Review article

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Certain immune mechanisms involved in neonatal sepsis development

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Development of neonatal sepsis, especially in preterm neonates, is the one of the main factors for high morbidity and mortality in neonatal period. Preterm neonates, with not fully maturated immune system, have enhanced susceptibility to sepsis development, compared to the term infants. Innate immune system activation represents the main protective mechanism, in preterm neonates, against sepsis development. Different components of innate immune system provide basic protection, as well as they may serve as early biomarkers for neonatal sepsis development. In this review, we analyze basic mechanisms of innate immune response to pathogen presence and different markers included in initiation of inflammatory process. Better understanding the mechanisms involved in sepsis development may provide earlier prediction of sepsis development and results with more potent therapeutic efficiency.

Key words: neonatal sepsis, preterm neonates, immune system, innate immunity

Pregledni rad

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Pojedini imunološki mehanizmi uključeni u razvoj neonatalne sepse

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Razvoj neonatalne sepse, posebno kod preterminske novorođenčadi, predstavlja jedan od glavnih faktora značajnog morbiditeta i mortaliteta u neonatalnom periodu. Prevremeno rodjena novorođenčad, kod kojih imunološki sistem nije u potpunosti razvijen, pokazuju pojačanu osetljivost za razvoj sepse, u odnosu na terminsku novorođenčad. Aktivacija urodjenog imuniteta kod prevremeno rodjene novorođenčadi jedan je od glavnih mehanizama koji se suprostavlja razvoju sepse. Različite komponente urodjenog imuniteta, omogućuju osnovnu zaštitu i mogu da posluže kao rani biomarkeri za razvoj sepse. U ovom radu, analizirali smo bazične mehanizme urodjenog imuniteta na prisustvo patogena, kao i različite markere koji su uključeni u inicijaciju inflamatornog procesa. Bolje razumevanje mehanizama uključenih u nastanak sepse mogu nam poslužiti za ranu predikciju sepse, što doprinosi efikasnijem terapijskom pristupu.

Ključne reči: neonatalna sepsa, prematurusi, imunološki sistem, urodjeni imunitet

Introduction

Neonatal sepsis represents a leading cause of morbidity and mortality in preterm infants. With high rate of morbidity and mortality, preterm neonates are especially vulnerable due to their immune system immaturity and lack of maternal protection (1). The coexistence of other respiratory or cardiovascular disorders may also have impact on preterm sepsis development (2). On the other hand, based on the time it occurs, preterm sepsis may be formed as early onset sepsis (EOS), which develops in the first 72h of life and late onset sepsis (LOS), which occurs after the first 72h of life. The development of EOS is associated with infections, transmitted vertically, from the mother to the infant, while LOS is usually caused by pathogens collected by delivery or community environment (3).

Appropriate and efficient treatment of neonatal sepsis may diminish morbidity and mortality rate in neonates. Therefore, recognition of early markers, signs and symptoms of neonatal sepsis, represent key factors to overcome harmful effects, especially in preterm neonates. However, since unspecific symptoms and signs are often presented during neonatal sepsis development the diagnosis of neonatal sepsis is very difficult and consensus definition still lacks (3, 4). Identification of specific pathogen, by positive blood culture, provides gold standard for sepsis diagnosis. Nevertheless, antibiotic administration and low bacteriemia may provide false or delayed results (5). Moreover, in recent years novel techniques (pathogen genome hybridization and polymerase chain reaction) were used to determine the pathogen presence. The results showed that these procedures provide no information about antibiotic resistance neither the distinction among viable or nonviable pathogens (6), indicating that positive blood culture still provides better results (3, 7).

Taking into account that inflammation has a key role in sepsis development, different studies have been conducted to evaluate potential role of some pro- and anti-inflammatory mediators (8, 9). However, the precise mechanism of neonatal response to infection is not clearly identified, which results with no reliable and rapid marker for neonatal sepsis development (7). Therefore, the current study intends to provide the basic mechanisms of immune system, as well as its components, involved in neonatal sepsis development and to provide better understanding of this pathology process with possible implications in therapeutic strategies.

