Leptin in Autoimmune Diseases

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Abstract

Over the last few years, a series of molecules known to play a function in metabolism have also been shown to play an important role in the regulation of the immune response. In this context, the adipocyte-derived hormone leptin has been shown to regulate the immune response both in normal as well as in pathological conditions. More specifically, it has been shown that conditions of reduced leptin production are associated with increased infection susceptibility. Conversely, immune-mediated disorders such as autoimmune diseases are associated with increased secretion of leptin and production of pro-inflammatory pathogenic cytokines. In this context, leptin could represent the “missing link” between immune response, metabolic function, and nutritional status. Strategies aimed at interfering with the leptin axis could represent innovative therapeutic tools for infections and autoimmune disorders. This chapter reviews the most recent advances in the role of leptin in autoimmune responses.

Key Words: Leptin; metabolism; autoimmunity; inflammation; immune tolerance.

1. INTRODUCTION

Over the past century, improved hygienic and nutritional conditions have significantly reduced the incidence of infectious diseases, at least in the most developed countries (1). In parallel with the improvement in nutritional status, however, an increase in susceptibility to autoimmune disorders has emerged (2,3). Recently, it has been proposed that the lifestyle in developed countries, with reduced exposure to environmental pathogens, could be relevant to the increase in the prevalence of autoimmune disorders (3). Conversely, in less-affluent societies, exposure to microorganisms, pathogens, and other environmental influences might promote the development of T-regulatory responses that protect against autoimmune responses (3,4). Leptin, an adipocyte-derived hormone of the long-chain helical cytokine family, has recently been proposed to act as a link between nutritional status and immune function (5,6). Leptin has multiple biological effects on nutritional status, metabolism, and the neuro–immuno–endocrine axis. The circulating concentration of leptin is proportional to fat mass (6), and reduced body fat or nutritional deprivation—typically associated with hypoleptinemia—is a direct cause of secondary immunodeficiency and increased susceptibility to infections (5,7,8). The reason for this association was not apparent until recently. Now, it can be hypothesized that a low concentration of serum leptin increases susceptibility to infectious diseases by reducing T-helper (Th)-cell priming and direct effects on thymic function.
Furthermore, congenital deficiency of leptin has been found to be associated with increased frequency of infection and related mortality (9,10). By contrast, the Th1-promoting effects of leptin have been linked recently to enhanced susceptibility to experimentally induced autoimmune diseases, such as experimental autoimmune encephalomyelitis (EAE), type 1 diabetes (T1D), antigen-induced arthritis (AIA), and others. These latter observations suggested a novel role for leptin in determining the gender bias of susceptibility to autoimmunity, because female mice and humans, which are relatively hyperleptinemic, have an increased frequency of autoimmune diseases compared with males, which are relatively hypo leptinemic (5,6). In view of these findings, we suggest leptin as a novel candidate able to explain at least in part the increased frequency of autoimmune disorders in the more affluent countries and in females. Further experimental evidence is needed to address the precise role of leptin in autoimmune disease susceptibility.

2. LEPTIN IN MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic, immune-mediated, inflammatory disorder of the central nervous system (CNS) myelin. The most studied model of multiple sclerosis in animals is the EAE that can be induced in susceptible strains of mice by immunization with self-antigens derived from myelin. The disease is characterized by autoreactive T-cells that traffic to the brain and the spinal cord and injury myelin, with the result of chronic or relapsing-remitting paralysis, depending on the antigen and the strain of mice used. It is known that myelin-reactive Th1 CD4+ cells induce and/or transfer disease and that Th1 cytokines are present in inflammatory EAE lesions in the central nervous system. In contrast, Th2 cytokines are associated with recovery from EAE or protection from the disease.

Leptin is involved in both the induction and progression of EAE in mice (11–13). Analysis of the disease susceptibility in naturally leptin-deficient ob/ob mice before leptin replacement revealed resistance to both active and adoptive EAE that was reversed by leptin administration. Leptin replacement converted Th2- to Th1-type response and shifted IgG antibodies from IgG1 to IgG2a. In addition, leptin administration to susceptible wild-type C57BL/6J mice worsened the disease by increasing proinflammatory cytokine release and IgG2a production (11). In addition, it has also been recently observed that a serum leptin surge precedes the onset of EAE in susceptible strains of mice (12). This peak in serum leptin is correlated with inflammatory anorexia, weight loss, and development of a pathogenic T-cell response against myelin (12). In animals with EAE, inflammatory brain infiltrates have also been shown to be a source of leptin, attesting to an in situ leptin production in active lesions (12). Systemic and/or in situ leptin secretion was not observed in EAE-resistant mice. Taken together, these data show an involvement of leptin in the pathogenesis of central nervous system autoimmunity in the EAE model.

In human MS, it has been reported that secretion of leptin is increased in serum and cerebrospinal fluid (CSF) of naïve-to-treatment MS patients and positively correlated with the secretion of interferon (IFN)-γ in CSF and inversely with the percentage of circulating regulatory T-cells (T_{Reg}), a key cellular subset in the suppression of immune and autoimmune responses, involved in the maintenance of T-cell tolerance (14). In