Cytokine & Growth Factor Reviews 35 (2017) 71–84

Contents lists available at ScienceDirect

Cytokine & Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

Mini review

Role of leptin as a link between metabolism and the immune system

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ARTICLE INFO

Article history:
Received 1 December 2016
Received in revised form 1 March 2017
Accepted 2 March 2017
Available online 4 March 2017

Keywords:
Leptin
Leptin receptor
Innate immunity
Adaptive immunity
Inflammation

ABSTRACT

Leptin is an adipocyte-derived hormone not only with an important role in the central control of energy metabolism, but also with many pleiotropic effects in different physiological systems. One of these peripheral functions of leptin is a regulatory role in the interplay between energy metabolism and the immune system, being a cornerstone of the new field of immunometabolism. Leptin receptor is expressed throughout the immune system and the regulatory effects of leptin include cells from both the innate and adaptive immune system. Leptin is one of the adipokines responsible for the inflammatory state found in obesity that predisposes not only to type 2 diabetes, metabolic syndrome and cardiovascular disease, but also to autoimmune and allergic diseases. Leptin is an important mediator of the immunosuppressive state in undernutrition status. Placenta is the second source of leptin and it may play a role in the immunomodulation during pregnancy. Finally, recent work has pointed to the participation of leptin and leptin receptor in the pathophysiology of inflammation in oral biology.

Therefore, leptin and leptin receptor should be considered for investigation as a marker of inflammation and immune activation in the frontier of innate-adaptive system, and as possible targets for intervention in the immunometabolic mediated pathophysiology.

Contents

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http://dx.doi.org/10.1016/j.cytogfr.2017.03.001
1359-6101/

1. Introduction

A link between body weight, adipose tissue, and immunity has been hypothesized for a long time, but the precise molecular mediators were unknown until the discovery of leptin in 1994, an adipocyte-derived hormone. Leptin is a non-glycosylated hormone of 146 aminoacids [1] with a tertiary structure resembling that of members of the long-chain helical cytokine family (that includes IL-6, IL-11, IL-12, LIF, G-CSF, CNTF, and oncostatin M) [2]. Leptin is synthesized mainly in adipose cells [3] to regulate weight control in a central manner [2]. Circulating leptin levels (normal range 1–15 ng/mL) directly reflect the amount of energy stored in the adipose tissue and are proportional to the body adipose mass both in mice and in humans. Thus, obese individuals typically produce higher leptin than leaner individuals [4–7]. During fasting period and after reduction of body fat mass, there is a decrease in leptin levels that leads to a reduction in total energy expenditure to provide enough energy for the function of vital organs, that is, the brain, the heart, and the liver [8]. However, there is now increasing evidence that leptin has systemic effects apart from those related to energy homeostasis, including regulation of neuroendocrine, reproductive, hematopoietic and immune functions [9]. Even though these effects of leptin decrease are aimed to improve the survival chances under starving conditions, the fall in leptin levels may lead to immune suppression [10], in addition to other neuroendocrine alterations affecting adrenal, thyroid, and sexual/reproductive function [11]. At least, these alterations observed during fasting parallel the decrease in circulating leptin levels. In fact, both ob/ob mice (lacking leptin secretion) and db/db mice (lacking leptin receptor) are not only obese but they also show the immune/endocrine deficiencies observed during starvation [11,12]. In this context, low plasma leptin levels are found in patients with impaired immune response, such as pulmonary tuberculosis patients, and effective treatment restores leptin levels [13] On the other hand obesity is now regarded as a pro-inflammatory state, and leptin participates with other adipokines in this pathophysiological state in obese subjects [14].

The pleiotropic nature of leptin is supported by the universal distribution of leptin receptor (LEPR), which may have several isoforms, differing in the length of their cytoplasmic regions [15]. LEPR also shows structural similarity to the class I cytokine receptor family [15–17] and similar to other receptors of this class, LEPR lacks intrinsic tyrosine kinase activity, but requires the activation of receptor-associated kinases of the Janus family (JAKs)

