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Review Article

LEPTIN: FROM APPETITE SUPPRESSION TO AUTOIMMUNITY

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Abstract. *The hormone leptin is released by adipocytes accordingly to current energy stores to suppress appetite. Apart from this, leptin acts as a proinflammatory cytokine and strongly stimulates inflammation. Immune-modulating properties are partly achieved by affecting T-cell maturation, polarization, and viability. Leptin rises inflammatory cells count, increases proinflammatory cytokine secretion, and impairs regulatory T-lymphocytes differentiation. Leptin secretion and signalization disturbances have recently started to be observed in the context of autoimmunity. In this review, we discuss signaling pathways affected by the satiety hormone, its effect on T-lymphocyte maturation, differentiation and polarization, and relation to other immune-modulating agents. In the end, we highlight the rising evidence connecting hyperleptinemia state which is almost always related to obesity, with autoimmune disorders and take a brief overview of possible mechanisms behind leptin's potency to induce self-reactivity.*

Key words: *leptin, leptin resistance, leptin receptor, autoimmunity.*

Introduction

Leptin (also: obese, satiety, starvation hormone) is a hormone made of 167 amino acids and released by adipocytes accordingly to current energy stores. The main role of the satiety hormone is to suppress appetite by delivering information about peripheral energy supplies towards CNS, more precisely to hypothalamic nuclei. In this manner leptin indirectly modulates the metabolic rate of the body [1–3].

The leptin gene (*LEP; OB*) is located at chromosome 7, while chromosome 1 carries the leptin receptor gene (*LEPR; DB*). Mutations in any of these genes result in obesity and multiple metabolic disorders related to leptin deficiency (*ob/ob*) or leptin resistance (*db/db*) [4]. The inability of leptin receptors to recognize and adequately respond to leptin stimulation is called leptin resistance. It is always coupled with hyperleptinemia as an attempt of the body to influence the hunger center in the hypothalamus and prevent further energy intake [5]. There are several mechanisms of leptin resistance development, but the particularly interesting one is where the mutation occurs only in receptors transporting leptin through the blood-brain barrier (BBB). The disorder results in peripheral hyperleptinemia with disabled leptin delivery to hypothalamic nuclei and dysregulated appetite suppression leading to obesity [6]. Although the highest density of LepRb is found in hypothalamic nuclei managing the appetite and energy expenditure, distribution of this receptor shows that other areas of CNS, liver, pancreas, perivascular intestinal tissue, heart, and immune cells are also liable to leptin [7]. The *LEPR* expression in immunologically active cells give leptin the immunomodulatory role and a whole new meaning to peripheral hyperleptinemia [8]. Considering the abundance of microinflammation in obese, the possible proinflammatory effect of leptin and hyperleptinemia has recently started to be examined.

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Leptin Signaling Pathways

So far, we have been familiar with six isoforms of the leptin receptor gene, of which one is "long" (LepRb), while the rest are "short" (LepRa, LepRc, LepRd, LepRe, LepRf) [9]. LepRb is a transmembrane form able to convey leptin signal towards the nucleus. Short receptor forms take part in leptin transport through BBB, leptin metabolism, and elimination [10].

Leptin binding to LepRb is followed by the activation of three signaling pathways: JAK-STAT, ERK, and PI3K. The first step in leptin-dependent signal transduction is autophosphorylation of janus kinase 2 (JAK2) attached to the intracellular part of LepRb. JAK2 directly phosphorylates three tyrosine residues: Tyr985, Tyr1077 and Tyr1138, also located at the intracellular portion of the receptor. Phosphorylated tyrosine residues further initiate activation of next-generation messengers (e.g. Tyr1138→STAT3 - signal transducer and activator of transcription 3) which travel to the nucleus and trigger transcription of various genes [11]. So far, studies have confirmed that leptin affects transcription of *socs3*, *pomc*, *cart*, *agrp*, and *npy*. SOCS3 (suppressor of cytokine signaling 3) plays an important role in the autoregulation of leptin signaling ince its binding to phosphorylated Tyr985 leads toJAK2 inhibition [12]. Phosphorylated Tyr985 also positively regulates the ERK pathway which is highly important in the differentiation, metabolism, and viability of T-helper lymphocytes (Th) [6]. The third, and the

fastest leptin signaling pathway starts with phosphorylation of insulin-substrate receptor (IRS) by JAK2, that via PI3K triggers two axes: Akt-FoxO1 and mTORC1. Their dominant effect on cell enzymatic systems over transcription regulation results in shortly notable changes [13].

