Role of Cytokines during Influenza Infection—What we need to Know?

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Abstract

The primary target of influenza virus infection is the airway epithelial cells lining the respiratory mucosa but also infect alveolar macrophages and dendritic cells (DCs) that reside in the airways. In vitro as well as in vivo studies suggest that pro-inflammatory cytokines such as IL-1, TNF-α and IFN-β are secreted by infected cells and immune cells to sustain inflammatory response as well as induction of the chemokines (i.e. MCP-1, interferon-gamma (IFN-γ)) which attract mononuclear leukocytes that occurs within two days of an influenza virus infection but most chemokines favour neutrophils.

Keywords: Inflammation; Influenza; Interleukins

Introduction

IL-6 is a multifunctional cytokine that can regulate immune and inflammatory responses involved in the activation, growth and differentiation of T-cells [1] and can contribute to T cell mediated inflammatory reactions. In fact, autopsy examination showed an increased CD3+ T cells in the interstitium of the lung from patients with H5N1 diseases [2]. In addition, IL-6 has been shown to be released by macrophages and epithelial cells during lung injury [3] and the effects of IL-6 are synergistic with those of IL-1 and TNF-α [4].

IL-8, also known as neutrophil chemotactic factor, has two primary functions. It induces chemotaxis in target cells, primarily neutrophils but also other granulocytes, causing them to migrate toward the site of infection. IL-8 also induces phagocytosis once they have arrived. IL-8 is also known to be a potent promoter of angiogenesis. In target cells, IL-8 induces a series of physiological responses required for migration and phagocytosis, such as increases in intracellular Ca2+, exocytosis (e.g. histamine release), and the respiratory burst. Interleukin-10 (IL-10), also known as human cytokine synthesis inhibitory factor (CSIF), is an anti-inflammatory cytokine. In humans, IL-10 is encoded by the IL10 gene [11]. IL-10 is a cytokine with pleiotropic effects in immune regulation and inflammation. It down regulates the expression of Th1 cytokines, MHC class II antigens, and co-stimulatory molecules on macrophages. It also enhances B cell survival, proliferation, and antibody production. IL-10 can block NF-κB activity, and is involved in the regulation of the JAK-STAT signaling pathway. Thus over all the importance of IL-10 for counteracting the hyperactive immune response in the human body [12].

Discussion

TNF-α is a pleiotropic pro-inflammatory cytokine that exerts multiple biological effects, including those on the inflammatory
response and host resistance to pathogens. Macrophages and members of the monocyte lineage are thought to be the predominant cells that synthesize TNF-α thereby contributing the most to the local and systemic TNF-α responses in vivo, although other immune cells such as natural killer cells, T and B lymphocytes and Kupffer cells are also found to produce TNF-α [13]. During infection, TNF-α is an important acute phase cytokine that triggers the local immune response and containment of infection. It initiates a cascade of cytokines and increase vascular permeability that aids in the recruitment of macrophages, neutrophils and lymphocytes to the site of infection. Recent studies have suggested that TNF-α is known as one of the main mediators causing ARDS [14], [Figure 1&2].

Interferons (IFNs) constitute a class of cytokines with antiviral activities and were first identified as a substance to suppress viral replication [15]. IFN-β, a type I interferon, is essential to inhibit board range of virus replication. The downstream effect of interferons particular on IFN-β was extensively studied. The interferon protein binds to its specific cognate receptor on the surface of cells leading to activation of the signaling system known as the Jak/STAT pathway [16]. The antiviral effects of IFN-β are mediated through this pathway to trigger the expression of many anti-viral genes. H5N1 viruses were found to resist the antiviral effects of IFNs in pig epithelial cells [17]. Previous studies from our group have demonstrated that both H5N1 and H1N1 influenza viruses induced IFN-β responses in primary human alveolar and bronchial epithelial cells [18], and this may be relevant in disease pathogenesis.

MCP-1 is produced in response to inflammatory stimuli by a variety of cells, including monocytes/macrophages, lymphocytes and airway epithelial cells [19,20]. It was shown to be a major contributor to the robust arrest of monocytes to inflamed endothelium under shear stress conditions in vitro [21,22]. MCP-1 also stimulates collagen synthesis and production of the pro-fibrotic factor transforming growth factor β (TGF-β) in fibroblasts, while MCP-1 antisense oligonucleotides reduce TGF-β production [23]. Although MCP-1 was originally described for its chemo tactic activity on monocytes, in vitro studies revealed an even higher activity on T cells [24]. This occurs through MCP-1 binding to its sole receptor CCR2.

**Conclusion**

The studies focusing upon detailed mechanism of anti-inflammatory response to different virus strains including influenza are needed to be carried out. The issue also needs to describe why different strain of virus show different anti-inflammatory response and disease severity.

**References**


