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ROLE OF HMGB1 PROTEIN EXPRESSION IN THE NEONATAL SEPSIS

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Neonatal sepsis is a significant global health concern, affecting approximately 3 million newborns annually and resulting in up to 375,000 deaths as of 2019. Despite advancements in molecular diagnostics, timely and accurate diagnosis of neonatal sepsis remains a challenge. The high-mobility group box 1 protein, a modulator of immune and metabolic processes, has been identified as a critical player in the pathogenesis of various diseases, including cancer and traumatic shock. This review explores the role of high-mobility group box 1 protein in the pathogenesis of neonatal sepsis, focusing on its secretion mechanisms, its involvement in inflammatory responses, and its potential as a therapeutic target. This role is complex and multifaceted, with studies indicating protective and detrimental effects depending on the context. Understanding high-mobility group box 1 proteins function could improve diagnostic markers and targeted therapies, ultimately enhancing outcomes for affected neonates.

Key words: high-mobility group box 1 protein, neonate, sepsis, inflammation, immunity.

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РОЛЬ ЕКСПРЕСІЇ БІЛКУ HMGB1 У НЕОНАТАЛЬНОМУ СЕПСИСІ

Неонатальний сепсис є важливою проблемою світової охорони здоров'я, щорічно вражаючи близько 3 мільйонів новонароджених та призводячи до 375 000 смертей на 2019 рік. Незважаючи на досягнення в галузі молекулярної діагностики, своєчасна та точна діагностика неонатального сепсису залишається проблемою. Високорухливий білок групи B1, модулятор імунних та метаболічних процесів, був ідентифікований як критично важливий гравець у патогенезі різних захворювань, включаючи рак та травматичний шок. У цьому огляді вивчається роль високорухомого білка групи box 1 у патогенезі неонатального сепсису, з упором на його механізми секреції, його участь у запальних реакціях та його потенціал як терапевтичну мішеню. Ця роль складна і багатогранна, і дослідження вказують як на захисні, так і згубні ефекти в залежності від контексту. Розуміння функції високорухливого білка групи B1 може призвести до покращення діагностичних маркерів та таргетної терапії, зрештою покращуючи результати для уражених новонароджених.

Ключові слова: білок групи високорухомого білка групи B1, новонароджений, сепсис, запалення, імунітет.

Every year, approximately 3,000,000 newborns develop sepsis [19], and according to 2019 data, up to 375,000 deaths from sepsis have been recorded [42]. Despite advances in molecular diagnostics, accurate and timely diagnosis of neonatal sepsis remains challenging [27]. Although microbial culture identification is still the gold standard for diagnosing sepsis, literature reports mention culture-negative or suspected sepsis diagnoses. Two large randomized controlled trials showed that culture-negative sepsis occurs in 56 % and 46 % of cases [41].

Neonatal sepsis is a significant cause of morbidity and mortality in newborns and is challenging to diagnose. Infants present with nonspecific clinical signs in response to sepsis; noninfectious conditions may cause these signs. The time to initiation of antibiotics influences the outcome of neonatal sepsis, so clinicians need to identify and treat neonates with sepsis [19] promptly.

Clinicians use serum biomarkers to measure inflammation and infection and assess the risk of sepsis in an infant. However, current biomarkers lack sufficient sensitivity or specificity to be useful diagnostic tools. Continued research to identify new biomarkers and new ways to measure them is urgently needed [4, 8].

Despite the frequent misuse of antibiotics and the prevalence of antibiotic resistance, the World Health Organization's data indicates that delayed sepsis diagnosis creates more significant problems [21]. Neonatal sepsis, especially in deficient birth weight infants, is associated with complications related to prematurity and neurodevelopmental disorders [34]. These unsatisfactory outcomes emphasize the need for early recognition of sepsis and prompt initiation of antibiotic therapy [15, 24, 33].

