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Review

Leptin in autoimmune diseases

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ABSTRACT

The past twenty years of research on leptin has provided crucial information on the link between metabolic state and immune system function. Adipocytes influence not only the endocrine system but also the immune response, through several cytokine-like mediators known as adipokines, which include leptin. Initially described as an antiobesity hormone, leptin has subsequently been shown also to influence hematopoiesis, thermogenesis, reproduction, angiogenesis, and more importantly immune homeostasis. As a cytokine, leptin can affect thymic homeostasis and the secretion of acute-phase reactants such as interleukin-1 (IL-1) and tumor-necrosis factor-alpha (TNF-α). Leptin links nutritional status and proinflammatory T helper 1 (Th1) immune responses and the decrease in leptin plasma concentration during food deprivation leads to impaired immune function. Conversely, elevated circulating leptin levels in obesity appear to contribute to the low-grade inflammatory background which makes obese individuals more susceptible to increased risk of developing cardiovascular diseases, diabetes, or degenerative disease including autoimmunity and cancer. In this review, we provide an overview of recent advances on the role of leptin in the pathogenesis of several autoimmune disorders that may be of particular relevance in the modulation of the autoimmune attack through metabolic-based therapeutic approaches.

Abbreviations: LepRb, leptin receptor b; Th, T helper; Tconv cells, conventional T cells; Treg cells, regulatory T cells; mTOR, mammalian target of rapamycin; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; EAE, experimental autoimmune encephalomyelitis; IBD, inflammatory bowel disease; RA, rheumatoid arthritis; T1D, type 1 diabetes; SLE, systemic lupus erythematosus; Pso, psoriasis; AT, autoimmune thyroiditis; HT, Hashimoto thyroiditis; EIC, experimental induced colitis; BMI, body mass index; CNS, central nervous system; NPY, neuropeptide Y; NOS, nitic oxide synthase; NOD, Non-obese diabetic; *ob/ob*, leptin-deficient; *db/db*, leptin-receptor-deficient; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; STAT, signal transducer and activator of transcription; SOCS-3, suppressor of cytokine signaling-3.

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1. Introduction

Leptin is one of the most important hormones secreted by adipose tissue [1] and its implication in energetic homeostasis at central level has been largely described [2]. The past twenty years of research on adipose tissue has provided important insights into the intricate network that links nutrition, metabolism and immune homeostasis. In this context leptin works not only as a "fasting hormone" by controlling body weight through the inhibition of food intake and stimulation of energy expenditure by increased thermogenesis [3] but also in the regulation of peripheral functions [4–9]. Indeed, it has been previously shown that *ob/ob* and *db/db* mice are not only obese but also show many other immune/endocrine alterations observed during starvation [10–12]. Although an important role of leptin is to regulate body weight through the inhibition of food intake, recent evidence has indicated that leptin is also involved in the modulation of several innate and adaptive immune responses [13]. Indeed, LepR is expressed by several immune cells, thus suggesting a key role displayed by leptin in the regulation of immune responses [14].

Modulation of the immune system by leptin is exerted at the development, proliferation, anti-apoptotic, maturation, and activation levels [15]. Indeed, LepRs have been found in neutrophils, monocytes, and lymphocytes, and they belong to the family of class I cytokine receptors. The overall leptin action in the immune system is a pro-inflammatory effect, activating pro-inflammatory cells, promoting Th1 responses, and mediating the production of the other pro-inflammatory cytokines, such as TNF-α, IL-2, or IL-6. Leptin is therefore able to modulate both innate and adaptive immune response [13]. Moreover, several studies in human revealed that leptin levels associated with autoimmune disorders, infections and endocrine/metabolic diseases, thus suggesting a central role of leptin in immune homeostasis and in the pathogenesis of several inflammatory disorders [16–18]. This review analyzes the role of leptin in immune homeostasis, and the direct and indirect influences of leptin on inflammation and autoimmunity.

