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НЕКРОТИЗИРУЮЩИЙ ЭНТЕРОКОЛИТ У НЕДОНОШЕННЫХ: РОЛЬ МИКРОБИОТЫ, TLR-СИГНАЛИНГА И НЕЗРЕЛОСТИ КИШЕЧНОГО БАРЬЕРА (ОБЗОР ЛИТЕРАТУРЫ)

Аннотация: *Некротизирующий энтероколит (НЭК) остается одной из ведущих причин заболеваемости и смертности среди недоношенных новорожденных. В основе патогенеза заболевания лежит сложное взаимодействие незрелости кишечного барьера, дисбиоза микробиоты и неадекватной активации врожденного иммунитета, в частности Toll-подобных рецепторов (TLR).*

Ключевые слова: *некротизирующий энтероколит, недоношенные новорожденные, микробиота, кишечный барьер.*

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NECROTIZING ENTEROCOLITIS IN PRETERM INFANTS: THE ROLE OF GUT MICROBIOTA, TLR SIGNALING, AND INTESTINAL BARRIER IMMATURITY (A LITERATURE REVIEW)

Abstract: *Necrotizing enterocolitis (NEC) remains one of the leading causes of morbidity and mortality in premature neonates. The pathogenesis of the disease is characterized involving a complex interplay of intestinal barrier immaturity, gut microbiota dysbiosis, and dysregulated innate immune activation, particularly through Toll-like receptors (TLRs).*

Keywords: *necrotizing enterocolitis; preterm infants; gut microbiota; intestinal barrier; Toll-like receptors.*

Objective: To review current literature on the roles of gut microbiota, TLR signaling, and intestinal barrier immaturity in the pathogenesis of necrotizing enterocolitis in preterm infants.

Materials and Methods: A narrative review of 10 recent publications addressing the etiopathogenesis of necrotizing enterocolitis in premature neonates was conducted.

Results

The analysis of contemporary literature supports the conclusion that NEC is a multifactorial disease whose pathogenesis reflects a failure of the immature gastrointestinal tract to adapt to postnatal conditions. The etiopathogenesis of NEC cannot be attributed to a single factor; rather, it represents a cascade of mutually reinforcing pathological processes in which three mutually exacerbating factors play a central role: intestinal barrier immaturity, microbiota dysbiosis, and hyperactivation of innate immunity via Toll-like receptors (TLRs) [1, 3]. The following sections sequentially examine the contribution of each component and their integrative interaction, which ultimately culminates in transmural intestinal necrosis [4].

1. Intestinal Barrier Immaturity as the Fundamental Basis of Pathogenesis.

The primary predisposing factor in the development of NEC in preterm infants is the profound morphofunctional immaturity of the intestinal wall. In contrast to term neonates, this population exhibits several critical structural deficiencies. The epithelial barrier is characterized by reduced crypt proliferative activity, incomplete enterocyte differentiation, and, consequently, insufficient tight junction density, leading to increased intestinal permeability [2, 8]. This structural immaturity is further compounded by defects in the mucous barrier, manifested as reduced mucin (MUC2) production by goblet cells, resulting in a thin and easily disrupted glycocalyx, as well as a deficit in antimicrobial peptide synthesis, including defensins and cathelicidins [1]. Consequently, the intestinal wall of the preterm infant becomes becomes highly permeable to bacteria and their antigens, which

under normal circumstances would not penetrate the submucosal layer. This susceptibility is exacerbated by clinical factors such as hypoxia, ischemia, and formula feeding, all of which can additionally compromise local blood flow and mucosal perfusion, thereby intensifying epithelial injury [6].

2. Microbiota Dysbiosis: From Colonization to Pathobiont Dominance.

The second critical determinant in the pathogenesis of NEC is the pattern of gut microbiota establishment during the early neonatal period. Under physiological conditions in term, breastfed neonates, the intestine is sequentially colonized by Bifidobacterium and Lactobacillus species, creating an acidic luminal environment, producing bacteriocins, and competing with pathogenic organisms for nutritional substrates [5]. In preterm neonates, however, this process is subject to profound disruption. As a result of prolonged intensive care unit admission, antibiotic exposure, and dependence on parenteral nutrition or formula feeding, initial colonization is dominated by nosocomial strains, primarily members of the Enterobacteriaceae family (including Klebsiella and Escherichia coli) and Enterococcus species. Data presented in the review by Tao E. et al. [9] confirm that the gut microbiota of preterm infants at high risk for NEC is characterized by low alpha-diversity and a high relative abundance of Proteobacteria. This state, defined as dysbiosis, generates a pathogenic environment. A key metabolic feature of such microbial communities is the substantial production of bacterial components, notably lipopolysaccharide (LPS) derived from Gram-negative bacteria, which acts as a potent activator of TLR4 [3, 5]. In contrast, the establishment of a healthy microbiota, by contrast, exerts a pronounced protective effect. Dong X. et al. demonstrated that 3-indoleacrylic acid – a metabolite produced by commensal microorganisms – can inhibit enterocyte necroptosis, representing one of the endogenous intestinal protective mechanisms that is disrupted under conditions of dysbiosis. Furthermore, Tao E. et al. [9] demonstrated that the pattern of microbiota establishment during the first weeks of life is a predictor of NEC risk, supporting the view of the microbiota not as a passive bystander but as an active participant in

pathogenesis, whose metabolic profile directly modulates the host inflammatory response [4].