However, unnecessary empirical antibiotic therapy also increases morbidity and mortality rates later in life [5, 6]. Therefore, earlier recognition or exclusion of sepsis should ensure diagnostic and therapeutic improvement. New molecular approaches and non-culture methods are needed for timely detection and accurate diagnosis of sepsis. Current biomarkers and ancillary hematological indices used in routine clinical practice are of limited value and difficult to interpret due to low sensitivity and changing normal ranges during the neonatal period. An ideal marker should have a sensitivity and negative predictive

value approaching 100 %; specificity and positive predictive value greater than 85 %. No single biomarker or combination of biomarkers has sufficient diagnostic accuracy for reliable use in diagnosing neonatal sepsis [10, 16, 17].

In neonates, the lack of reliable criteria for a definitive diagnosis and the assumption that early antibiotic use may reduce the development of sepsis in at-risk infants has led to a corresponding overuse of antibiotics for both prophylaxis and therapy [6].

Our review used the materials published in Scopus, Web of Science, and PubMed databases within 2019–2025 years. For research, the key words used were: high-mobility group box 1 protein, neonatal sepsis, pathway of inflammation, biomarkers. In the research process, the specific studies of various biomarkers and their role in the pathogenesis of neonatal sepsis were analyzed.

Since sepsis is not a specific organ disease characterized by the body's systemic response to infection, immune response functions and pathways affecting the immune system for treatment purposes have been studied. Yet, no specific diagnostic marker has been identified.

NICE guidelines use ancillary laboratory tests (eg C-reactive protein) to guide clinical decisions and determine the duration of treatment. In contrast, US sepsis guidelines state that assessment of inflammatory markers should not decide which infants require antibiotics. NICE guidelines suggest a sepsis risk calculator as an alternative strategy, but only in the context of a research or audit project [20, 23].

Damage-associated molecular patterns (DAMPs, alarmins) such as high-mobility group box 1 (HMGB-1) and uric acid are released from damaged cells and induce cytokine production, coagulation cascade, and regulate polymorphonuclear cell function. Anti-inflammatory cytokines such as transforming growth factor-β (TGF-β), IL-4, IL-10, IL-11, and IL-13 are expressed to control and balance inflammation.

Acute phase reactants such as C-reactive protein, procalcitonin, serum amyloid A are produced predominantly in the liver in response to complement activation and proinflammatory cytokine secretion [7, 10]. In case of an infection, these levels continue to rise and signify an infection, which may progress to sepsis [26].

The time of changing biomarkers' levels is also important. In patients with sepsis at the time of admission, presepsin, procalcitonin, C-reactive protein, and IL-8 are significantly higher. Presepsin, procalcitonin, and IL-8 levels significantly decrease after 72 hours of admission [1]. Albuali WH showed that in postoperative pediatric trauma patients aged>2 weeks old procalcitonin levels at 48–72 hours exhibited the largest level also in patients [2].

Kumar R, et al by studying several biomarkers of gram-negative late-onset sepsis and necrotizing enterocolitis (NEC) increasing IL-6 level and concordant increasing pulse oximetry sepsis warning score. They concluded that inflammatory plasma biomarkers discriminate sepsis due to gram-negative bacteremia or NEC and correlate with cardiorespiratory physiomarkers [28].

There was information about chemerin, a novel adipokine, as a potent chemoattractant molecule with antimicrobial properties, which plays important role in immune responses. Circulating chemerin is increased early in sepsis and these changes may have diagnostic and prognostic value in patients with severe sepsis. Further studies are needed to shed light on the role of chemerin in sepsis [27].

Li AT, et al with the purpose to evaluate the diagnostic performance of all biomarkers studied to date for the early diagnosis of sepsis in hospitalized patients with burns searched Medline, Embase, Cochrane CENTRAL, Biosis Previews, Web of Science, and Medline In-Process to February 2020. In an analysis of 28 studies assessing 57 different biomarkers and including 1517 participants, procalcitonin was moderately sensitive (73 %) and specific (75 %) for sepsis. C-reactive protein was highly sensitive (86 %) but poorly specific (54 %). White blood cell count had poor sensitivity (47 %) and moderate specificity (65 %). All other biomarkers were not well studied to include in the meta-analysis, but brain natriuretic peptide, stroke volume index, and tumor necrosis factor (TNF)-alpha showed the greatest promise in individual studies. There was moderate to substantial heterogeneity reflecting different study populations, sepsis definitions, and test cutoff values [17, 31].

