The Role of Interleukin (IL)-12 and IL-18 During Endotoxemia and Bacterial Infection

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Introduction

Cytokines are a family of small proteins that are important for the orchestration of the host inflammatory response to infections. They are produced by a large variety of cells, including leukocytes, endothelial cells, epithelial cells and fibroblasts upon stimulation by various immunologic and infectious stimuli. Cytokines interact in a complex network in which they can influence each other’s production and function. The cytokine family consists of pro-inflammatory cytokines, of which tumor necrosis factor-α (TNF) and interleukin (IL)-1 are best known, and anti-inflammatory cytokines, including IL-10. IL-12 and IL-18 are cytokines with pro-inflammatory properties. They share many biological activities, and synergistically induce the production of interferon (IFN)-γ. IL-12 and IL-18 have been implicated as important mediators in the host immune response during systemic and local infections by bacteria, intracellular pathogens like mycobacteria, viruses, and parasites. In this chapter, we will discuss the role of IL-12 and IL-18, and their interactions during sepsis and endotoxemia, and during bacterial infections.

Structure and Production of IL-12 and IL-18

IL-12, originally named natural killer stimulatory factor (NKSF), was identified as a product of Epstein-Barr virus (EBV)-transformed human B cell lines [1]. Structurally, IL-12 is a unique cytokine since it is composed of a heterodimer consisting of two covalently linked chains of approximately 40 kDa (p40) and 35 kDa (p35) [2, 3]. These chains are encoded by separate and unrelated genes, and production of both chains within the same cell is required to lead to the formation of the biologically active p70 heterodimer. The p40 subunit mediates binding of IL-12 to its receptor, while the p35 subunit is essential for signal transduction. Interestingly, the p35 subunit shows a strong homology with IL-6 and granulocyte colony-stimulating factor (G-CSF), while the p40 subunit is not related to any other cytokine, but shows a sequence homology with the IL-6 receptor family. This suggests that IL-12 is evolutionarily derived from a cytokine/cytokine-receptor complex, which resulted in an association through a covalent linkage between the two chains. Neither subunit alone has been shown to have biological activity. When IL-12 production is stimulated, a large excess of free p40 chains is produced, consisting of inactive p40 monomers and a small percentage of p40 homodimers, which can antagonize IL-12 function by competi-
tion for binding to its receptor. Recently however, it has been described that the p40 homodimer may also possess immunostimulatory effects on CD8+ T cells, resulting in IFN-γ production [4].

IL-12 is mainly produced by monocytes, macrophages, and other antigen-presenting cells (APC). The production of IL-12 can be induced by either T-cell-independent or by T-cell-dependent mechanisms. The T-cell-independent pathway involves the stimulation of IL-12 production by bacteria and bacterial products, like endotoxin (lipopolysaccharide, LPS) and bacterial DNA, and by intracellular pathogens [5]. The T-cell-dependent pathway of IL-12 production is mediated by the expression of CD40 ligand (CD40L) on activated T cells, and the interaction with its receptor CD40 on the surface of IL-12-producing cells [6]. Cytokines can regulate the capacity of APC to produce IL-12. IFN-γ and granulocyte-macrophage colony-stimulating factor (GM-CSF) can up-regulate IL-12 production, while transforming growth factor β (TGF-β), IL-4, IL-10 and IL-13 are potent inhibitors of IL-12 production.

Since it has been demonstrated that IL-12 induces the production of IL-10, IL-12 presumably can regulate its own activity by inducing factors that enhance (IFN-γ) or inhibit (IL-10) its own production. Also, other soluble mediators like prostaglandin E2 and glucocorticoids, which inhibit IL-12 release, and nitric oxide (NO), which up-regulates IL-12 gene expression, can influence IL-12 production.

IL-18, also known as IFN-γ-inducing factor (IGIF), is a recently discovered protein [7]. It was purified from extracts of liver tissues from Propionibacterium acnes primed and LPS-challenged mice, as a factor that induces IFN-γ production. Although IL-18 shares many biological activities with IL-12, structurally it is related to the IL-1 cytokine family [8, 9]. Similar to IL-1β, IL-18 is first produced as a precursor protein (pro-IL-18, 24 kDa), which requires splicing by IL-1β-converting enzyme (ICE) to liberate the 18 kDa mature active protein [10, 11]. The importance of ICE for IL-18 production has been demonstrated in ICE-deficient mice which produce less IL-18 and IFN-γ after LPS challenge, an effect which is restored by treatment with recombinant IL-18 protein [10, 11].

IL-18 is mainly produced by activated macrophages and Kupffer cells, but can also be produced by other cell types, including keratinocytes and osteoclasts. The regulation of IL-18 production has not been elucidated completely. Macrophage stimulators, like LPS and other bacterial products, bacteria, and intracellular pathogens have been shown to induce IL-18 production. Cytokines are also likely to regulate IL-18 production. While IL-12 stimulates the production of IL-18, we have found that IL-10 dose-dependently inhibits LPS-induced release of IL-18 during whole blood stimulation in vitro [12].

Structure and Function of IL-12 Receptor and IL-18 Receptor

The IL-12 receptor (IL-12R) is composed of two subunits, designated IL-12Rβ1 and IL-12Rβ2, which both belong to the gp130 subgroup of the cytokine receptor superfamily [3]. Individually, the subunits bind IL-12 with low affinity, but co-expression of IL-12Rβ1 and IL-12Rβ2 results in high affinity IL-12 binding sites. The IL-12Rβ1 subunit primarily contributes to binding of IL-12, while the IL-12Rβ2 appears to be the signal-transducing component of the receptor complex. IL-12 signal transduc-