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Proinflammatory cytokines in a newborn: a literature review

ŽELIMIR ERIĆ[1], STOJISLAV KONJEVIĆ[2]

1 Department of Physiology, Faculty of Medicine University of Banjaluka, Banjaluka, RS, BiH
2 Clinic for childrens diseases, University Clinical Centre of the Republic of Srpska, Banjaluka, RS, BiH

Corresponding author:
Želimir Erić
Deparment of Physiology Faculty of Medicine University of Banjaluka
Save Mrkalja 14, 78 000 Banjaluka, RS, BiH
Phone: 00 387 51 234 151
E-mail: zelimireric@gmail.com

ABSTRACT

Inflammation is a protective response to infection or injury. The inflammatory response is controlled primarily by cytokines, which are endogenous mediators of the immune system. Cytokines are produced by various different cell types in response to multiple types of stimuli and have overlapping biologic activity. Cytokines also are directly involved in the activation of cells at the inflammatory site. Movement of leukocytes to the inflammatory site is directed along a chemotactic gradient, where the strongest concentration of chemoattractants is at the site of inflammation. Cytokines are involved at each step of this process and act both locally and systemically to initiate, maintain, and finally resolve the inflammatory response. The interplay among these proinflammatory cytokines, antiinflammatory cytokines, and naturally occurring cytokine inhibitors determines the inflammatory response and its effectiveness. Because of the immaturity of the immune system of newborn cytokine is specific. Tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) amplify the immune response through activation of the cytokine cascade and the production of other proinflammatory cytokines and chemokines. In a group of proinflammatory cytokines TNF-α and IL-6 have undoubtedly significant role in the cytokine cascades of physiological and pathophysiological responses.

Key words: interleukin-6, tumor necrosis factor-alpha, newborn

INTRODUCTION

Cytokines are potent endogenous mediators whose synthesis and secretion are under tight regulatory control. These endogenous mediators are not stored as preformed molecules in producer cells; rather, new synthesis is required for secretion. Once these mediators are released, their half-life is relatively short and limiting their activity. Cytokines act in minute quantities (10^{-9} to 10^{-12} mole) by binding to specific cellular receptors that are members of distinct structural families. Very important function of cytokines is cell-to-cell communication. Cytokines can communicate in autocrine, paracrine, or endocrine mode. (1) Most cytokine activity occurs on the local level. Some cytokine producer cells also express cytokine receptors, and secreted cytokines can bind to their producer cells, whereby they can modulate cell function. Cytokines also can leave the local environment, enter the circulation, interact with different organ systems, and alter host physiology. A group of cytokines is produced specifically in response to inflammatory stimuli. The function of these proinflammatory cytokines is to communicate to surrounding tissue the presence of infection. (2) Proinflammatory cytokines are tumor necrosis factor-α (TNF-α); the interleukins IL-1, IL-6, IL-8, IL-12, IL-18; and interferon-γ (IFN-γ). TNF-α and IL-1 are the principal mediators of the inflammatory response and have a critical role in the local response through cell activation and triggering a cytokine cascade. (3) Proinflammatory cytokines also can enter the systemic circulation and can produce immune cell activation and significant alterations in host physiology, such as fever and the acute phase reaction. Inflammatory stimuli also trigger the synthesis of antiinflammatory cytokines. Antiinflammatory cytokines limit the inflammatory response by inhibiting proinflammatory cytokine synthesis. Antiinflammatory cytokines are IL-4, IL-10, IL-11 and IL-13. The interplay among proinflammatory and antiinflammatory cytokines determines the inflammatory response. In comparison with adult data, considerably less is known regarding the production and release of cytokines in the newborn infant. Many evidence suggests that the fetal inflammatory response plays a major role in the induction of several neonatal diseases.

PROINFLAMMATORY CYTOKINES

Tumor Necrosis Factor

TNF-α is the principal mediator of the inflammatory response and has a critical role in the local inflammatory response and initiation of a cytokine cascade. TNF is synthesized as a 26-kDa transmembrane protein, which is processed to the mature 17-kDa form after cleavage of the residue signal peptide by a matrix metalloproteinase disintegrin. (4) TNF can exert activity as a transmembrane cell-associated species as well as in a secreted form. TNF synthesis is triggered by enterotoxin, endotoxin, toxic shock syndrome toxin-1, viruses, mycobacterial cord factor, C5a, fungal antigens, IL-1, and TNF itself. (5, 6) The primary producer cells of TNF are monocytes and tissue macrophages. TNF is produced by many other cell which include natural killer (NK) cells, neutrophils, lymphocytes, mast cells, endothelial cells, keratinocytes and smooth muscle cells. TNF is produced by human fetal Kupffer cells as well as placental mononuclear cells in response to stimulation by LPS. (7, 8) We can found TNF in amniotic fluid during the second and third trimesters and levels of TNF increase with premature rupture of membranes. (9) Preterm infants born before 30 weeks of gestation demonstrated