Some authors proposed the predictive role of neutrophil-to-lymphocyte-ratio for sepsis diagnosis [38].

Recently, few reports were available about the use of proteomic analysis in patients with sepsis, and the results have not been confirmed by well-established methods. A recent review identified about 200 proteins in response to sepsis using proteomic analysis of septic blood, some of which may serve as sepsis markers.

Biomarkers identified through proteomic studies have shown promise. Proteomics is a large-scale study of proteins from organisms, tissues, and cells, and this approach has the potential to identify fetuses at risk for sepsis. Based on proteomic analyses, a mass-limited assessment strategy was developed using relevant proteomic biomarkers. These amniotic fluid measurements provided information on the fetal response to intra-amniotic inflammation and successfully predicted early-onset sepsis [12].

The problem with proteomic assays that identify specific proteins and peptides by randomly sampling case and control plasma from different patients and clinical settings is the retrospective interpretation of the results. For early detection of septic neonates, we face the same old problems of each biomarker as shown in this review. Moreover, this is also true for metabolomics in septic patients [9, 10].

Additionally, since sepsis is characterized by severe hemodynamic disturbances leading to reduced tissue perfusion due to ischemia and hypoxia, the resulting metabolic disorders determine the severity of the process [43].

Molecular methods for pathogen detection, primarily evaluated in neonatal studies, have used amplification methods such as PCR rather than hybridization- or mass spectrometry-based methods.

Molecular diagnostics hold the promise of more rapid and sensitive results, particularly as molecular assays can be completed in less than 12 hours, and will be useful in settings where there is antimicrobial pretreatment, low-density bacteremia, and culture-negative sepsis is common. Of the various amplification methods studied, broadband conventional PCR and real-time PCR have been documented to provide higher diagnostic sensitivity and specificity than other assays, although other methods have not been adequately studied [27, 31].

On the other hand, there have also been concerns that molecular diagnostics may be too sensitive. Prospective studies using PCR to diagnose neonatal sepsis have shown that despite the increased sensitivity and rapid detection of pathogens it allows, the uncertainty as to whether the bacteria present were the cause of a particular patient's sepsis symptoms was not reduced [31].

Recently, studying the pathogenesis of diseases and managing them by targeting different stages of pathogenesis has been considered a primary treatment method. Therefore, the study of HMGB1 protein, which is a modulator of immune and metabolic processes, is of great significance.

The high-mobility group family was first isolated and identified by Ernest Jones, Graham Goodwin, and Clive Sanders in 1973 [40].

The highly conserved 215-amino-acid-residue high-mobility group protein 1, consisting of two proximal homologous DNA-binding domains, and an uncharged C-terminal acidic tail, was the most highly expressed of all high-mobility group protein family members. HMGB1, has multiple functions related to its redox state, cellular distribution, post-translational modification, and the type of cells, tissues, and organs in which it resides [29].

A substantial number of preclinical studies of Gram-negative sepsis and endotoxemia document how HMGB1 and LPS cause tissue damage responsible for multi-organ failure via different mechanisms [14].

The role of HMGB1 has been studied in the pathogenesis of various diseases, such as cancer, traumatic shock, and others. HMGB1-dependent autophagy mediates chemotherapy resistance in leukemia and multiple myeloma and plays a role in carcinogenesis, progression, prognosis, and potential clinical applications in various hematopoietic malignancies [49]. Gergues M, et al, by the long-term culture-initiating cell assays with or without NK-A (NK2) receptor antagonist showed a suppressive effect of HMGB1 on hematopoietic progenitor cells and an increase in long-term culture-initiating cell assays (primitive hematopoietic cells). Mice treated with the HMGB1 antagonist glycyrrhizin confirmed the effects of HMGB1 in vitro. Thus, HMGB1 may be required to prevent depletion of hematopoietic stem cells to ensure immune homeostasis [22].

HMGB1, along with its downstream receptors such as Toll-like receptors (TLRs) and receptors for advanced glycation end products (RAGE) serve as a suitable target for diabetes mellitus. Future research in the diabetes field will potentially focus on developing alternative approaches to targeting the inflammatory pathway primarily mediated by HMGB1 to improve diabetes-related complications [3].