3. TLR Signaling: The Switch Between Homeostatic Protection and Hyperinflammation.

The third and central component, integrating the effects of barrier immaturity and dysbiotic microbiota, is the innate immune system – specifically, the Toll-like receptor signaling pathway. The intestinal epithelium of the preterm infant expresses a wide range of TLRs, among which TLR4, which recognizes LPS from Gram-negative bacteria, and TLR2, whose ligands include cell wall components of Gram-positive microorganisms, play key roles in NEC pathogenesis [3, 8]. Under conditions of an intact epithelial barrier and a balanced microbiota, basal TLR signaling serves an important homeostatic function, supporting epithelial proliferation and repair. In NEC, however, this balance is fundamentally altered. Extensive translocation of LPS from the intestinal lumen into the submucosal layer across the immature barrier leads to hyperactivation of TLR4. As described in the clinicopathological analyses of Belyaeva I.A. et al. [1], this triggers a potent pro-inflammatory cascade mediated by the nuclear factor NF-κB. The consequent overproduction of pro-inflammatory cytokines – including TNF-α, IL-1β, IL-6, and IL-8 – drives the recruitment of neutrophils and macrophages to the site of inflammation. Critically, TLR4 activation in enterocytes produces not only immunological consequences but also direct pathological effects on the intestinal wall itself: it induces the expression of pro-apoptotic proteins and suppresses factors responsible for epithelial repair and tight junction maintenance. This creates a vicious cycle in which TLR-mediated inflammation further disrupts the epithelial barrier, thereby facilitating additional bacterial antigen translocation and escalating the inflammatory response. Extrapolating the data of Iqbal F. et al. to the context of NEC suggests that TLR-dependent bacterial translocation constitutes the critical trigger that converts local intestinal inflammation into the systemic inflammatory response characteristic of severe disease [4,8].

4. Integrative Model of Pathogenesis and Emerging Therapeutic Horizons.

Synthesis of the presented data permits the formulation of a contemporary integrative model of NEC pathogenesis. Two key factors, often co-occurring serve as the initiating events: intestinal barrier immaturity (compromising both mechanical and chemical defense) and iatrogenic dysbiosis (a microbial shift toward Proteobacteria dominance). Their interaction lead to an aberrant TLR signaling pattern that transitions from physiological (reparative) to pathological (necrotizing). This drives a progressive escalation of inflammation, microthrombosis, ischemia, and, ultimately, transmural intestinal necrosis. Understanding this three-component pathogenesis opens new strategies for both treatment and prevention of NEC. The following approaches, supported by the reviewed literature, are currently under investigation as promising directions:

1. Probiotics and Microbiota Modulation. Data from international investigators provide compelling evidence that deliberate promotion of a healthy microbiota – for example, through early introduction of probiotic strains such as Lactobacillus and Bifidobacterium – may reduce the risk of NEC by competitively displacing pathogenic flora and restoring the production of protective metabolites, such as 3-indoleacrylic acid [5].

2. Minimization of TLR Activation. At the experimental level, the use of TLR4 antagonists or inhibitors of NF-κB-associated signaling pathways is under investigation; however, these approaches remain far from clinical translation due to the risk of systemic immunosuppression [7, 10].

3. Barrier Maturation Therapy. An important avenue involves the administration of specific nutrients – including glutamine, arginine, and long-chain polyunsaturated fatty acids – that may stimulate enterocyte differentiation and reinforce tight junction integrity [2].

Accordingly, the synthesis of the reviewed data unequivocally demonstrates that NEC results from a tripartite pathological insult: an immature intestinal barrier, a pathobiont-dominated microbiota, and a hyperactivated innate immune response.

This necessitates a comprehensive preventive approach targeting all three components from the earliest hours of the preterm infant's life.

Conclusion

This review of current literature on the etiopathogenesis of necrotizing enterocolitis in preterm neonates has both confirmed and expanded the understanding of the complex pathophysiological basis of this severe disease. The main conclusion of this work is that all three examined components – the intestinal barrier, the gut microbiota, and TLR signaling – function not as isolated links but as elements of a unified functional system. Intestinal barrier immaturity in preterm infants creates the anatomical and physiological basis for bacterial antigen translocation. Dysbiosis induced by iatrogenic factors generates an excessive pool of such antigens, primarily LPS from Gram-negative organisms. The combination of these conditions in the context of impaired innate immune regulation leads to a transformation of physiological TLR signaling into a pathological inflammatory cascade, triggering a cytokine storm, enterocyte apoptosis, and ischemic necrosis of the intestinal wall. Particularly important are findings related to the gut microbiota and its metabolites. Whereas the microbiota was previously regarded merely as a risk marker, compelling evidence has now emerged for its active pathogenetic role. This repositions microbiota modulation – including the use of promising probiotic strains – not as an adjunctive intervention but as one of the primary preventive strategies aimed at interrupting the vicious cycle of inflammation at the earliest stages. However, that any preventive or therapeutic strategy should be carefully individualized, given that microbiota establishment is a highly variable process dependent on numerous factors, including gestational age, feeding type, and the extent of antibiotic therapy. At the same time, this review identifies several unresolved questions and promising directions for future research. First, the complex metabolic crosstalk between the host and the microbiota requires further investigation. Although this work addressed data on protective metabolites, the full spectrum of bacterial metabolites and their modulation of TLR signaling remains incompletely characterized. Second, the overwhelming majority of fundamental

discoveries have been made in experimental models, and their extrapolation to clinical practice warrants caution. Large-scale prospective cohort studies are urgently needed to track the dynamic changes in all three pathogenetic components in real time within the same patient, with the aim of developing precise predictive algorithms. In conclusion, necrotizing enterocolitis remains a multifactorial disease that requires an interdisciplinary approach integrating immunology, microbiology, and neonatology. Continued advancement in understanding the molecular mechanisms underlying the interactions between the intestinal epithelium, the microbial community, and the immune system is the key to developing novel, more effective preventive and therapeutic strategies – strategies that may substantially reduce morbidity and mortality in the most vulnerable patient population: preterm infants.

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