significantly diminished LPS-stimulated TNF secretion when compared with neonates of later gestational ages. (10) Levy demonstrated a specific inhibitory effect of adenosine on TNF production during the perinatal period. (11) When analyzed in culture, monocyte-macrophages derived from newborn infants also secreted diminished amounts of TNF when compared with adult cells. (12) Some investigators examined TNF production by cord blood mononuclear cells in response to several stimuli. (13) In contrast with the immediate response to LPS (in which TNF, IL-1β, IL-6, and IL-8 appeared almost simultaneously), stimulation by group B streptococci resulted in increased TNF production but a delayed appearance of the other cytokines. Abnormalities of TNF production and release, particularly in preterm infants, may increase susceptibility to bacterial infection in this age group. TNF receptor expression also may be diminished.

Tumor Necrosis Factor Receptors

The regulation of TNF signaling is important in the control of TNF-induced cellular alterations. Most cell types possess two TNF receptors: a 55- to 60-kDa receptor, TNFR-1 (CD120a) and a 75- to 80-kDa receptor, TNFR-2 (CD120b). (14, 15) These two receptors are members of the tumor necrosis factor (TNF)/tumor necrosis factor receptor (TNFR) family. The extracellular domains of the TNFR-1 and TNFR-2 share 28% homology. The lack of homology of the two receptors suggests that they mediate discrete signaling pathways. (16) TNFR-1 is responsible for proinflammatory cellular responses. (5, 17, 18) TNFR-1 also is signaling pathways linked to both proapoptotic and antiapoptotic responses. (6) TNFR-1 contains a cytoplasmic sequence of approximately 80 amino acids termed the death domain. This region regulates apoptosis through its association with effector proteins that activate programmed cell death, but the death domain also is the region in this receptor that mediates the cell's survival or antiapoptotic pathways. (19) Activation of the TNFR-1 by TNF results in the formation of a receptor trimer through selfassociation with the death domains. Receptor trimerization leads to recruitment of effector proteins to form a signaling complex at the plasma membrane. (17) The TNFR-1–associated death domain protein (TRADD) associates with TNFR-1 and acts as a scaffold for recruitment of the effector proteins RIP (receptor-interacting protein) and TRAF2 (TNFR-associated factor 2) to form the complex TNFR-1:TRADD:TRAF2:RIP. This complex, we called complex I, controls both antiapoptotic and proinflammatory pathways primarily through activation of mitogen-activated protein (MAP) kinases and transcription factors such as nuclear factor-κB (NFκB) and activator protein-1 (AP-1), leading to the coordinated expression of antiapoptotic proteins, proinflammatory cytokines, chemokines and adhesion molecules. (20, 21) A second complex termed complex II can be assembled when TRADD-TRAF2-RIP complex disassociate from TNFR-1 to form a second cytosolic complex with FADD (fas-associated death domain protein). FADD is essential for apoptosis through its association with and activation of caspase-8. (17)

Interleukin-6

IL-6 is a very important pleiotropic cytokine with a wide range of biologic functions and is regulator of immune responses, inflammation, hematopoiesis and oncogenesis. (22, 23) IL-6 is a potent inducer of the acute phase response, as well as specific cellular and humoral immune responses including B cell differentiation and T cell activation. (23) IL-6 also is regulator of the transition from acute to chronic inflammation and of the shift from neutrophil to mononuclear cell infiltration. (24) IL-6 is not expressed constitutively, and IL-6 production is triggered in response to bacterial and viral infections and other cytokines such as IL-1β, TNF, and IFN-γ. IL-6 is a single-chain 21- to 28-kDa protein produced by a variety of cells including monocytes, B and T cells, endothelial cells and fibroblasts. (25, 26) After stimulation with LPS, IL-6 is produced by human fetal Kupffer cells as early as 13 weeks after conception. (8) This cytokine also has been detected as TNF in the amniotic fluid during infection. (27) Several studies have evaluated IL-6 production by monocytes from newborn infants. (10, 28) Liechty and colleagues demonstrated equivalent IL-6 production by fetal and maternal mononuclear cells after stimulation with IL-1. (27) Angelone and colleagues demonstrated that LPS-stimulated cord blood IL-6 production and IL-6/TNF ratios were higher than in adult peripheral blood. (28) IL-6 production was reduced in cells from preterm neonates, perhaps contributing to their enhanced susceptibility to bacterial infection. (27, 29) Schultz and colleagues demonstrated that both term and preterm monocytes displayed a higher percentage of IL-6–positive cells than in those from adults, suggesting an enhanced inflammatory response in these infants. (30) Cord blood lymphocytes express both the gp80 and the gp130 IL-6 receptor, although generally at lower levels than in adult cells. (31)