Xu C, Chen Y, studied the influence of various factors on HMGB1/RAGE/TLR4 pathway of inflammation in renal tissue and revealed that the therapeutic effects of HPS on mice with diabetic kidney damage may be mediated by inhibiting the high mobility group box 1/receptor, so these findings could provide insight for the treatment of diabetic kidney disease [46].

HMGB1 is synthesized by various immune cells like pro-inflammatory cytokines. When these cytokines are released in excessive amounts, they can lead to tissue damage, multiple organ dysfunction and failure, and even death [49].

The human HMGB1 gene is located on chromosome 13 and is highly evolutionarily conserved [28]. The structure of HMGB1 is extremely conserved in eukaryotes among species, with 99 % amino acid homology between rodents and humans. HMGB1 binds DNA through its autologous structural domain to maintain the stability of the nucleosome and regulate transcription, translation, and DNA repair [37].

HMGB1 is primarily secreted from cells in two ways: active secretion and passive secretion [49]. Despite the clinical significance of HMGB1, its secretion mechanisms are not fully understood. Extracellular HMGB1 exerts its pro-inflammatory functions by combining with immunostimulatory molecules such as RNA, histones, lipopolysaccharides, and IL-1a. It acting as a damage-associated

molecular pattern, can activate the immune system by binding tightly to its high-affinity receptor RAGE to initiate mitogen-activated protein kinase (MAPK) and NF-κB signaling downstream [37].

As known, HMGB1 is one of the major non-histone proteins that plays a key role in triggering the inflammatory response. Once released into the extracellular environment, HMGB1 acts as an "alarm signal" for the immune system to initiate tissue repair as a component of the host defense system [3].

Active secretion of HMGB1 occurs from monocytes through a non-classical, vesicle-mediated secretory pathway. Mechanically, the activation of monocytes facilitates the distribution of HMGB1 from the nucleus to cytoplasmic organelles. Subsequently, HMGB1 secretion is triggered by lysosomal exocytosis [25, 30].

The first phase of HMGB1 secretion occurs actively between the nucleus and cytoplasm in all types of cells. Later, the translocation of HMGB1 from the nucleus to the cytoplasm requires significant post-translational modifications, such as phosphorylation and acetylation, although these pathways are not fully understood [40].

Deng et al. suggest that the calmodulin-dependent kinase IV pathway is involved in the phosphorylation process during the release of HMGB1 from macrophages stimulated with lipopolysaccharide (LPS) [46].

From monocytes and macrophages, HMGB1 is secreted via acetylation after LPS stimulation under the influence of PCAF, CBP, and p300. Additionally, hyperacetylation of HMGB1 in quiescent macrophages causes its relocalization to the cytosol. Thus, cytosolic HMGB1 accumulates in secretory lysosomes and is secreted as monocyte cells receive a secondary signal [37].

In addition, HMGB1 can bind to TLR2 and TLR4 pattern receptors on the cell membrane surface to activate the NF-κB signaling pathway nodes, which upregulates various inflammatory factors and promotes inflammatory cascades. [36].

Some authors previously reported that activation of the HMGB1 pathway mediates the inflammatory response and epithelial-mesenchymal transition in HK-2 cells.

Furthermore, HMGB1 secretion induced by IFN-γ is partially regulated by TNF-dependent mechanisms. Previous studies have shown that extracellular HMGB1, as a key pro-inflammatory factor, can bind to RAGE/TLR on the surface of monocytes, promoting the synthesis and release of pro-inflammatory factors such as TNF-α, IL-1, and IL-6, with NF-κB potentially playing a direct role in this regulatory process induced by HMGB1 [18].

Some researchers demonstrated that IFN-γ also affects the release of HMGB1, TNF, and NO in a dose-dependent manner. Neutralization of TNF with antibodies reduced IFN-γ-induced HMGB1 secretion. The JAK2 pathway, a specific inhibitor of Janus kinase (JAK 2), reduced HMGB1 levels in a dose-dependent manner. IFN-β, IFN-γ, and LPS activate the JAK2/STAT1 pathway, leading to hyperacetylation of HMGB1 [16].

