological roles. Since its discovery in 1994, leptin has attracted increasing interest in the scientific community for its pleiotropic actions (1,2). Leptin influences the neuroendocrine system at several levels, including the hypothalamic-pituitary-adrenal, thyroid, gonadal, and growth hormone axes. However, leptin levels correlated with body mass index (BMI), but not with disease activity. Therefore, it is possible that the interplay between these endocrine systems and the immune response may have influenced, indirectly. Leptin also plays a regulatory role in immunity, inflammation. Although leptin is well known for its regulatory effects on

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immune cells, its expression and release is reciprocally under the control of different inflammatory stimuli. Moreover, leptin can activate monocytes, dendritic cells and macrophages and stimulate them to produce Th1 type cytokine. The cytokine-like structural characteristic of leptin is implicative of its function in regulating immune responses. It has been shown that disease conditions of reduced leptin production are associated with increased infection susceptibility (3,4). Leptin stimulates the production of reactive oxygen species (5). Leptin stimulates the release of pro-inflammatory cytokines and prostaglandins (6-9). One of its functions is the relationship between nutritional status and immune competence (10).

It has reported that fasting leads to an improvement of clinical and biological measures of disease activity, which was associated with a marked decrease in serum leptin. Leptin also prevents apoptosis of T cells that normally accompanies fasting through up-regulation of anti-apoptotic protein bcl-xL via leptin receptors on lymphocytes. The leptin-induced metabolic pressure sets the basis for an exaggerated immuno-inflammatory response to altered self or non-self, leading to chronic inflammation, metabolic dysregulation, and autoimmunity in subjects with risk factors (8).

Role of leptin in immune system

The role of leptin in regulating immune responses has been assessed in vitro as well as in clinical studies. Importantly, leptin has also been shown to modulate the adaptative immune system, via enhancing T-cell survival and skewing T-cell differentiation towards a Th1 response. Recent studies showed that leptin plays an important role in T lymphocyte responses. Without doubt, leptin is an important modulator of T cell function. The immune system in turn, modifies leptin's production. In adaptive immunity, leptin markedly stimulates proliferation of naïve T cells and secretion of IL-2 by these cells, whereas it minimally affects the proliferation of memory T cells. On memory T cells leptin promotes the switch towards T helper 1 (Th1) cell immune responses by IFN-γ and TNF secretion. As a cytokine, leptin also affects thymic homeostasis and, similar to other proinflammatory cytokines, leptin promotes Th1 cell differentiation and cytokine production. Further effect of leptin involves suppression of $CD4^+CD25^+$ regulatory T cells proliferation (8,9).

It has been shown that acute inflammation and pro-inflammatory cytokines, such as TNF-α, IL-1, IL-6, and LIF positively regulate leptin expression in adipose tissue and circulating leptin levels, whereas long-term expression to IL-1 or TNF-α negatively regulated leptin levels (10-12).

Leptin exerts inhibitory effects on Th2 cells. Leptin inhibits CD4(+)CD25(+)Foxp3(+) regulatory T cells, which are known to contribute significantly to the mechanisms of peripheral immune tolerance. It also remains largely unclear how leptin might regulate the tolerogenic immunity and whether leptin modulates immune suppression by inhibiting the production of the Th2 cytokines such as transforming growth factor-β (TGF-β) (3-5).

These findings suggest that the immune effects of leptin deficiency in the context of nutritional deficiency may be far reaching, and conversely that antagonism of the leptin axis may have potential in the field of immunotherapy.

Recently, several papers demonstrated that leptin also affects homeostasis and function of $CD4^+CD25^+$ regulatory T (Treg) cells. Low leptin levels result in a Th2 skewing and an increased risk for microbial infection and thereby increase the risk for disease induction and/or disease relapses. In contrast, high leptin levels favour Th1 immune responses and negatively affect Treg cells and peripheral tolerance (13).

It structurally resembles proinflammatory cytokines, such as IL-6 and IL-12. In Th1 cells, leptin increases their IL-6, TNF-α and IFN-γ production. Leptin levels correlate very well with circulating IL-6, TNFα, C-reactive protein (CRP) and alpha 1-antitrypsin levels (14).

Many aspects concerning leptin's interactions with inflammation and immune system remains unclear. We review herein recent advances on the role of leptin in the pathophysiology of immune responses.