2. Role of leptin in immune response

Mice lacking leptin or its functional receptor have a number of defects in both cell-mediated and humoral immunity [19,20]. Similarly, humans with congenital leptin deficiency have a much higher incidence of infection-related death during childhood [21], whereas recombinant human leptin administration in two children with congenital leptin deficiency and in females with acquired hypoleptinemia [22,23] normalized absolute numbers of naive $CD4^+CD45RA^+$ T cells and nearly restored the proliferation response and the cytokine release profile. 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 [12,24–26]. Leptin has a well-established role in innate immunity control. In macrophages/monocytes, leptin up-regulates phagocytic function [27] via phospholipase activation [28] as well as proinflammatory cytokine secretion, such as TNF-α, IL-6, and IL-12 [29,30]. Leptin stimulates the proliferation and activation of human circulating monocytes *in vitro* [31]. Moreover, leptin can induce chemotaxis of neutrophils and the release of oxygen radicals [32–34]. In NK cells, leptin is involved in all processes of cell development, differentiation, proliferation, activation, and cytotoxicity [35,36].

The effects of leptin on adaptive immune responses have been extensively investigated on human $CD4^+$ T cells (Fig. 1) [37]. Addition of physiological concentrations of leptin to a mixed lymphocyte reaction induces a dose-dependent increase in $CD4^+$ T cell proliferation [10]. Leptin induces early (CD69) and late activation markers (CD25, CD71) in both $CD4^+$

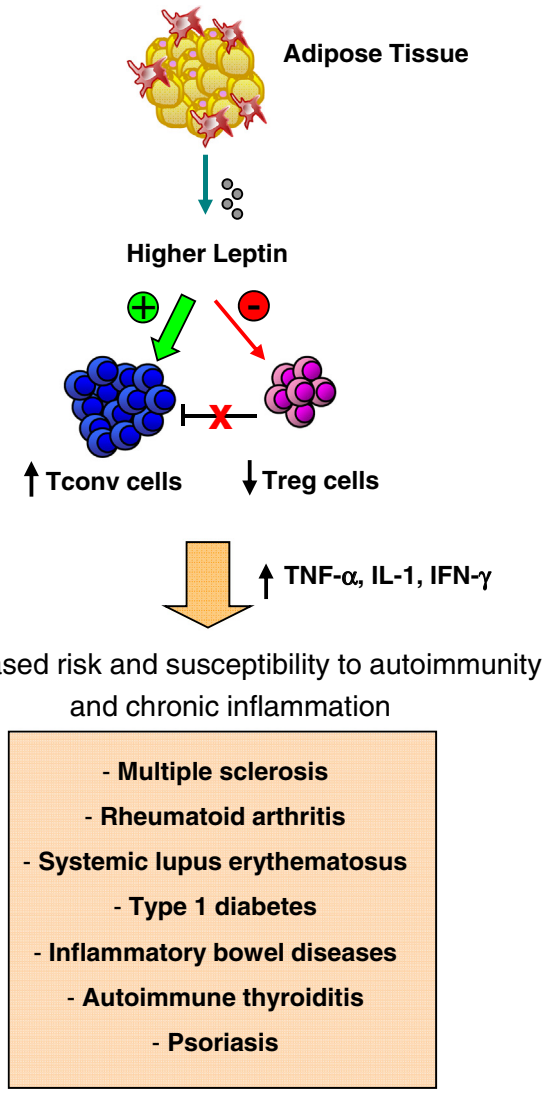

Fig. 1 – Schematic model of leptin role in pathogenesis of autoimmunity. The high amount of leptin secreted by adipocytes in inflammatory conditions, such as overweight, is associated with an high frequency and expansion of peripheral and in situ conventional $CD4^+$ T cells (Tconv), secreting high amount of pro-inflammatory cytokines (IFN-γ, TNF-α, IL-1) and a low proportion of regulatory T cells (Treg); this imbalance could generate an altered control of metabolic functions, an increased incidence of autoimmune disorders and chronic inflammation.

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