Considering intracellular pathways activated by the obese hormone, as well as the LepRb distribution, leptin turns into much more than the plain messenger in the chain of appetite control. Apart from the primary role in energy expenditure adjustment, its involvement in immunological processes has gained importance lately, especially in regulatory T-lymphocytes (Tregs) maturation and favored proinflammatory over anti-inflammatory response [11, 14].

Leptin as a Proinflammatory Agent

The satiety hormone brings the signal about sufficient energy supplies to CNS so it can coordinate immune functions, as directing energy towards immune cells maturation and specialization or uplifting and maintaining the immune reaction. Further, LepRb is found in certain types of immune cells (neutrophils, monocytes, macrophages, T-lymphocytes, B-lymphocytes, mastocytes, dendritic cells, natural killer cells) which implies leptin's direct effect on counted cells metabolism and functions [8, 15]. Although various immune cells are affected by leptin, it dominantly supports proinflammatory T-cells subtypes (Th1, Th17, Th22, Th9) and simultaneously suppress anti-inflammatory Th2 cells and Tregs [16]. Also, proinflammatory cytokines: LPS, TNF-α, and Il-1 were shown to increase leptin secretion, so its involvement in inflammation became even more certain [17, 18].

Leptin stimulates the expression of IL-7, also familiar as a thymocyte growth factor, in medullary thymic epithelial cells. This role in T-lymphocyte maturation is confirmed in leptin-deficient conditions which are always coupled with thymus atrophy [19, 20]. Leptin also affects matured, peripheral T-cells by managing their proliferation, differentiation, and viability [16]. Hence, leptin increases the proliferation of naïve cells and their differentiation towards proinflammatory phenotypes, while memory T-cells production remains suppressed under leptin impact [21, 22]. Also, T-cells viability is significantly improved by leptin-dependent mTOR activation [23].

Th1/Th2 polarization is dependent on leptin signalization and it significantly decreases in leptin-deficient conditions. However, Th1 response is prominently supported and Th2 response is suppressed by the satiety hormone [24]. Additionally, leptin promotes the production of several proinflammatory cytokines: Il-1, TNF-α, INF-γ, IL-2, IL-6, IL-12, IL-17, IL-21, and simultaneously decreases secretion of IL-10 and IL-4, known to suppress inflammation and restore pre-inflammatory, physiological condition [25].

In addition to proinflammatory, leptin shows autoimmune features as well. Tregs are Th subset supervising lymphocyte reactivity, peripheral tolerance to own antigens, and maintenance of an adequate inflammatory reaction with consequent resolution [26]. Considering the origin, Tregs are divided into two subgroups: naturally occurring Tregs (nTregs) originating from precursor cells in the thymus, and inducible Tregs (iTregs) formed from naïve T-helper cell under certain conditions [27]. Leptin can affect nTregs differentiation in the following mechanism: leptin induces hypoxia inducible factor (HIF) -1α expression, leading to FoxP3 (master regulator of differentiation and function in Tregs) degradation and Tregs inhibition [28]. Oppositely, leptin-stimulated HIF-1α activity in Th17 subset ameliorates glycolysis and increases energy for proliferation, maturation, and activity [24, 29, 30]. More importantly, HIF-1α provokes the secretion of pro-autoimmune cytokines (Il-17, IL-21,and IL-22) in Th17 precursor and its differentiation. Also, the ERK pathway activated by leptin-dependent Tyr985 phosphorylation maintains Th17 inflammatory response [31, 32]. The main producing cytokine in this cell subtype, IL-17, was shown to promote autoimmune response and inflammation [33, 34]. Figure 1 shows leptin impact on nTreg and Th17 precursors.

The urgency of understanding leptin's proinflammatory action and a strong inhibiting effect on inflammatory process resolution rises considering the number of obese patients with central leptin resistance and multiple metabolic disorders. Since leptin cannot pass BBB, the patient feels hunger, keeps ingesting food, and stores the energy, making adipocytes secrete more leptin which expresses its actions peripherally, on immune cells. Joining hyperleptinemia to existing metabolic disorders (dyslipidemia, hyperinsulinemia, hypertension, increased production of proinflammatory cytokines with TNF-α, IL-1 and IL-6 on the lead, etc.), makes a perfect base for multiple focal microinflammation with the tendency to autoimmune reaction development, and decreased potency of immune system monitoring.

