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Mini-review

Leptin in autoimmune mechanisms of systemic rheumatic diseases

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ABSTRACT

In the last two decades, white adipose tissue (WAT) has been recognized as a key actor of many physiological and pathological conditions. WAT is able to produce mediators, named "adipokines", which may affect systemic homeostasis. In particular, leptin is not only involved in appetite and energy metabolism, but also in immune system. Increasing evidence established that leptin can regulate both innate and adaptive immunity mainly with pro-inflammatory effects but also, to a lesser extent, with anti-inflammatory features. In autoimmune diseases, a failure or breakdown of the mechanisms of self-tolerance is observed. Leptin, which plays an important role in the control of immune balance, has been involved in autoimmunity generation and maintenance. In this review, it has been provided an up-to-date report about the role of leptin in systemic autoimmune diseases, with particular reference to connective tissue diseases, inflammatory arthritis, and vasculitis.

Introduction

In the last two decades, increasing evidence has deeply changed our knowledge about white adipose tissue (WAT) biology. WAT is not only an energy storage tissue, but it is also an active contributor to systemic homeostasis synthetizing and secreting a large number of mediators, including adipokines [1,2]. The adipokines are able to regulate energy metabolism and appetite and intriguing data have demonstrated that they exert pivotal features on cardiovascular, gastrointestinal, nervous, reproductive and immune systems [3]. Many studies have demonstrated its role on immune cells and autoimmune disorders, in which pharmacological actions on adipokines network could represent in next few years a promising perspective [4].

The aim of this review is to provide critical discussion about what we currently know with regard to the role of leptin in immune system and its implications in systemic autoimmune disorders, such as connective tissue diseases, inflammatory arthritides, and vasculitides.

Leptin

Leptin, from the Greek root leptos, meaning "thin", is a peptide hormone which belongs to the long-chain helical cytokine family, such as interleukin-6 (IL-6), IL-11, IL-12, leukocyte inhibitory factor (LIF), granulocyte colony-stimulating factor (G-CSF), ciliary neurotrophic factor (CNTF), and oncostatin M [5,6]. It is produced mainly in adipose tissue in order to control body weight in a central manner [7]. Plasma levels of leptin are strictly related to body mass (BMI) and body fat mass [8,9]. Leptin secretion is increased during short-term caloric intake [10] and reduced during acute fasting and prolonged weight loss [11]. Obesity, insulin-resistance, glucocorticoids, estrogens, and chronic inflammation are associated with high levels of leptin, while catecholamines production, androgens, free fatty acids, growth hormone, and peroxisome proliferator-

Abbreviations: WAT, white adipose tissue; IL, interleukin; BMI, body mass index; PPAR, peroxisome proliferator-activated receptor; JAK, janus kinases; STAT, signal transducers and activators of transcription; PI3K, phosphatidylinositol 3-kinase; MAPK, mitogen-activated protein kinase; PBMCs, peripheral blood mononuclear cells; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; LTB4, leukotriene B4; NK, natural killer; IFN, interferon; LIF, leukocyte inhibitory factor; G-CSF, granulocyte colony-stimulating factor; CNTF, ciliary neurotrophic factor; IP-10, interferon-γ-inducible protein; MIP-1-α, macrophage inflammatory protein; Th, T helper cells; Treg, Regulatory T cells; LPS, lipolysaccharide; SLE, systemic lupus erythematosus; sTNFR2, soluble TNF receptor 2; MSC, mesenchymal stem cells; NAP-2, neutrophil activating peptide 2; PUFA, polyunsaturated fatty acids; SS, Sjögren's syndrome; SSc, systemic sclerosis; IIM, Idiopathic inflammatory myopathies; DM, dermatomyositis; PM, polymyositis; CK, creatine kinase; RA, rheumatoid arthritis; PsA, psoriatic arthritis; AxSpA, axial spondyloarthritis; SI, sacroiliac; DMARD, disease modifying anti-rheumatic drugs; CRP, C-reactive protein; anti-CCP, anti-cyclic citrullinated peptide; CAIA, collagen-antibody-induced arthritis; TA, Takayasu artheritis; LepR, leptin receptor; eCBs, endocannabinoids.

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activated receptor (PPAR)-γ stimulation are related to low levels of leptin [4]. During fasting and after reduction of fat mass, the leptin levels are decreased in order to minimize systemic energy expenditure and privilege the vital organs functioning [12]. Many cytokines, like tumor necrosis factor (TNF)-α, IL-6, and IL-1β, are able to enhance the production of this adipokine in physiologic and pathological conditions [6,13]. Leptin has pleiotropic effects and leptin receptor (LepR), that has different isoforms, is distributed in almost all organs and tissues [14]. Leptin is able to cross the haematoencephalic barrier and through the interaction with LepRB receptor is able to strongly regulate appetite and energy balance, to increase hypothalamus-hypophysis-thyroid axis and to decrease hypothalamus-hypophysis-adrenal gland axis. Leptin is also well known to be able to promote endothelial dysfunction and atherosclerosis plaque formation and destabilization, to enhance glucose and free fatty acids intake and fatty acid β–oxidation in smooth muscle, pancreas and liver, to block lipogenesis and modulate gluconeogenesis in liver, to modulate nutrient absorption and intestinal motility, and to promote insulin-resistance [4].

