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Minireview

The role of leptin in the pathophysiology of rheumatoid arthritis

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ABSTRACT

The past 20 years of research on leptin has provided important insights into its role in rheumatoid arthritis (RA). Leptin is one of the different adipokines produced by the adipose tissue that influences the endocrine system, energy homeostasis and the immune response in several ways. Leptin is known to have predominantly pro-inflammatory effects, especially in the setting of chronic inflammation. Animal models of arthritis have illustrated well the participation of leptin in the inflammatory response within the joints. In patients with RA, numerous studies have evaluated the concentrations of leptin in the bloodstream and/or the joint cavity, showing higher levels compared to control populations. Leptin has also been found to correlate with clinical or biological measurements of disease activity of RA. Conversely, the relationship between serum leptin and joint structural damage is less evident. Leptin may also promote the development of atherosclerosis in RA and may contribute to the cardiovascular consequences of the metabolic syndrome that coexists with RA. Indeed, leptin could be a link between inflammation, metabolic risk factors and cardiovascular diseases in RA. Finally, due to abnormal body composition phenotypes with an increased prevalence of obesity in RA, the therapeutic response to traditional DMARDs and/or biological agents may be attenuated. This review discusses the multiple interplays that have been described between leptin and the clinical, radiographic and therapeutic aspects of RA.

Contents

1. Introduction

The adipose tissue is now considered as an active organ, sending out and responding to a wide range of biological signals. Indeed, for a long

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time, fat mass has been regarded as a storage depot for body energy and as a thermoregulator. The discovery of leptin 20 years ago has shone light on the contribution of adipose tissue to whole body homeostasis. In fact, adipose tissue is responsible for the production of a substantial number of soluble mediators or adipokines that are involved in the regulation of several physiological processes, including energy homeostasis, insulin secretion, angiogenesis, endocrine functions, reproduction, bone formation and also the control of immunity [1–3]. The adipokines are a vast range of disparate soluble proteins that are mostly but not exclusively secreted by adipose tissue. A low grade of inflammation is observed in obese patients while malnutrition is associated with increased susceptibility to infections, changes in cytokine production and altered immune response [1,4]. Thus, the influence of adipokines on the immune response is now well described and these peptides may be differentiated between those inducing predominantly pro-inflammatory (leptin, resistin and visfatin) or anti-inflammatory (adiponectin) effects [2,3,5].

Leptin is the first adipokine to have been described. Its most evident function is the control of appetite and energy balance. A considerable interest in this adipokine has emerged these past fifteen years, especially in autoimmune diseases [4,6]. Changes in body composition are described in autoimmune diseases such as rheumatoid arthritis (RA) and obesity is currently viewed as a predisposing factor for the development of some of these diseases, including psoriasis and RA [7]. Rheumatoid arthritis is a severe chronic inflammatory rheumatic disease leading to joint destruction and deformities. Its pathophysiology is complex and includes environmental and genetic factors, leading to active inflammation of the synovium. The key drivers of inflammation in RA have been identified as pro-inflammatory cytokines such as TNFα, IL-6 and IL-1. Rheumatoid arthritis is associated with a reduced life expectancy linked to cardiovascular (CV) morbidity and mortality that are partially explained by traditional CV risk factors [8,9]. Obesity is among these risk factors that may impact on CV risk. The adipokines produced by an excess of fat mass could therefore contribute to this altered CV risk in RA.

This review aims to describe the role and contribution of leptin in RA. We will discuss its potential role in disease activity, its influence on radiographic damage, and also whether fat mass and/or leptin could influence the therapeutic response to conventional drugs or biological agents. The relationship between leptin and CV risk in RA will also be analyzed.

2. The biological activities of leptin

Leptin, the product of the *Lep* gene, is a 16-kDa non-glycosylated peptide hormone. It belongs to the type I cytokine superfamily and has a long helix structure similar to IL-2, IL-6, IL-12 and G-CSF [10]. In mice, a single mutation in the *ob* gene (an equivalent of the *Lep* gene in humans) leads to obesity. The same phenotype is observed in mice lacking the leptin receptor (*db*/*db* genotype) [6,10]. Circulating leptin levels correlate with the amount of fat and body mass index (BMI). Leptin synthesis is inhibited by testosterone and stimulated by ovarian sex steroids, explaining why higher serum leptin levels are observed in women compared to men, even after adjustment for body mass index (BMI). Leptin plays a major role in the control of appetite, resulting from its action on the hypothalamus by indicating the size of adipose tissue stores. In fact, leptin exerts its action by inducing the expression of anorexigenic factors and reducing the hypothalamic synthesis of orexigenic peptides [11]. The production of leptin is influenced by insulin levels, energy status, sex hormones and a wide range of inflammatory mediators, including TNFα and IL-1 [1,4,6] (Fig. 1).