Epidemiology

Usually, preterm birth is termed as birth before 37 week of gestation and still remains main cause of neonatal death (10). It is estimated that preterm birth incidence in USA is around 13%, in other developed countries is between 4.5-8%, while in European Union is in range of 5-10% (11, 12). Also, it is observed that, besides preterm mortality, consequences of preterm birth may persist in neonatal period as well as in adulthood (12). On the other hand, EOS incidence is around 20 per 1000 infants (infants born before 29 week of gestation) and LOS incidence is in range of 12-28% (infants born before 26 week of gestation), with increasing incidence as gestational age decreases (13, 14). Furthermore, neonatal sepsis (EOS and LOS) induce neonatal mortality rate between 5-20% in developed countries while the rate of mortality rises up to 70% in middle or low-income countries (2). Accordingly, rapid and respectable marker for neonatal sepsis prediction is a major challenge in neonatal sepsis treatment.

Certain immune mechanisms in neonatal sepsis development

In recent years, most of the research was focused to determine specific inflammatory component which may serve as potential biomarker for early diagnosis of neonatal sepsis. Initial research proposed potential role of some acute phase reactant proteins, including C reactive protein (CRP) and procalcitonin (PCT). Even CRP has ability to induce opsonization and to activate complement system, this protein has 24-48h half-life and needs 10-12h to reach elevated plasma levels (15), indicating that CRP is not able to serve as early predictor of neonatal sepsis development but, rather, as monitoring factor of sepsis therapy efficiency (3). Additionally, levels or PCT showed physiological altered values during neonatal period (16), suggesting that this biomarker may not provide enough diagnostic ability to rule out neonatal sepsis (4).

Innate Immunity

Following the birth, immune system in neonates is not fully developed, especially in preterm neonates (17). Incomplete developed innate and adaptive immune system, together with lack of communication between these both immune system parts, often leads to sepsis development in preterm neonates (4). Transplacental antibodies transmission from mother to fetus, represents the main defense mechanism from different pathogens. Taking into account that this process is enhanced after 32 week of gestation, preterm neonates usually lack this way of protection (18). Consequently, immune system protection is

mainly based on the innate immunity, which is not very potent due to its prematurity. In line with this, previous findings demonstrate that various soluble proteins and peptides in blood plasma, with antimicrobial properties and opsonization ability, have been significantly reduced in preterm neonates (19). These antimicrobial proteins and peptides (APP) are mainly cationic molecules released by neutrophils, eosinophils, monocytes and epithelial cells of gastrointestinal or respiratory system, including defensins, caprotectin, protegrins, lactoferrin and lysosomes (20). All APPs have ability of binding to various pathogens and to provide elimination of pathogens through different mechanisms. This was supported by previous findings indicating that application of lactoferrin reduces the incidence of LOS in preterm neonates (21).

As the part of the innate immunity, complement system activity (classical, alternative and lectin patway of activation) is also reduced in preterm neonates (4). Namely, in preterm neonates there is decreased production of C1 and C4 components (involved in classic pathway activation), factor B (included in alternative pathway activation) and mannose binding lectin (necessary for lectin pathway activation) compared to the term infants (22). Inability of complement activation leads to reduction of phagocytosis activity and eradication of different pathogens, enabling preterm neonates especially susceptible to infection.

The presence of different pathogens initiates the formation of inflammatory process, together with production of innate proteins and activation of leukocytes. Polymorphonuclear leukocytes, during sepsis in preterm neonates, rapidly decreases in number, have delayed apoptosis and show potential to aggregate with decreased diapedesis function (23). Since their number in medulla is depleted, immature and dysfunctional forms of leukocytes are released and process of phagocytosis is globally reduced (4). On the other hand, initiation of inflammatory process results with innate immunity protein production, including CRP, PCT, collectins, lactoferrin and others. In addition, sepsis development induces elevation of serum proteins with opsonization function (mainly IgM). Nevertheless, total number of these proteins, as well as opsonization activity of blood plasma, is reduced in preterm neonates, comparing to the term infants (24).