Leptin and immune system

It is well established that leptin exerts mainly pro-inflammatory but also anti-inflammatory features on immune system, which are summarized in Fig. 1. Sequence homology between LepRB receptor and members of class I cytokine receptor (gp130) superfamily, which includes for example IL-6R, has been clearly demonstrated [15,16]. The isoform LepRB, which is present on almost all immune cell types [17,18], activates the same signal transducers as IL-6-type receptors, like janus kinases (JAK), signal transducers and activators of transcription (STAT)-1, STAT-3, STAT-5, STAT-6, phosphatidylinositol 3-kinase (PI3K), and mitogen-activated protein kinase (MAPK) [16,19,20]. Particularly, through STAT-3 pathway, leptin is able to mediate activation of macrophages and lymphocytes [6,20–22] and contributes to development, differentiation, proliferation, activation and cytotoxicity of natural killer (NK) cells [23]. Through MAPK pathway, leptin can induce chemotaxis in neutrophils [24] and protect peripheral blood mononuclear cells (PBMCs) against apoptosis [25,26]. Through PI3K, leptin activates NF-κB, a well-known pro-inflammatory mediator [27], especially in dendritic cells [28].

Overall, leptin is able to deeply affect innate immunity. In neutrophils, leptin induces chemotaxis [18,29] and oxygen radicals production and could represent survival mediator [30,31]. On dendritic cells, leptin is able to increase IL-8, IL-12, IL-6, and TNF-α secretion, decrease MIP-1-α production, direct them towards Th1 priming and induce survival through PI3K-Akt activation [7]. On mast cells, leptin could have immunomodulatory features [32]. On monocytes/macrophages, it induces activation, expression of adhesion molecules, production of pro-inflammatory cytokines (such as TNF-α, IL-1, and IL-6), synthesis of IL-1 receptor antagonist and interferon-γ-inducible protein (IP-10), nitric oxide release, phagocytosis [33] via phospholipase activation [34] and leukotriene (LT)B4 secretion. On NK cells, it induces maturation, activation, and cytotoxic phenotype [4]. On eosinophils and basophils, leptin is able to induce chemotaxis; on basophils it is able to induce the production of pro-inflammatory cytokines as well [4].

Leptin has a central effect on adaptive immunity as well. In ob/

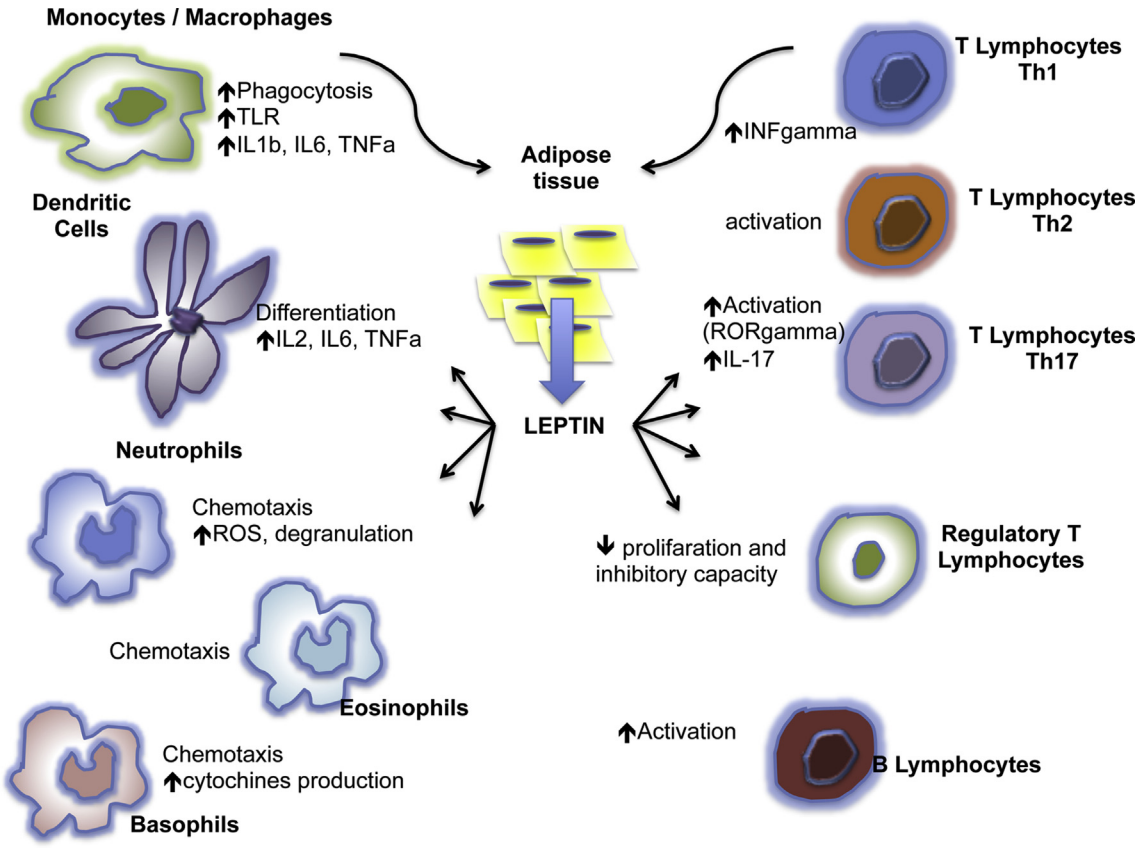

Fig. 1. Role of leptin on immune system.
Leptin exerts many functions both on innate and adaptive immune system. Overall, it acts mainly as a pro-inflammatory cytokine, enhancing inflammatory features on different cells types and reducing proliferation and inhibitory capacity on Tregs lymphocytes.