Leptin is involved in both innate and adaptive immune responses: leptin levels increase during infection and inflammation, possibly as a result of enhanced production mediated by IL-1β, TNFα and IL-6 [4,5,12]. Leptin's role in immunity has been suggested by early observation of thymic atrophy in *db*/*db* mice. During malnutrition or starvation, levels of leptin are low and these conditions are associated with thymic atrophy and impaired immune responses [1]. Leptin activity on the immune system is basically pro-inflammatory and has several actions similar to those of acute phase reactants. Leptin up regulates the production of inflammatory cytokines including TNFα, IL-6 and IL-12, and conversely, TNFα and IL-1β increase the expression of leptin in adipose tissue, such as a loop whose components influence each other [4,6]. The level or expression of leptin increases in serum or adipose tissue after administration of inflammatory stimuli such as lipopolysaccharide (LPS) or in experimental models of inflammation [13]. In innate immunity, leptin can stimulate monocytes, macrophages, dendritic cells, neutrophils and NK cells. Leptin enhances the phagocytic activity of monocytes/macrophages and induces them to produce eicosanoids, nitric oxide and several cytokines [4]. Leptin stimulates the chemotaxis and release of reactive oxygen species such as hydrogen peroxide by neutrophils [1]. Leptin promotes NK cell differentiation, proliferation, activation and cytotoxicity [14]. In adaptive immunity, leptin stimulates secretion, maturation and survival of thymocytes, proliferation of naïve T lymphocytes and activation of Th1 and B cells [15]. Leptin promotes T cell activation and shifts the T cell cytokine production towards a Th1 phenotype, increasing the production of IFNγ and IL-2 and suppressing the production of IL-4 [16]. In Th1 cells, leptin stimulates the production of TNFα and IFNγ. In humans with leptin deficiency, circulating CD4 + T lymphocytes are decreased in number and impaired in proliferation and cytokine release [4–6]. In addition, leptin inhibits the production of regulatory T cells (Treg) which are critical mediators of peripheral immune tolerance [17]. Indeed, leptin has a negative influence on the proliferation of naturally occurring CD4 + CD25 + Foxp3 + Treg cells. Recent data indicated that freshly isolated Treg can produce leptin and express significant amount of leptin receptors on their cell surface. In addition, in vitro neutralization with anti-leptin monoclonal antibody following anti-CD3/CD28 stimulation resulted in Treg proliferation. The Treg that had expanded in this context of anti-leptin monoclonal antibody had increased expression of Foxp3 and suppressive properties [18]. Reduced numbers of circulating Treg have been described in obese subjects, with an association between the number of these cells and measures of adiposity, BMI and inflammation [19]. Finally, recent reports have shown that normal adipose tissue is a site for the preferential accumulation of Treg cells [20]. The IL-23/IL-17 pro-inflammatory axis is increased in obese women [21]. During a two year follow-up study of plasma leptin in patients with RA, changes in the score of disease activity paralleled those of IL-17 levels, suggesting a link between leptin and Th17 lymphocytes [22].

3. Leptin and animal models of RA

Different animal models of arthritis have demonstrated well the pro-inflammatory role of leptin in the joint cavity. Leptin was found to be expressed in the synovial fluid of rats with antigen-induced arthritis [23]. Using this experimental model, a less severe arthritis was observed in leptin deficient mice [24]. The expression of TNFα and IL1β was reduced in these mice as compared to the wild-type mice. In addition, a shift towards a Th2 response characterized the in vitro Ag specific T cell proliferative response [24]. Systemic administration of leptin into normal rats did not induce arthritis, but worsened the severity of K/BxN arthritis in mice. When given leptin receptor antagonists, the leptin-induced disease activity was attenuated in this model of arthritis [25]. In adjuvant arthritis, leptin and leptin receptor antagonists reduced the extent of joint swelling and the number of arthritic joints [25]. In collagen-induced arthritis, a rich diet feeding induced leptin resistance and arthritis was reduced [26]. In mice, leptin induced Th17 differentiation and proliferation from naïve CD4 + cells. Leptin injected in the joints of mice with collagen-induced arthritis resulted in an early onset of arthritis and increased the severity of clinical symptoms. In this model, leptin was found to be expressed in the joint tissue and synovial fluid [27]. All these data strongly support the hypothesis of a pro-inflammatory role for leptin in various models of arthritis. However, leptin may stimulate the production of anti-inflammatory cytokines