Pathogens and their products are sensed by transmembrane pattern recognition receptors (PRR), including toll-like receptors (TLRs), which are binding to the surface of the microorganisms. Up to now, there are 11 different TLRs in humans and they provide key role in controlling the inflammation process

(25). TLRs are able to recognize lipopolysaccharide endotoxins (LPS) on Gram-negative bacteria surface and byproducts of Gram-positive bacteria, mycoplasmas and yeast (26). Activation of TLRs leads to increased neutrophil activity, elevated cytokine and chemokine production and enhanced chemotaxis and immunoglobulin secretion. However, these mechanisms are significantly decreased in preterm neonates compared to the term infants (12). Furthermore, it has been shown that sepsis development in preterm neonate results with markedly reduced expression of genes related to TLRs, suggesting the depleted innate immune response in preterm neonates (27). Similar findings revealed overexpression of genes related to innate immune response and inflammatory processes in preterm neonates, but fold change are decreased than those observed in term infants (28).

Other Immune mechanisms

The TLRs activation leads to immune response characterized by production of pro-cytokines and chemokines (IL-1, IL-6, TNF-α, IL-12, IL-18, IL-8, MCP-1) via mitogen-activated protein kinases (MAPK) and the transcription nuclear factor κB (NF- κB) (29). The majority of cytokines are produced by activated lymphocytes and macrophages. Produced pro-inflammatory cytokines provide activation of endothelial cells and expression of cellular adhesion molecules, which results with increased leukocytes requirement and diapedesis. However, developed sepsis in preterm neonates markedly reduces production of most pro-inflammatory cytokines, mainly by decreased production of Myeloid Differentiation Factor (MyD88) (30). In line with previous findings, earlier report showed reduced signaling through TLRs in preterm neonates, indicating reduced protection against different pathogens (31).

The characteristics of secreted cytokines and pathogen, have huge effect in process of differentiation of T helper precursors cells (Th) toward Th1 or Th2 cells. IFN-γ, IL-2 and TNF-β are main cytokines produced by Th1 cells and they provide cellular and phagocytic activity. Th2 cells produce IL-4, IL-5, IL-6, IL-9, IL-13 and promote antibodies production and humoral immunity. On the other hand, to control the intensity of inflammatory response, anti-inflammatory cytokines (IL-4, IL-10, IL-13, TGF- β) are secreted by lymphocytes, Th2 cells and macrophages (4). Balanced control of cytokines secretion is crucial to control inflammatory activity and to prevent multiple organ dysfunction. Therefore, monitoring the total amount of these cytokines may provide better understanding of sepsis development and treatment efficiency, since appropriate treatment would turn these cytokines to the baseline levels.

However, overexpression of curtained component, named before, may lead to inconsistent inflammatory response in different population, especially in preterm neonates where all the components of the immune system show relative immaturity (3).

Conclusion

With high morbidity and mortality rate, neonatal sepsis is preterm neonates, represents one of leading major public health concern around the world. Immaturity of immune system in preterm neonates may contribute to increased susceptibility to infection. Innate immune system activation usually provides basic protective mechanisms against inflammatory response, initiated at the begging of the neonatal sepsis development. Production of different biomarkers during initiation of immune response, secretion of various cytokines and chemokines, may serve as a potential predictive factors for neonatal sepsis development. Additionally, better understanding the basic immune mechanisms, especially during innate immune system activation, may clarify sepsis development and simultaneously enable potent treatment efficiency. Further research and additional cohort studies are required to develop effective preventive methods for reduction the neonatal morbidity and mortality.

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