Role of leptin in autoimmune disorders

Both *in vitro* and *in vivo* studies support involvement of leptin in the pathophysiology of autoimmune diseases (15-17). Recent studies have shown that leptin is involved in the induction and progression of experimental autoimmune encephalomyelitis (EAE) (18). The immunomodulatory effects of leptin have also been

linked to enhanced susceptibility to other autoimmune disease such as EAE, a model of MS (18-20). The role of leptin in the pathogenesis of human MS is not fully understood. 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. Increased leptin secretion is present both in the serum and in the CSF of patients with MS and does not correlate with BMI. 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. Serum leptin anticipates the onset of clinical manifestations of EAE (18).

In relation to the important role of leptin in autoimmunity, women are 2-3 times higher in serum leptin levels than men adjusted for age and BMI, and are predisposed to autoimmune diseases such as RA, SLE, and MS (20). It has been speculated that leptin could in part contribute to the gender-biased susceptibility to autoimmunity. The influence of leptin on T cell immunity is sufficiently profound to control susceptibility to autoimmune disease.

Recent evidence demonstrates a detrimental involvement of leptin in promoting the pathogenesis of various autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), ulcerative colitis (UC). The prevalence of autoimmune diseases such as RA is increased with high serum leptin levels. Conversely, immune-mediated disorders, such as autoimmune diseases, are associated with the increased secretion of leptin and the production of proinflammatory pathogenic cytokines (21,22).

Recent evidence indicates that leptin is involved in the dysregulated balance between Th1 and Th2 cytokines and contributes to the pathogenesis of RA. Leptin may probably contribute to joint inflammation by regulating both humoral and cell-mediated immune responses. It was reported that fasting leads to an improvement of RA activity associated with a marked decrease in serum leptin and a shift toward the cytokine production. In contrast, leptin deficiency has a protective effect on autoimmune diseases by altering the balance of Th1:Th2 cytokine production and promoting a Th2 response (23).

As mentioned earlier, circulating leptin is increased under inflammatory conditions, both in acute and in chronic inflammatory diseases such as RA (24). The role of leptin in the modulation of the immune response and inflammation has been regarded as important in RA patients (25). These features suggest that leptin may also influence the inflammatory mechanism of arthritis. Nevertheless, it remains to be studied whether leptin regulate Treg cells directly or via the action of other immune cells (26).

Elevated serum leptin levels have been described in patients with SLE. Leptin cannot be used to assess disease activity in RA and SLE. Furthermore, serum leptin levels in SLE patients with arthritis and CNS involvement were significantly lower in comparison with SLE patients without arthritis and CNS involvement, which suggests that active chronic inflammation may lower plasma leptin concentrations (27-30).

Active ANCA-associated vasculitis is characterized by decreased serum leptin. Therefore, leptin dysregulation may be involved in the pathogenesis of autoimmune diseases such as ANCA-associated vasculitis (31,32).

In contrast, in systemic sclerosis (SS) patients, decreased serum leptin levels were found. There was no correlation between serum leptin levels and the duration of the symptoms of SS, while serum leptin levels correlated with BMI (33).

In patients with Behçet's disease, leptin levels were significantly higher than in healthy controls and correlated positively with disease activity (34).

In the acute stage of UC increased serum leptin levels may contribute to anorexia and weight loss (35). Data do not seem to indicate a direct role of leptin in the perpetuation of the autoimmune response in primary biliary cirrhosis (36).

In obese patients with acute hyperglycemic crises, insulin treatment is followed by rapid and significant increase in leptin concentration. The low serum leptin level may be the result of impaired adipocyte glucose utilization (37,38). The leptin levels are associated with thyroid autoimmunity independent of bioanthropometric, hormonal, and weight-related determinants. Obesity increases the susceptibility to harbor autoimmune thyroid disease with an emerging role for leptin as a peripheral determinant (39).

It is clear that leptin is a pleiotropic molecule with effects on multiple biological systems, of which the immune system is but one. That is why the investigation of the role of leptin in the regulation of the immune response remains a challenge for the future. Recent clinical studies on autoimmune disease patients demonstrate that high serum leptin levels may either play a causal role in the disease progress or serve as a diagnostic marker for clinical application. It remains to be established of leptin can serve as a potential therapeutic target in treating human autoimmune diseases (40,41).

Further studies are warranted to further characterize the functions of leptin during the natural history of autoimmunity.

CONCLUSION

There is an increasing evidence that leptin is involved in the pathogenesis of inflammatory and autoimmune diseases. Leptin plays a role in the activation of the immune system, and it is a mediator of inflammation. Leptin may be considered as a therapeutic target in some clinical situations, such as proinflammatory states or autoimmune diseases. ❑

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