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Review Article

Fetal and early neonatal interleukin-6 response

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ABSTRACT

In 1998, a systemic fetal cytokine response, defined as a plasma interleukin-6 (IL-6) value above 11 pg/mL, was reported to be a major independent risk factor for the subsequent development of neonatal morbid events even after adjustments for gestational age and other confounders. Since then, the body of literature investigating the use of blood concentrations of IL-6 as a hallmark of the fetal inflammatory response syndrome (FIRS), a diagnostic marker of early-onset neonatal sepsis (EONS) and a risk predictor of white matter injury (WMI), has grown rapidly. In this article, we critically review: IL-6 biological functions; current evidence on the association between IL-6, preterm birth, FIRS and EONS; IL-6 reference intervals and dynamics in the early neonatal period; IL-6 response during the immediate postnatal period and perinatal confounders; accuracy and completeness of IL-6 diagnostic studies for EONS (according to the Standards for Reporting of Diagnostic Accuracy statement); and recent breakthroughs in the association between fetal blood IL-6, EONS, and WMI.

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Contents

Abbreviations: AUC, area under the curve; CI, confidence interval; CRP, C reactive protein; EONS, early-onset neonatal sepsis; FIRS, fetal inflammatory response syndrome; gp130, glycoprotein 130; IL-6, interleukin-6; IL-6R, interleukin-6 receptor; NICU, neonatal intensive care unit; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PPROM, preterm premature rupture of the membranes; PVL, periventricular leukomalacia; sgp130, soluble glycoprotein 130; sIL6-R, soluble interleukin-6 receptor; STARD, Standards for Reporting of Diagnostic Accuracy; TLRs, Toll-like receptors; WMI, white matter injury.

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1. Introduction

Interleukin-6 (IL-6) is a pleiotropic cytokine that is produced by a variety of cells in response to infection and tissue injury. In the last two decades, the body of literature concerning the use of blood concentrations of IL-6 as a hallmark of the fetal inflammatory response syndrome (FIRS), a diagnostic marker of early-onset neonatal sepsis (EONS) [1] and a risk predictor of white matter injury (WMI) has grown rapidly, leading to improved understanding as well as new questions about the role of this cytokine in the perinatal period. In this article, we comprehensively review: (1) IL-6 biological functions; (2) current evidence on the association between IL-6, preterm birth, FIRS and EONS; (3) IL-6 reference intervals and dynamics in the early neonatal period; (4) IL-6 response during the immediate postnatal period and perinatal confounders; (5) accuracy and completeness of IL-6 diagnostic studies for EONS [including the design, conduct, analysis and results of such studies according to the Standards for Reporting of Diagnostic Accuracy (STARD) statement]; and (6) recent breakthroughs in the association between fetal blood IL-6, EONS, and brain injury.

2. IL-6 biological functions and signaling pathways

Systemic inflammatory response syndrome, which is characterized by an excessive proinflammatory response, is a hallmark of sepsis [2]. Many proinflammatory cytokines including IL-6 have been implicated in the pathogenesis of sepsis [2]. Until recently, it was not known how the cytokine-driven inflammatory process is initiated. It is now known that microorganisms interact with a family of toll-like receptors (TLRs) belonging to the innate immune system, which trigger intracellular activation of nuclear factor kappa B and various kinases, leading to the production and release of cytokines [3]. Among these, IL-6 has been reported to be produced in the early phase of infectious inflammation by monocytes and macrophages immediately after the stimulation of TLRs, with distinct pathogen-associated molecular patterns [4]. In noninfectious inflammatory conditions, such as tissue injury, damage-associated molecular patterns from damaged or dying cells stimulate TLRs to produce IL-6 [5]. This acute IL-6 expression plays a central role in the body's defense against infection or injury by stimulating various cell populations [6].

IL-6 is produced by various cells, such as T-cells, B-cells, monocytes, fibroblasts, keratinocytes, endothelial cells, mesangial cells, adipocytes, and some tumour cells [7]. While serum concentrations of IL-6 in healthy donors are hardly detectable or in the low pg/mL range [8,9], during an inflammatory episode IL-6 is highly expressed, and circulating levels can rise dramatically from 1–5 pg/mL to several μg/mL in extreme cases [10,11]. Consequently, IL-6 is one of the most highly expressed mediators of inflammation [11].