Leptin in Autoimmune Diseases

The leptin role in autoimmunity may be discussed from three aspects: (a) the Tregs suppression, (b) the Th17 stimulation, and (c) an increase in proinflammatory cytokines secretion [35, 36]. Such an environment makes a perfect lining for autoimmune reaction, as soon as plenty of metabolic disturbances are also seen contemporary with leptin sensitivity disorders, as mentioned above. Yet, there are only a few clinical studies connecting leptin with autoimmune diseases since the role of the starvation hormone as an immunomodulator has recently started to be examined.

Hyperleptinemia related to obesity was shown to be part of the pathogenesis in several autoimmune diseases, such as rheumatoid arthritis (RA), multiple sclerosis (MS), psoriasis, autoimmune thyroiditis, and type 1 diabetes mellitus (T1DM). Moreover, inflammatory bowel diseases (IBD) and systemic lupus erythematosus (SLE) activity seemed to be dependent on leptin concentration as well [37].

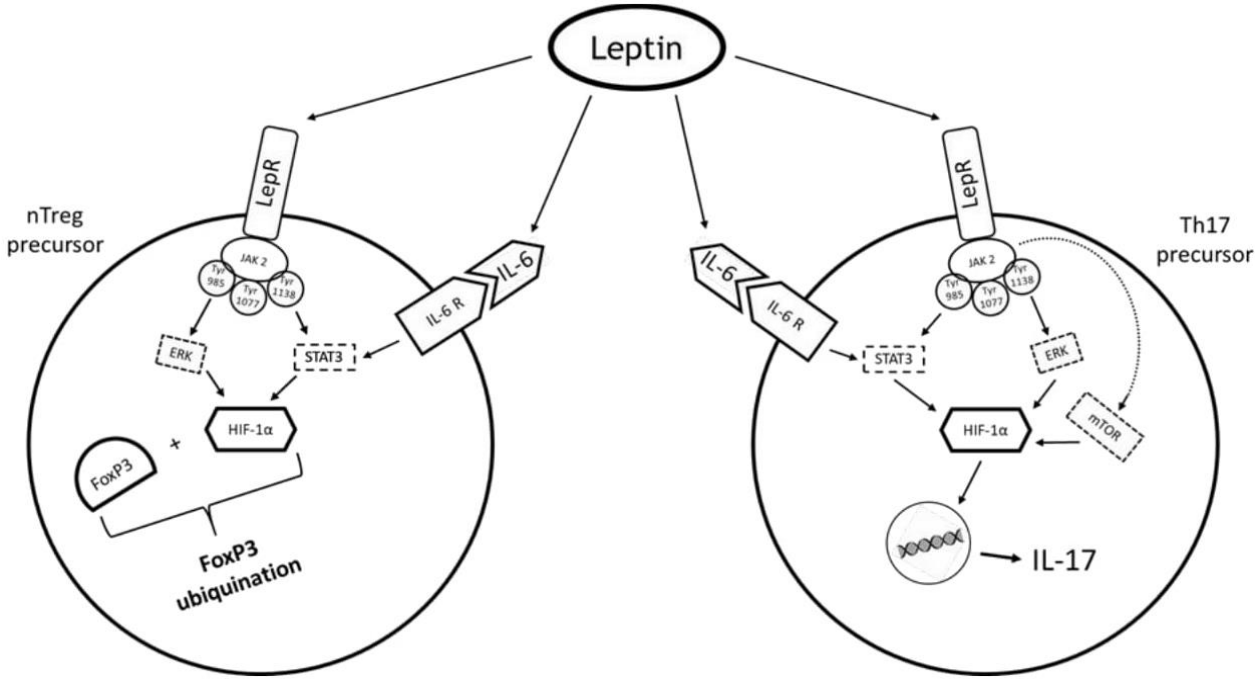

Fig. 1 Leptin impairs nTreg maturation and promotes Th17 differentiation.
Figure legend: Leptin increases HIF-1α in T-helper precursor cells directly by binding to its own receptor (LepRb), and indirectly by stimulating IL-6 production. In nTreg precursors HIF-1α binds to FoxP3 and promotes its degradation, delaying the cell maturation. Oppositely, the differentiation of Th17 is encouraged by HIF-1α *relaying to its stimulating effect on IL-17 production*. FoxP3 and IL-17 are regulators of differentiation in these two cell subtypes.
Abbreviations: LepR – leptin receptor, IL-6 R – interleukin-6 receptor; JAK2 – janus kinase 2; HIF-1α - intracellular hypoxia inducible factor 1α; STAT3 - signal transducer and activator of transcription 3; ERK – extracellular signal regulated kinase; FoxP3 – forkhead box P3 protein; mTOR – mammalian target of rapamycin.

