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The neutrophil: one of the cellular targets of interleukin-10

Abstract Interleukin-10 exerts a wide spectrum of in vitro and in vivo biological activities implicated in the regulation of the inflammatory and immune responses. Among the different cell types affected by interleukin-10, monocyte/macrophages and lymphocytes appear to be particularly modified with regard to their function, morphology, and phenotype. However, recent studies performed in our laboratory, as well as by other groups, suggest that a number of functional activities of polymorphonuclear neutrophils are also subject to regulation by interleukin-10. In view of the central role of polymorphonuclear neutrophils in host defense processes and in amplifying inflammatory and immune reactions, the ability of interleukin-10 to act as a potent modulator of this cell type opens new perspectives as to the potential therapeutic utility of interleukin-10. This article reviews what is currently known about the effects of interleukin-10 on neutrophils.

Key words Neutrophil • Interleukin-10 • Interleukin-8 • Respiratory burst • Apoptosis

Introduction

Human interleukin-10 (IL-10) is a 18 kilodalton (kDa) non-glycosylated protein, mainly synthesized by activated monocytes, macrophages, helper T cells, B cells, and keratinocytes. As a general rule, IL-10 has the capacity to attenuate a wide range of inflammatory and immune responses [1]. IL-10 was originally identified as a cytokine synthesis inhibitory factor generated by T helper 2 (Th2) cells acting upon Th1 cells [1]. By inhibiting the antigen presentation and accessory cell functions of monocytes/macrophages, Langerhans cells, and dendritic cells, IL-10 indirectly prevents antigen-specific T cell activation [1, 2]. IL-10 also downregulates a variety of effector functions in monocytes, natural killer (NK) cells, and Th1 cells, and is known to suppress the production of proinflammatory cytokines and chemokines, while promoting the release of the IL-1 receptor antagonist (IL-1ra) in activated monocytes/macrophages and polymorphonuclear neutrophils (PMN) [1, 3]. In addition, IL-10 is a potent inhibitor of both eosinophil survival and secretion of IL-8, granulocyte-macrophage colony-stimulating factor (GM-CSF), and tumor necrosis factor-α (TNF-α) induced by lipopolysaccharide (LPS), but not of eosinophil survival mediated by GM-CSF [4]. Such in vitro data led to the proposal that IL-10 might inhibit inflammatory processes mediated by Th1 cells in vivo. Indeed, systemic administration of IL-10 in rodents inhibited LPS- or staphylococcal enterotoxin B-induced lethal shock, delayed-type hypersensitivity, and experimental autoimmune encephalitis [1–3, 5]. Conversely, IL-10-deficient mice develop chronic inflammatory bowel disease, which could be reduced or prevented by IL-10 treatment [1]. Finally, studies performed in vitro have further suggested that IL-10 is a potent co-stimulant of B cell differentiation and immunoglobulin secretion [1, 2], and recent findings indicate that IL-10 might also be used to prevent allergic inflammation induced by Th2 cells [5].

Neutrophils are the principal cell type that is initially recruited to sites of acute tissue injury, and have long been recognized as playing a sentinel role in the protection of the host against foreign pathogens [6]. However, if their effector functions are not tightly controlled, neutrophils may also promote tissue injury [7]. Numerous studies conducted over the past years have demonstrated that the development, activation, recruitment to sites of tissue injury, and function of neutrophils can be regulated by soluble and cell-associated mediators, including cytokines [6]. In this context, a number of recent studies have demonstrated that many functional activities of PMN are regulated by IL-10 (Table 1). The focus of this review is to summarize the data that have implicated the neutrophil as one of the cellular targets of IL-10 and discuss the potential pathophysiological significance of these findings.
Table 1 Biological activities of neutrophils reported to be influenced by interleukin-10 (IL-10) (TNFα tumor necrosis factor-α, IL-1ra, IL-1 receptor antagonist, GROα growth-related gene product-α, MIP macrophage inflammatory protein, IP-10 interferon-γ-inducible protein-10).

<table>
<thead>
<tr>
<th>Cytokine production (TNFα, IL-1α/β, IL-1ra, IL-8, GROα, MIP-1α/β, IL-12, IP-10)</th>
<th>2 h</th>
<th>4 h</th>
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<tr>
<td>medium</td>
<td>LPS</td>
<td>IL-10+LPS</td>
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Cytokine production (TNFα, IL-1α/β, IL-1ra, IL-8, GROα, MIP-1α/β, IL-12, IP-10)

Prostanoid production
Platelet-activating factor synthesis and release
Respiratory burst
Phagocytosis
Antibody-dependent cell cytotoxicity
Apoptosis
Membrane antigen expression
Tissue migration

Effect of IL-10 on cytokine production in neutrophils

Until recently, the biological role of the neutrophil in the inflammatory response was believed to be limited to the phagocytosis and clearance of pathogens and tissue debris. However, it is now becoming evident that neutrophils may also play an important and active role in regulating the development of the inflammatory and immune responses, due to their ability to produce cytokines such as IL-1α and IL-1β, IL-1ra, IL-12, TNFα, transforming growth factor-β1 (TGFβ1), and chemokines, such as IL-8, macrophage inflammatory protein-1α (MIP-1α), and MIP-1β, growth-related gene product-α (GROα), and interferon-γ-inducible protein-10 (IP-10) [8, 9]. Additional studies have further revealed that cytokine release can be positively or negatively regulated by immunomodulatory mediators, including interferon-γ (IFNγ), IL-4, and last but not least, IL-10 [8, 9]. The majority of the studies addressing the control of cytokine production by PMN have been conducted using LPS as a stimulus, probably because of its being a potent inducer of many different cytokines in this cell type. Nevertheless, other important biological agonists for neutrophils, such as formyl-methionyl-leucyl-phenylalanine (fMLP), IgG-opsonized Saccharomyces cerevisiae (Y-IgG), and TNFα, have also been used as cytokine inducers [8, 9].

IL-10 negatively modulates the production of IL-1, IL-8, and TNFα in neutrophils

IL-10 was originally reported to inhibit the extracellular production of TNFα, IL-1β, and IL-8 triggered by LPS and Y-IgG [10]. While IL-10 almost completely abrogates the release of TNFα and IL-1β over a time course ranging from 2 to 18 h, it does not significantly influence the production of IL-8 after 2–3 h of neutrophil stimulation with LPS. Conversely, IL-10 markedly reduces the extracellular accumulation of IL-8 by 6 h, and this is even more evident at 18 h [10]. Northern blot analyses revealed that IL-10 also diminished the LPS-induced accumulation of TNFα, IL-1β, and IL-8 mRNAs, albeit in a delayed manner — i.e., at later time points (4–5 h), but not at the onset of mRNA accumulation (2 h or less) (Fig. 1). The peculiar effects of IL-10 on neutrophil mRNAs were substantially confirmed by other investigators [11], as well as by studies in other cell types, such as human monocytes [12] and murine macrophages [13]. Further experiments suggested that in neutrophils, the inhibitory effect of IL-10 on LPS-induced IL-8 release was the result of the suppression of TNFα and IL-1β secretion [10]. Indeed, the combined use of TNFα and IL-1β (at concentrations equivalent to those detected in LPS-stimulated PMN supernatants) produced an additive effect on the release of IL-8 from PMN, that was not inhibited by IL-10 at all [10, 14]. Moreover, by using anti-TNFα and anti-IL-1β neutralizing antibodies, it was shown that within the first 6 h of LPS stimulation, anti-TNFα and anti-IL-1β had little effect, but that over the remainder of the time course, the release of IL-8 by neutroph-