IL-6 is a multifunctional cytokine involved in regulating the immune response, hematopoiesis, the acute phase response and inflammation. Its many biologic activities are at the root of its pathogenic properties. IL-6 engages in two distinct downstream signaling pathways to achieve these activities: classic and trans-signaling.

In classic signaling, IL-6 first binds to its specific membrane-bound α–receptor (IL-6R), which in turn associates with and activates the signal-transducing β-receptor chain gp130. Whereas gp130 is expressed by most, if not all, cells in the body [12], IL-6R is only expressed on a limited number of cell types including epathocytes, megakaryocytes and some leukocytes, namely monocytes, macrophages, B cells and subtypes of T cells [12,13]. In hepatocytes, IL-6R expression is essential for the production of acute phase response proteins including C reactive protein(CRP) and fibrinogen. Being transiently expressed on lymphocytes, macrophages, and megakariocytes, the IL-6R also orchestrates phases of the immune response [12]. All other cells, which do not express membrane-bound IL-6R, obtain IL-6 signals by trans-signaling. IL-6 binds to the soluble form of IL-6R (sIL-6R), and this complex not only protects IL-6 and prolongs its circulating half-life [14], but also acts as an agonist capable of directly activating many cell types via the ubiquitously expressed gp130 in a process termed trans-signaling [11]. It has been shown that sIL-6R strongly sensitizes target cells [14]. Embryonic stem cells, early hematopoietic progenitor cells, T cells, many neural cells, smooth muscle cells, mesothelial cells, and endothelial cells, among others, are only responsive to IL-6 in the presence of sIL-6R [12]. sIL-6R is present in the sera of healthy subjects at high concentrations (25–145 ng/mL), and these levels increase during inflammation [15–17]. sIL-6R in humans is generated through differential mRNA splicing but primarily through proteolytic cleavage and subsequent shedding of membrane-bound IL-6R [18,19]. In contrast to classic signaling, comprising the anti-inflammatory or regenerative activities of IL-6, evidence suggests that IL-6 trans-signaling via soluble IL-6R accounts for the proinflammatory properties of IL-6 [20]. In fact, while IL-6 classic signaling plays a role in developmental processes, tissue homeostasis, and acute phase response [21], trans-signaling is involved in many processes that are important in sepsis: activation of endothelial cells and smooth muscle cells [22,23], mononuclear cell recruitment [24], and apoptosis of neutrophils and T cells as well as the expression of chemokines [12,25,26].

Since the cellular responses to the IL-6/sIL-6R complex can be dramatic, ranging from the induction of hepatocyte proliferation to a massive increase in hematopoiesis [27,28], there must be a "buffer" acting as a control mechanism to prevent excessive IL-6 trans-signaling [8]. The soluble form of gp130 (sgp130), which is found at concentrations between 100 and 400 ng/mL in the sera of healthy humans [17], has been suggested to be the natural antagonist of the IL-6/sIL-6R complex *in vivo* [21], probably to prevent systemic IL-6 trans-signaling during inflammatory diseases [29].

The concentrations of IL-6, sIL-6R and sgp130 have to be considered. Under steady state conditions, levels of sIL-6R and sgp130 are roughly 1000 times higher than IL-6 levels [8]. However, during inflammatory conditions, IL-6 levels can increase up to a million-fold [10], whereas serum concentrations of sIL-6R and sgp130 show much smaller differences between healthy and diseased and in most cases do not rise by more than a factor of 2 [15]. These concentrations imply that IL-6, once secreted, will bind to sIL-6R in the serum and this complex will associate with sgp130, and thereby be neutralized [8]. Only when IL-6 levels exceed the levels of sIL-6R and sgp130, IL-6 can act systematically-as seen under septic conditions [10]. Because IL-6 alone does not interact with sgp130, with a molar excess of IL-6 over sIL-6R, sgp130 would only be able to block trans-signaling because free IL-6 will not, or will only, be partially trapped in IL-6/sIL-6R/sgp130 complexes. In contrast, under physiologic conditions, IL-6 is thought to act in a paracrine fashion [30]. Physiological conditions are a molar

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