Cytokine 74 (2015) 27–34

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.journals.elsevier.com/cytokine

Interleukin-10 paradox: A potent immunoregulatory cytokine that has been difficult to harness for immunotherapy

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ARTICLE INFO

Article history:
Received 15 August 2014
Received in revised form 28 October 2014
Accepted 29 October 2014
Available online 4 December 2014

Keywords:
Interleukin-10
Autoimmunity
Fas pathway
gld
B-cells

ABSTRACT

Interleukin-10 (IL-10) is arguably the most potent anti-inflammatory cytokine. It is produced by almost all the innate and adaptive immune cells. These cells also serve as its targets, indicating that IL-10 secretion and action is highly regulated and perhaps compartmentalized. Consistent with this notion, various efforts directed at systemic administration of IL-10 to modulate autoimmune diseases (type 1 diabetes, multiple sclerosis, rheumatoid arthritis, psoriasis) have produced conflicting and largely inconsequential effects. On the other hand, IL-10 can promote humoral immune responses, enhancing class II expression on B cells and inducing immunoglobulin (Ig) production. Consequently, the high IL-10 level in systemic lupus erythematosus (SLE) patients is considered pathogenic and its blockade ameliorates the disease. In this perspective, we review preclinical findings and results of recent clinical studies using exogenous IL-10 to treat the aforementioned autoimmune diseases. In addition, given the limited success of IL-10 supplementation, we suggest that future studies should be expanded beyond modulating the delivery modes to include developing new strategies to protect and replenish the endogenous sources of IL-10. As an example, we provide evidence that aberrant Fas-mediated deletion of IL-10-producing B cells subverts the immunoregulatory role of IL-10 in autoimmune diabetes and that modulation of the Fas pathway preserves the IL-10-producing B cells and completely protects NOD mice from developing the disease.

1. Introduction

Interleukin 10 (IL-10) is a potent anti-inflammatory cytokine that was originally labeled CSIF or – cytokine synthesis inhibitory factor – due to its ability to inhibit production of proinflammatory (IFN-γ and TNFα) cytokines by T helper l (Th1) cells [1]. Subsequent studies showed that multiple cell types are targets of IL-10 action and that through its inhibitory effects on macrophages and DCs, IL-10 restrains immune responses to pathogens and microbial flora and prevents their pathologies [2]. These properties prompted early and extensive efforts to utilize IL-10 to modulate inflammatory and autoimmune diseases both in mice and humans [3–9]. However, reaching this goal has been challenging as indicated by the limited success of varied strategies to immunomodulate autoimmune diseases using recombinant IL-10. The difficulties are related to the complexity of the mechanisms controlling IL-10 production and suppressive function. These include multiple sources and targets, and feed-forward conditions that modulate its production. This intricate regulatory network enables IL-10 signaling to be tightly and locally controlled, hence hard to recapitulate through simple provision of exogenous IL-10. New approaches based on modulating endogenous sources of IL-10 may prove more effective than simple provision of IL-10. In this perspective, we review preclinical findings and results of recent clinical studies using exogenous IL-10 to treat the aforementioned autoimmune diseases. In addition, given the limited success of IL-10 supplementation, we suggest that future studies should be directed towards developing new strategies to protect and replenish the endogenous sources of IL-10. As an example, we will provide evidence that aberrant Fas-mediated deletion of IL-10-producing B cells subverts the immunoregulatory role of IL-10 in autoimmune diabetes and that modulation of the Fas pathway preserves the IL-10-producing B cells and completely protects NOD mice from developing the disease.

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http://dx.doi.org/10.1016/j.cyto.2014.10.031
1043-4666/

2. Cellular sources of IL-10

Almost all leukocytes, including T and B cells, dendritic cells, γδ T cells, NK cells, mast cells, neutrophils, eosinophils, and keratinocytes produce IL-10 [10–16]. The reasons underlining the evolution of ubiquitous sources of IL-10 are poorly understood, but clearly underscores its physiologic significance and the complexity of its regulation. IL-10 has a short half-life and short range of activity. Thus, endowment of so many cell types with the ability to produce IL-10 could be necessary to ensure its rapid availability at different locales when needed. Also, it could be important to compartmentalize IL-10 action. Additionally, special roles for different cell types in mediating IL-10 function has not been ruled out. For example, regulatory T cells are particularly known for utilizing IL-10 to suppress inflammation and autoimmunity. This was initially demonstrated in a colitis model [17] and subsequently in other disease models [18–20]. Likewise, regulatory B cells (Bregs) are increasingly being investigated for their roles in maintaining self-tolerance via secretion of IL-10 [19]. These B cells differ in their phenotypes, yet they commonly use IL-10 to suppress excessive inflammatory responses in various disease models and to support generation of Tr1 cells [19]. Further support for specialized roles of various cell types in delivering IL-10 is indicated by the studies that implicated altered homeostasis of Breg cells in the pathogenesis of several autoimmune diseases, including contact hypersensitivity (CHS), inflammatory bowel disease (IBD), experimental autoimmune encephalomyelitis (EAE), collagen-induced arthritis (CIA), and type I diabetes (T1D) [20–22]. Antigen-presenting cells (APCs) and innate immune cells are also important and rapid sources of IL-10 that can serve, in autocrine feedback fashion, to constrain activation of APCs and the development of adaptive immune responses. On the other hand, natural killer (NK) cells have also been described as another innate source of IL-10 [23]. This multitude of cell types that produce IL-10 is symbolic of a complex function that is yet to be successfully recapitulated through provision of exogenous IL-10.