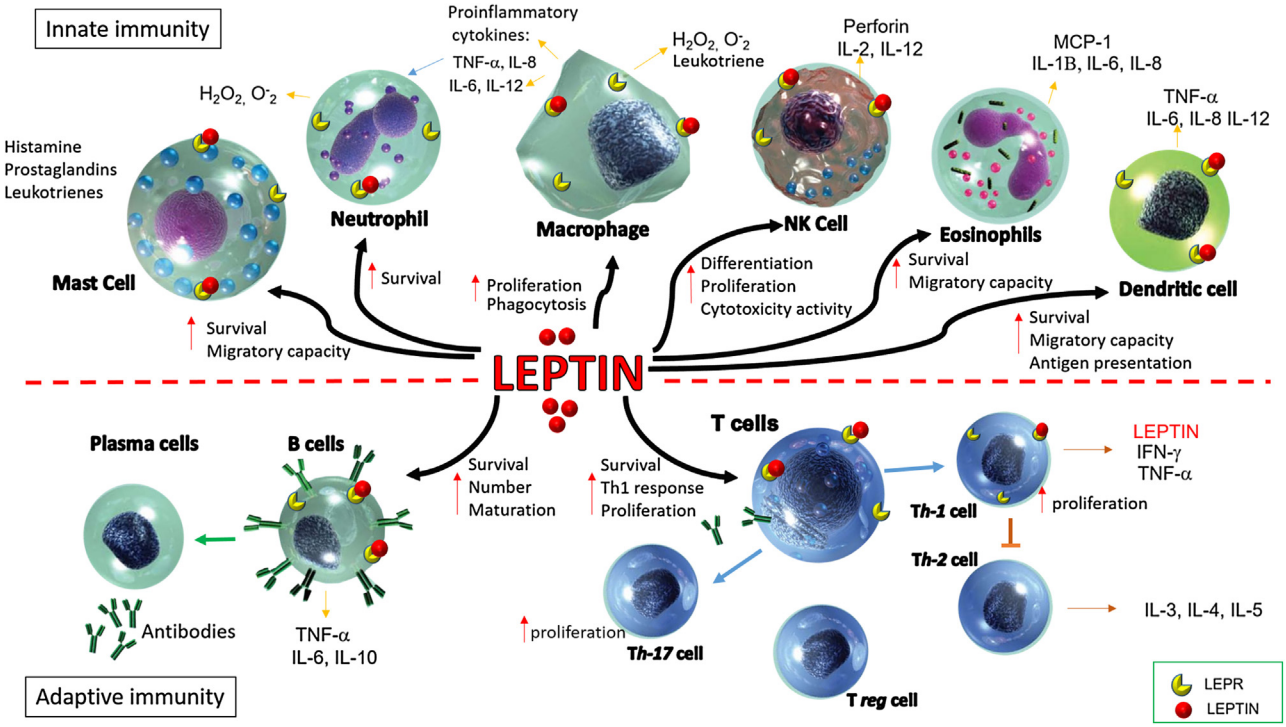

Fig. 1. Effects of leptin on innate and adaptive immune responses.
Leptin affects both innate and adaptive immunity. In innate immunity, leptin modulates the activity and function of Mast cells by enhancing migratory capacity and their survival rate. Leptin also modulates the activity and function of Neutrophils by increasing chemotaxis and the secretion of oxygen radicals (such as hydrogen peroxide, H_2O_2, and superoxide, O^2) through direct and indirect mechanisms. The leptin action seems to be mediated by tumour necrosis factor (TNF) secreted by monocytes/macrophages. Leptin increases phagocytosis by monocytes/macrophages and enhances the secretion of pro-inflammatory mediators. On natural killer (NK) cells, leptin increases cytotoxic capacity and the secretion of perforin and interleukin-2 (IL-2). Leptin can also modulate migratory capacity of human eosinophils, as well as their survival and migratory capacity. Leptin stimulates the release of inflammatory cytokines (including IL-1β, IL-6, IL-8) and chemokines (monocyte chemotactic protein-1). Finally, leptin induces functional and morphological changes in human DCs, licensing them towards Th1 priming and promoting DC survival. Moreover, leptin also increases immature human DC migratory capacity and antigen presentation capacity. In adaptive immunity, leptin affects the generation, maturation and survival of T cells by reducing their rate of apoptosis. On memory T cells, leptin promotes the switch towards T helper 1 (*Th1*) cell immune responses by increasing interferon-ɣ (IFN-ɣ) secretion, and facilitate Th17responses. Conversely, leptin can act as a negative signal for the expansion of human regulatory T cells (Treg). This process is then sustained by an autocrine loop of leptin secretion by *Th1* cells. Finally, leptin activates B cells to secrete cytokines (ie., TNF-α,IL-6, IL-10, and TNF-a) as well as the production of IgG2α and delayed-type hypersensitivity responses.