A positive association between RA and obesity has been observed earlier [38]. A milieu of proinflammatory cytokines in the environment of dyslipidemia has a certain impact on synovial destruction and chondrocyte phenotype loss in RA. As a potent adipokine, leptin stimulates the secretion of NOS, IFN-γ,IL-1, and metalloproteinases in chondrocytes, as well as the activity of autoreactive T lymphocytes, causing the deterioration of the disease [39]. Clinical studies observed that RA activity was positively related to leptin serum level since the secretion of pathogenic enzymes and cytokines was strongly ameliorated by leptin [40, 41]. Although the meta-analysis in 2016 confirmed a positive correlation between serum leptin level and disease activity in humans [42], the understanding of leptin's impact on the disease activity is not yet fully understood.

In MS both serum and liquor leptin levels were elevated and correlated with Th17 count and IFN-γ activity in neural structures [43]. An increased serum leptin level in children is considered to be one of several obesity-related factors related to a twofold higher risk of MS onset in adulthood, as reported in several longitudinal studies [44, 45].

Further, in animals fed with high-fat diet leptin caused a significant increase in IFN-γ production and T1DM rapid onset [14]. As animal studies have shown, leptin administration is capable of inducing spontaneous T1DM in non-obese animals [46], while human studies reveal hyperleptinemia state in children suffering from T1DM [47]. However, the complexity standing behind the leptin's effect on glucose metabolism on the one hand, and leptin's proinflammatory effects on the other, should be briefly considered while summarizing a protentional leptin's role in T1DM onset and course.

Leptin-dependent Th17 inflammatory reaction and IL-17 hyperproduction were among the leading causes of autoimmune thyroiditis [48, 49], MS [50], SLE [51, 52], and many other systemic and organic autoimmune diseases [53]. Although the crucial role of this adipokine in the development remains unclear, its impact on differentiation and survival of autoreactive T lymphocytes cannot be neglected. A meta-analysis including 1333 patients suffering from SLE and 1048 healthy controls concluded that serum leptin level was significantly increased in SLE patients [54]. In particular, deterioration in renal function seems to be in strong positive relation with leptin secretion [55].

Weight loss, followed by basal leptin decrease, showed amelioration in the course of the autoimmune diseases and increased Tregs count [56]. Finally, studies also confirmed that experimental models carrying *ob/ob* genotype were protected from certain autoimmune dis-

eases, like experimental autoimmune encephalomyelitis (equal to MS in humans) [57], SLE [58], and chronic inflammation in distinct tissues [59–61].

Conclusion

Low grade, sterile inflammation coupled with extracellular matrix remodeling and fibrosis in adipose tissue occurring in obesity leads to dysregulation of adipokines secretion and permanently active immune response. Disturbance in adipokines relation is followed by systemic inflammation and obesity comorbidities. For example, leptin, resistin, TNF-α, and IL-6 serum levels are elevated in obesity, leading to oxidative stress, angiogenesis, and thrombosis [62–64]. On the other hand, adiponectin, known by its anti-inflammatory properties is decreased in conditions of adipose inflammation [65]. With increased proinflammatory immune modulators supporting not only inflammation but autoreactivity as well, obesity becomes one of the risk factors for autoimmune disorders.

Theoretically, cell types and pathways affected by the satiety hormone make leptin a remarkable player in autoimmunity [11, 14, 29]. Its dominant effect on Th1 versus Th2 differentiation, Tregs suppression, and macrophage stimulation inflames immune response. On the other hand, conditions with the lack of leptin, like lipid dystrophia or deletion of the leptin gene, are linked to a higher risk of fatal outcome due to infection. This could be attributed to irregular thymic function, T lymphocyte differentiation, disturbances in the function of other immune cells like macrophages, neutrophils, and NK cells. Current findings highlight leptin's role in the proper development of immune response. Also, conditions with elevated leptin secretion, like leptin resistance and obesity, are followed by multiple immune defects often ending with cardiovascular diseases and autoimmune disorders. Clinical studies on humans are needed in order to reveal the exact leptin's role in the interplay of many other mediators secreted in the obesity state. One is sure for now: leptin is much more than just a plain appetite suppressor.

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