3. Cellular and molecular mechanisms of IL-10 action

As a potent immunosuppressive cytokine, IL-10 blocks immune responses at different levels by acting directly and indirectly on both the innate and adaptive arms of the immune system. Consequently, IL-10 can inhibit production of proinflammatory cytokines, antigen presentation, and cell proliferation [24–27]. IL-10 performs these regulatory functions by binding to a specific cell surface receptor (IL-10R) that is made of two chains, IL-10R1 and IL-10R2. Both chains are transmembrane glycoproteins whose intracellular domains differ in length and amino acid sequence [28]. The IL-10R1 is located on human chromosome 11 and the IL-10R2 on chromosome 21 [29,30]. The IL-10R2, which is widely expressed [31,32], binds IL-10 only after IL-10 binds to the IL-10R1 [33–35]. On the other hand, IL-10R1 expression is restricted mainly to the immune cells [36,37] and particularly highly on monocytes and macrophages [38]. It is also expressed on placental cytotrophoblasts [39] and colonic epithelium [40]. Among T cells, the expression level of IL-10R is higher on memory than on naïve CD4 T cells [41]. Binding of IL-10 to IL-10R1 leads to conformational changes in IL-10 that allows its association with the IL-10R2 and the generation of IL-10/IL-10R complexes. These complexes can suppress immune responses by multiple mechanisms, but inhibiting nuclear translocation of the NF-κb and its DNA-binding activity is considered the main one [42]. In addition, IL-10 inhibits TLR-triggered production of proinflammatory mediators via inhibition of MyD88 translation [43] and ubiquitination [44]. Furthermore, IL-10 inhibits IFN-α and -γ induced-gene transcription (e.g. CXCL10, ISG-54) and STAT1 phosphorylation [26,45]. IL-10 also inhibits major histocompatibility complex class II expression, limiting costimulation, and reducing proinflammatory cytokine production by antigen-presenting cells (APC), particularly DCs and macrophages [24,46]. Besides its effects on APCs, IL-10 can directly inhibit activation and proliferation of T cells by suppression of IL-2 production and CD28 signaling [27,47,48]. The effects of IL-10 on humoral immune responses, however, is considered stimulatory and depend on several factors that regulate generation, maintenance, and propagation of B cells [49]. For example, IL-10 promotes B cell differentiation, proliferation, survival, and antibody production. A stimulatory role for IL-10 in antibody production has been implicated in the pathogenesis of multiple sclerosis and SLE [50–52]. IL-10 is also reported to promote proliferation of mast cells [53] and thymocytes [54]. For natural killer (NK) cells, contradictory effects have been described for IL-10, depending on the cellular context. IL-10 inhibits interferon-γ (IFN-γ) production by NK cells in the presence of APCs, partially as a result of a decrease of IFN-γ-inducing cytokines [25,55]. Thus, consistent with its multiple sources, IL-10 engages multiple cellular and molecular pathways to suppress and in certain instances to stimulate immune responses.

4. IL-10 and pathogenesis of autoimmune diseases

Given the broad anti-inflammatory effects of IL-10, a variety of clinical studies were undertaken to assess efficacy of recombinant IL-10 to treat autoimmune diseases. Unfortunately, despite initial high hopes, results of most clinical trials were less than encouraging. In hind sight, however, these poor results should not have been unexpected. One evolutionary indicator is the existence of a complex network of cells that act as sources and subjects to IL-10 action, indicating highly regulated and perhaps compartmentalized effects of IL-10 that is unlikely to be recapitulated by simple infusion of recombinant IL-10. This notion is reinforced by the lack of clear patterns of IL-10 serum level with disease development or activity in most autoimmune diseases. The notable exceptions, however, are SLE and psoriasis, where most published studies indicated high serum levels in SLE and low levels in psoriasis [56–58]. Consistently, blockade of IL-10 appears to be a promising therapeutic strategy against SLE, whereas direct injection of IL-10 in lesions appears effective against psoriasis. Below we will review major autoimmune diseases where IL-10 directed therapies have been assessed and results published (Fig. 1). In addition, we will discuss our suggestion that future studies should be expanded beyond modulating the delivery modes to include developing new strategies to protect and replenish the endogenous sources of IL-10.

4.1. Type-1 diabetes (T1D)

This is a chronic organ-specific autoimmune disease that is caused by autoreactive T cells that infiltrate and destroy insulin-producing pancreatic beta-cells [60], leading to insulin deficiency and hyperglycemia [61]. In healthy individuals, such autoreactive T cells are kept in check by peripheral tolerance mechanisms [62,63]. Analysis of the role of IL-10 in the pathogenesis of T1D, using the NOD mouse model, produced conflicting results. Early studies in 1990s showed that injection of NOD mice with IL-10 delayed [8] or resulted in a long lasting protection [64,65]. By contrast, transgenic expression of IL-10 in pancreatic islets of NOD mice accelerated the disease [66,67]. Furthermore, neutralization of endogenous IL-10 at the age of three weeks inhibited the development of insulitis [68], whereas treatment of in NOD mice at later ages had no significant effects on the disease development [8].