Interleukin-6 Receptors

The IL-6 receptor system consists of two parts. The ligandbinding molecule or IL-6R, is an 80-kDa glycoprotein. (32) The second component of the IL-6 receptor system is gp130, a non–ligand binding signal transducer. (33) IL-6 binding to the IL-6R leads to the association of gp130 with the receptor complex. IL-6R and gp130 are members of the cytokine receptor family, which is characterized by four conserved cysteine residues and a tryptophan-serine-X-tryptophan-serine motif above the transmembrane domain. (34) The gp130 also is the common signaltransducing subunit for other members of the cytokine receptor family including oncostatin-M, ciliary neurotrophic factor, IL-11, cardiotrophin-1 and interleukins IL-27 and IL-31. (35, 36) Although the membrane IL-6R is expressed on hepatocytes, monocytes, macrophages, neutrophils and some types of lymphocytes, a soluble form of the IL-6R (sIL-6R) also is present in many body fluids. (36) IL-6 binding to sIL-6R triggers the association with the signal-transducing gp130 component in cells that do not express the membrane-bound form of IL-6R. (36, 37) Thus, unlike most other soluble cytokine receptors, sIL-6R can act as an agonist and through trans-signaling can activate cell types which do not express the IL-6R. In contrast with sIL-6R, soluble gp130 (sgp130) inhibits IL-6 activity by binding to IL-6/sIL-6R complexes and interfering with IL-6 trans-signaling. (36) Formation of the IL-6 receptor complex leads to activation of gp130 associated tyrosine kinases of the Janus family (JAK) resulting in tyrosine phosphorylation of the cytoplasmic domain of gp130. (38, 39)

CLINICAL APPLICATION OF CYTOKINE PHYSIOLOGY

The newborn period represents a time of increased risk for the development of bacterial infection and sepsis. (40) Among other factors known to increase this risk is a functional immaturity of newborn immune mechanisms. Immunoglobulin and complement levels are low, and leukocyte functions, including the secretion of inflammatory mediators, may be deficient. (41) The fetus and newborn infant are

unique from the standpoint of immunity and infection. The fetus lives in a sterile, immunologically protected environment. During this time that the development of the immune system is initiated a highly complex process mediated, at least in part, by the expression of cytokines. (42) Fetal cytokines are known to play a role in the regulation of hematopoiesis and to protect the fetus against rejection. Placental and fetal cytokines also protect against infection. (42) Evidence suggests that cytokines in the fetus and neonate play a role in the pathophysiology of severe neonatal diseases including sepsis, necrotizing enterocolitis and bronchopulmonary dysplasia. (30, 43) It has become evident, however, that many infants die despite the sterilization of blood cultures with antimicrobial agents. (44, 45) It is now appreciated that the physiologic derangements that occur during sepsis are secondary to the host response induced by pathogenic microorganisms. During overwhelming sepsis, the host produces proinflammatory cytokines that initiate a cascade of events resulting in tissue injury at distant sites and generalized multiorgan system failure. (45, 46) The balance of proinflammatory and antiinflammatory cytokines may ultimately determine the outcome with sepsis in newborn infants. This inflammatory response may have its origins during the fetal period. (42) Thus the heightened morbidity and mortality in neonatal sepsis result from physiologic deficiencies in immune function, as well as the pathophysiologic alterations produced by bacterial products. (44, 45)

CONCLUSION

In a group of proinflammatory cytokines TNF-α and IL-6 have undoubtedly significant role in the cytokine cascades of physiological and pathophysiological responses. The development of the inflammatory response in the fetus and neonate, production of inflammatory mediators and their role in the inflammatory response in newborn infants is very specific and future multicenter studies in a large populations are needed to give a more informations and findings about these processes.

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