Subsequently, HMGB1 translocates from the nucleus to the cytoplasm. HMGB1 translocation from the nuclear region to the cytoplasm, and this effect was abolished by RAGE overexpression [50]. Sirtuin 1 (SIRT1) directly interacts with HMGB1 at its N-terminal lysine residues and prevents HMGB1 secretion. Conversely, LPS and TNF-α separate it from SIRT1, leading to acetylation [39, 48].

Additionally, HMGB1 secreted by platelets plays a role in the development of inflammation and thrombosis. Activated platelets secrete large amounts of HMGB1, which translocates to the plasma membrane when the vascular wall is damaged [49].

Passive secretion of HMGB1 occurs in response to severe inflammation during sepsis and trauma or from dying cells, such as in necrosis, pyroptosis, and necroptosis. HMGB1 loosely binds to chromatin in interphase and mitotic cells and is rapidly secreted into the environment during cell lysis or increased cell permeability.

Cells that release HMGB1 are less likely to trigger inflammation. It is believed that, along with HMGB1 secretion, a death signal is also transmitted to the cell. Cells undergoing apoptosis, even when subjected to secondary necrosis and partial autolysis, do not secrete HMGB1 and do not trigger inflammation. In apoptotic cells, HMGB1 tightly binds to chromatin, as generalized hypoacetylation of histones occurs; only if chromatin deacetylation is inhibited can it be secreted into the extracellular environment. All of this suggests that passively secreted HMGB1 is non-acetylated and remains within the nucleus [45].

The proportion of passively and actively secreted HMGB1 during inflammation has been studied. It has been determined that during passive secretion, HMGB1 is in a reduced form, affecting its pro-inflammatory functions. Lipid peroxidation and aerobic glycolysis trigger the secretion of HMGB1 from activated inflammasomes during sepsis [40].

Fully understanding these mechanisms may pave the way for therapeutic interventions to prevent lytic cell death or active HMGB1 secretion during infection and inflammation.

As an effective pro-inflammatory cytokine, HMGB1 plays a key role in various inflammatory diseases.

These functions realized by promoting DNA damage repair in the nucleus, sensing nucleic acids and inducing innate immune responses and autophagy in the cytosol and binding protein partners in the extracellular environment and stimulating immunoreceptors. In addition, HMGB1 is a broad sensor of cellular stress that balances cell death and survival responses essential for cellular homeostasis and tissue maintenance. HMGB1 is also an important mediator secreted by immune cells that is involved in a range of pathological conditions, including, ischaemia–reperfusion injury, autoimmunity, cardiovascular and neurodegenerative diseases, metabolic disorders and cancer [40].

Specifically, it has been determined that HMGB1 significantly increases in circulation in sepsis models and septic patients, and circulating HMGB1 levels positively correlate with disease severity and the extent of inflammation [2, 45]. Additionally, the increase in HMGB1 during inflammation can lead to anemia and cognitive impairment, which is thought to be associated with neuroinflammation, particularly in people recovering from sepsis [32].

Compared to other early-phase pro-inflammatory markers, such as TNF and IL-1β, HMGB1 begins to increase 8 hours later and then rises significantly, creating a broad clinical window for HMGB1 in septic patients [23, 35].

Since significant inflammation occurs in the early stages of sepsis, organ dysfunction ensues, and continued inflammation leads to more severe consequences, such as organ failure. By intervening during the therapeutic window period, it may be possible to prevent excessive activation of the immune response. Research shows that blocking HMGB1 expression can alleviate inflammatory diseases such as rheumatoid arthritis, myositis, and systemic lupus erythematosus. Studies targeting HMGB1 have demonstrated that reducing HMGB1 can also mitigate sepsis-associated organ damage, primarily by enhancing neutrophils' ability to destroy bacteria and reducing persistent inflammation. So, recently the novel strategies such as HMGB1 receptor antagonists, inhibitors of its signaling pathway, antibodies, RNA inhibitors, vagus nerve stimulation, etc. have been used to inhibit the expression, release or activity of HMGB1 [43].

In sepsis mice and patients recovering from septic shock, HMGB1 has been shown to reduce neutrophils' ability to kill bacteria by promoting the function of neutrophil nicotinamide dinucleotide oxidase in bacteria. Interestingly, in mouse models of abdominal sepsis, platelet-derived HMGB1 aids neutrophil activation and the generation of reactive oxygen species, playing a critical role in neutrophils' ability to kill bacteria [34, 47].

