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Review

Prolactin: A versatile regulator of inflammation and autoimmune pathology

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ABSTRACT

Prolactin (PRL) has long been proposed as an immune-stimulating and detrimental factor in autoimmune disorders. However, recent findings have challenged this common view, showing that PRL does not play a crucial role in the development of experimental autoimmune encephalomyelitis, animal model for multiple sclerosis (MS), and even protects against adjuvant-induced model of rheumatoid arthritis (RA). In this review we provide a critical overview of data supporting a role for PRL in the regulation of immune responses. In addition, we focus on studies exploring the involvement of PRL in autoimmune diseases, such as systemic lupus erythematosus, MS and RA, in light of the recently-outlined regenerative properties of this hormone.

Contents

Abbreviations: Ag, antigen; BCR, bromocriptine; CNS, central nervous system; EAE, experimental autoimmune encephalomyelitis; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon-γ; Ig, immunoglobulin; IL, interleukin; iNOS, inducible nitric oxide synthase; IP-10, interferon gamma-induced protein-10; IRF-1, interferon regulatory factor-1; JAK, Janus kinase; LFA-1, leukocyte functional antigen-1; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MHC, major histocompatibility complex; MIP-1α, macrophage inflammatory protein-1α; MS, multiple sclerosis; NK, natural killer; PBMC, peripheral blood mononuclear cells; PRL, prolactin; PRLR, prolactin receptor; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; STAT, signal transducer and activator of transcription; SVZ, subventricular zone; Th, T helper; TNF-α, tumor necrosis factor-α; VLA-4, very late antigen-4.

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1. Introduction

Prolactin (PRL) is a polypeptide hormone discovered more than eighty years ago as a pituitary factor stimulating mammary gland development and lactation in rabbits [1]. Since its first discovery, several extra-pituitary sources of PRL have been identified and a great number of other functions have been associated with this hormone in various vertebrate species [2]. One of the most controversial and enigmatic aspects of PRL biology is related to its role in regulating immune responses and autoimmune inflammation. Indeed, a plethora of studies since the late 70s has documented the ability of PRL to stimulate the proliferation and the inflammatory activity of immune cells. This remarkable amount of work, along with several reports describing hyperprolactinemia in autoimmune disorders, has set the background for the general belief that PRL is a detrimental factor in autoimmunity, and has prompted to investigate in both preclinical models and clinical studies if PRL depletion by pharmacological treatments might ameliorate the clinical course of autoimmune diseases. With the exception of systemic lupus erythematosus (SLE), in diseases such as multiple sclerosis (MS) and rheumatoid arthritis (RA) these studies have led to inconclusive results and the actual contribution of PRL has long remained elusive. Also, the relevance of PRL in the immune system (and consequently in autoimmunity) has been revaluated in the last decade, since no evident immune deficits have been identified in PRL- and PRL receptor (PRLR)-deficient mouse models. The interpretation of the effect of PRL in autoimmune pathology has been further complicated since an increasing number of studies has uncovered that PRL is unexpectedly endowed with regenerative properties for several tissues, including the central nervous system (CNS) [3,4] and the bone and cartilage [5,6], which are target of autoimmune attacks in MS and RA, respectively. The aim of this review is first to provide a general overview on the main established functions of PRL in the immune system, as emerged by both in vitro and in vivo experimental approaches. Second, to discuss major studies exploring the contribution of PRL to autoimmune disorders, with specific emphasis on latest work performed in experimental models of SLE, MS and RA, which have shed light on new and unexpected effects exerted by PRL in autoimmunity.

2. The biology of PRL

PRL is mainly produced by lactotroph cells of the anterior pituitary gland, but, in humans, an alternative promoter (also known as superdistal or extrapituitary promoter) drives *PRL* expression in several extra-pituitary sites, such as immune, decidual, mammary, epithelial and fat cells [7]. The superdistal promoter is located upstream of the pituitary promoter and generates an alternative transcript, 150 bp longer than the classical pituitary mRNA. Both *PRL* transcripts encode for an identical mature protein of 199 amino acids (23 kDa) [7]. PRL can undergo several post-translational modifications, such as phosphorylation and glycosylation. Proteolytic cleavage originates 14-, 16- and 22-kDa PRL variants [8]. Other PRL isoforms have been identified in human sera and result from processes of polymerization or aggregation with immunoglobulins (Igs), such as "big PRL" (45–50 kDa), "big big" PRL or macroprolactin (>100 kDa). These higher molecular weight variants have less biological activity than the monomeric 23 kDa PRL [9].

