Leptin in Inflammation

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Leptin is an important regulator of basal metabolism and food intake, with a pivotal role in obesity. Leptin exerts many different actions on various tissues and systems, including cancer, and is considered as a linkage between metabolism and the immune system.

Keywords: leptin ; obesity ; inflammation ; cancer ; immune system ; immunotherapy

1. Introduction

Leptin is a non-glycosylated hormone consisting of 167 amino acids whose existence was predicted for the first time in leptin deficient (ob/ob) and leptin receptor deficient (db/db) mice [1][2] and later described as the product of the *obese (Ob)* gene [3]. In vertebrates, leptin structures show differences in their primary amino acid sequences, but secondary and tertiary structures are similar [4], being alike to the long-chain helical cytokine family, which includes interleukin (IL) 6, IL-11, IL-12, G-CSF or oncostatin M, among others [5].

Leptin is mainly expressed in adipose tissue, but it has also been found in other tissues, such as the gastrointestinal system, the brain, or muscles [6]. In physiological conditions, leptin expression is regulated by cortisol [7], insulin [8], and IL-1b [9] during inflammation, and is an essential part of the healing process since it restores both physiological functions and homeostasis. Leptin plays a key role in inflammation due to a huge variety of metabolic effects, e.g., it increases both fatty acid oxidation [10] and glucose uptake [11]. However, inflammation sometimes takes a long period of time and could downregulate immune system functions, producing homeostatic changes and chronic pathological states, such as chronic inflammation [12]. In this context, leptin has a proinflammatory capacity, not only with a key role in obesity and food intake [13][14][15], but also in neuroendocrine regulation [16], reproduction [17][18] and diseases such as rheumatoid arthritis [19] and other autoimmune diseases [20].

Furthermore, leptin is well known to play a protumoral role, since it promotes angiogenesis, the proliferation, and survival of tumor cells, as well as the inhibition of apoptosis, leading to progression and metastasis [21]. In preclinical models, important findings related to both leptin and Ob-R levels have been found by using different strategies to overcome cancer, e.g., leptin receptor signaling has been shown to support cell metabolism in breast cancer [22], and vitamin D was found to mitigate breast tumor growth and dropped leptin levels in another study [23]. Moreover, high leptin and resistin levels impaired the therapeutic effects of dacarbazine in melanoma and their reduction improved the drug efficacy [24], which supports the importance and influence of leptin in obesity-associated conditions [25].

Conversely, leptin has been shown to reverse the immunosuppressive effects of acute starvation in mice [26]. In line with this, novel aspects have been reported in cancer. For example, leptin had antitumoral functions in human pancreatic cancer cell lines [27]. Recently, obese patients have been shown to obtain better responses to cancer immunotherapies [28][29][30], that may be related to leptin levels.

2. Role of Leptin in Inflammation

2.1. Leptin Receptors and Leptin Signaling Pathways

Leptin presents pleiotropic effects due to the huge variety of leptin receptors (known as Ob-R or LEPR), which belong to the class I cytokine superfamily [31][32], differing from each other in the lengths of their cytoplasmic regions and named Ob-Ra, Ob-Rb, Ob-Rc, Ob-Rd, Ob-Re and Ob-Rf. Short leptin isoforms (Ob-Ra, Ob-Rc, Ob-Rd, and Ob-Rf) can bind Janus kinases (JAK) and activate other signal transduction cascades, the soluble isoform (Ob-Re) is able to regulate leptin levels in serum, and the long leptin isoform (Ob-Rb) can fully transduce activation signals into cells via JAK2/signal transducer and activator of transcription (STAT) 3, mitogen activated protein kinase (MAPK)/extracellular-signal-regulated

kinase (ERK) 1/2 or phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathways [33][34]. Ob-Rd and Ob-Rf have only been described in mice and rats, respectively [35].

2.2. Leptin, Inflammation, and Immune System

One of the pleiotropic effects of leptin involves the immunometabolism. Adipose tissue plays an important role in both energetic balance and storage of energy and, depending on the availability of energy, can limit or promote biological responses, such as the activation of the immune system to fight against infections [36]. Adipose tissue is also involved in inflammatory conditions by releasing hormones, anti-inflammatory, and proinflammatory factors, including leptin or adiponectin [37][38]. Leptin acts as a proinflammatory mediator in obesity-associated immune-metabolic disorders, such as diabetes, cardiovascular or autoimmune diseases, and cancer [12] by regulating hematopoiesis, lymphopoiesis, and myelopoiesis [39][40] at the development, proliferation, antiapoptotic, maturation and activation levels [41][42].

Ob-R expression is found in immune cells [36], thus leptin is involved in inflammatory/immune-related processes, e.g., by stimulating the proliferation of circulating monocytes [43]. In polymorphonuclear cells, leptin inhibits apoptosis [44][45], promotes chemotaxis [46][47], and improves the expression of CD11b via monocytes by releasing TNF-α [48], as well as stimulating the production of reactive oxygen species (ROS) [49]. Specifically in eosinophiles, leptin could suppress Intercellular Adhesion Molecule 3(ICAM-3) and enhances the expression of surface markers (e.g., ICAM-1 and CD18), and inflammatory cytokines such as IL-1β, IL-6, or IL-8 [50]. Leptin also upregulates the expression of CD63 in basophils and allows the production of type 2 cytokines such as IL-4 or IL-13 [51], which play an important role in some types of cancer [47].

In mast cells, leptin also acts as a chemoattractant and provokes the generation of histamine, cysteinyl leukotrienes, CCL2 or ROS [52], as well as causing an eosinophilic inflammation through the activation of mast cell secretory activity mediated by TNF-a, CCL5 or PGD2 [53]. Moreover, leptin-deficient mast cells take part in anti-inflammatory processes [54]. On the other hand, leptin has been described as a critical regulator for NK cell development and activation [55], since its impact on the NK immunomodulatory cytotoxicity and cytokine secretion seems unclear [56][57]. Additionally, leptin leads dendritic cell (DC) differentiation and survival [58] and helps to improve both the activation and proliferation of CD4+ and CD8+ T cells [59][60], as well as promoting Th17 differentiation [61] and Th2 responses [62]. By contrast, this hormone reduces the levels of regulatory T cells (Tregs) [63][64] and induces immunosenescence in B cells, decreasing the production of antibodies [65].

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