Systemic HMGB1 levels significantly increase in mouse sepsis models [13], and after lipopolysaccharide administration, HMGB1 levels in mice begin to rise after 8 hours, reaching high levels after 16–32 hours. The late increase in HMGB1 levels provides a window for using HMGB1 antibodies in septic patients [47]. Studies have shown that reducing HMGB1 secretion effectively increases the survival rate of mice suffering from sepsis [11].

Studies have recently demonstrated that increasing the level of cellular HMGB1 promotes pyroptosis and apoptosis to mediate organ injury in sepsis. Therefore, targeting HMGB1/RAGE may be a potentially effective strategy for clinical therapy in sepsis. However, the effects of HMGB1/RAGE on cell pyroptosis in sepsis-induced ALI remain unclear [11, 48].

Moreover, research has shown that platelet-derived HMGB1 stimulates neutrophil extracellular traps, and animal models of septic shock demonstrate that extracellular neutrophil trap levels significantly increase. These elevated traps recruit neutrophils to the lungs, leading to the formation of an inflammatory environment in the lungs.

In addition to this effect, neutrophils also stimulate macrophages, which then produce massive amounts of inflammatory mediators such as TNF-α, stimulating HMGB1 secretion, thereby accelerating the systemic inflammatory response [23].

In animal models, pulmonary fibrosis has been associated with HMGB1 binding to phosphatidylserine on apoptotic neutrophil surfaces, delaying their engulfment and phagocytosis by macrophages. Additionally, apoptotic neutrophils continue to synthesize pro-inflammatory substances and reactive oxygen species, accelerating the inflammatory environment in the lungs and further damaging lung tissue. Further studies are needed to explore the role of HMGB1 in sepsis. Under physiological conditions, HMGB1 levels in the cytoplasm and serum are low. However, during tissue damage, they increase sharply [47].

Lung injury during sepsis is one of the most common conditions. Sepsis-related lung injury typically shows higher mortality rates than lung injuries due to other causes [39].

In one work lung injury by inhibiting HMGB1 in an animal model of acute respiratory distress syndrome (ARDS) was reduced using a compound called salidroside. In vitro animal studies in this direction have shown the inflammatory role of HMGB1 in ARDS. Additionally, studies have shown that inhibiting HMGB1 with a compound called resveratrol in liver injury models during sepsis reduces serum ALT and pro-inflammatory cytokine levels [46].

The significant increase in mRNA transcription levels of IL-1 and IL-6 in renal tubular epithelial cells during sepsis is accompanied by the accumulation of HMGB1 in renal tissue. It was demonstrated that HMGB1 triggers inflammation after binding to TLR4. The physiological role of HMGB1 in the immune response and the results of studies suggest that this protein also plays a role in the pathogenesis of sepsis. However, conflicting results from studies indicate that the role of HMGB1 in sepsis is complex and diverse.

Although research on HMGB1 has been ongoing for several decades and it has been studied and validated in various disease models, multiple pathophysiological processes, and signaling pathways, most of these studies have been conducted in adult experimental animals, and clinical studies have also been primarily focused on adults, while studies in children are still scarce [29].

Conclusion

As outlined in this review, there is an important role for HMGB1 in the pathogenesis of sepsis. Clinical trials investigating HMGB1 neutralization to improve sepsis outcomes are scarce. One reason is that HMGB1 is a very difficult molecule to target in vivo with HMGB1-binding antagonists because HMGB1 can change its structure during dynamic biological processes. Extracellular HMGB1 forms complexes with many other molecules that gradually accumulate extracellularly during tissue injury, and these complexes can alter receptor occupancy. Thus, specifically, studying HMGB1 protein in neonatal sepsis is very relevant both diagnostically and therapeutically, necessitating further focused scientific research. The availability of biomarkers of neonatal sepsis that could alert the clinician to the early diagnosis of neonatal sepsis could improve the short- and long-term outcomes of true sepsis cases and reduce the indiscriminate and harmful use of prophylactic antibiotics.

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