PRL secretion is under dual regulation by hypothalamic hormones such as thyrotropin-releasing factor and dopamine via the pituitary portal circulation [8,10]. The biological effects of PRL are mediated by its interaction with PRLR, a member of the cytokine receptor superfamily, which includes receptors for interleukin (IL)-2, IL-6, granulocyte–macrophage colony-stimulating factor (GM-CSF) and leptin [11,12]. This receptor is present in nearly all organs and tissues and is particularly interesting because it can be activated by three sequence-diverse human hormones: PRL, growth hormone, and placental lactogen. Binding of PRL to its receptor [13] activates at least three signaling pathways including the Janus kinase/signal transducer and activator of transcription (JAK/STAT), the phosphoinositide 3-kinase and the mitogen-activated protein kinase (MAPK). Most current knowledge on PRL has been obtained from the study of PRL- and PRLR-deficient mice [14,15] providing strong proof of the main PRL signaling pathway.

The multiple biological functions of PRL have been subdivided into the following categories: water and electrolyte balance, growth and development, endocrinology and metabolism, brain and behavior, reproduction, and finally immunoregulation [2]. However, the extremely wide spectrum of PRL activities must be regarded as a panel of functions that are modulated by, rather strictly dependent on, PRL.

3. PRL and immune functions

3.1. In vitro studies

Many studies have analyzed the immune-modulating functions of PRL in vitro, suggesting that PRL has the ability to affect the development, survival and function of cells belonging to both innate and adaptive arms of the immune system (Fig. 1) [16,17].

PRL has been shown to sustain the phagocytic and inflammatory activities of macrophages. PRL enhances the release of reactive oxygen intermediates by human macrophages [18] and supports the cytotoxic activity of mouse tumor-associated macrophages against tumor cells [19]. Murine peritoneal macrophages treated with low-to-high amounts of PRL (the optimal dose was 100 ng/ml) display activation of p38 MAPK and STAT3 signaling pathways and produce higher quantities of nitric oxide and pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, IL-1β, interferon (IFN)-γ and IL-12 [20,21]. Interestingly, very high PRL concentration (1000 ng/ml) significantly enhances the secretion of the anti-inflammatory cytokine IL-10 in these cells [22]. PRL also stimulates macrophages to release several chemokines, e.g. macrophage inflammatory protein (MIP)-1α, interferon gamma-induced protein (IP)-10 and monocyte chemoattractant protein (MCP)-1 [22]. Human granulocytes exposed to PRL exhibit the activation of STAT1 and p38 MAPK intracellular pathways and the upregulation of inflammation-related genes such as inducible nitric oxide synthase (iNOS) and interferon regulatory factor 1 (IRF-1) [23]. PRL also stimulates the release of IFN-γ by human natural killer (NK) cells and sustains their cytolytic activity [24]. In synergy with IL-15, PRL has been shown to increase the proliferation of a human NK cell line and to induce the transcription of perforin gene [25]. Also dendritic cells (DCs) are affected by PRL treatment [26]. Low levels of PRL, in combination with GM-CSF, polarize monocytic precursors obtained from human peripheral blood mononuclear cells (PBMCs) toward an immature DC phenotype, enhancing the expression of MHC class II and co-stimulatory molecules such as CD80 and CD86 [27]. Further exposure of immature DCs to high concentrations of PRL promotes their maturation to functional antigen presenting cells, characterized by increased ability to stimulate the proliferation and IFN-γ production of T cells [27,28]. Similar findings have been obtained with rat thymic DCs [29].

PRL has been reported to directly shape several lymphocyte functions. Human B cell hybridomas [30] and peripheral blood B cells [31] secrete higher levels of antibodies following treatment with PRL in a dose-dependent manner. Rat fetal thymic cultures exposed to PRL exhibit enhanced thymocyte proliferation and differentiation of double negative $CD4^{-}CD8^{-}$ precursor cells to double positive $CD4^{+}CD8^{+}$ cells [32]. An anti-PRL antiserum was shown to inhibit the proliferation of a non-immortalized murine T helper (Th) cell clone in response to IL-2 [33,34]. However, PRL was not found at either transcript or protein levels in this Th cell clone [33] and was suggested to derive from culture medium. In line with these data, in more recent work PRL was not detected at either mRNA or protein levels in mouse primary $CD4^{+}$ T cells [35]. In human T cells, PRL has been proposed to support proliferation [36], survival [37], and to act as an autocrine factor. Indeed, an extrapituitary *PRL* transcript has been found in human T cells [38], and its levels are increased following stimulation with cyclic AMP [39], as