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Gut microbiota and Lactobacillus species maintain the small intestine stem cell niche and ameliorate the severity of necrotizing enterocolitis

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Gut microbiota and *Lactobacillus* species maintain the small intestine stem cell niche and ameliorate the severity of necrotizing enterocolitis

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The microbiota plays an undisputed role in mammalian development and physiology. It enhances energy extraction from ingested food, protects against harmful pathogens, regulates immune function, and strengthens biochemical signaling. In mammals, including humans, colonization of the gut by microbes begins at birth[1], and several recent studies have shown that the microbiome contributes to postnatal host development in early childhood. In this sense, microbial dysbiosis in infancy has been associated with certain diseases such as inflammatory bowel disease, cardiometabolic disorders, cancer, and neuropsychiatric disorders[2].

The intestinal epithelial cells are in direct contact with a large number of bacteria and the external environment, forming a barrier between inside and outside while fulfilling a critical role in the absorption of nutrients. The small intestine crypt-villus architecture is a unique structure that provides a microenvironment in which intestinal stem cells (ISCs) differentiate into a variety of different epithelial subtypes. These subtypes include enterocytes, also known as intestinal epithelial cells (IECs), Paneth cells, goblet cells, enteroendocrine cells, tuft cells, and microfold cells (M cells)[3].

Kim et al. demonstrated that early life gut microbiota exposure promotes the differentiation of intestinal stem cells into Paneth cells by regulating numbers of $CD206^{+}$macrophages associated with epithelial Wnt signaling, which maintains mesenchymal niche cell proliferation (Figure 1). They suggested that the maintenance of this stem cell niche is critical for small intestinal homeostasis and its disruption (e.g., by antibiotic administration) can lead to inflammatory conditions, which can manifest as necrotizing enterocolitis (NEC). NEC is a severe inflammatory disease affecting the small intestine, especially in preterm infants, and is the leading cause of death in this group.

To investigate the role of the microbiota and intestinal stem cell differentiation in the pathogenesis of NEC, Kim et al. induced NEC-like phenotypes in neonatal mice by exposing them to hypoxia and gavage feeding of hyperosmolar formula and LPS. ATB-induced dysbiosis resulted in further impaired stem cell niche in the small intestine and led to severe NEC manifestation. They also confirmed previous findings that microbial dysbiosis in NEC is associated with an increased abundance of*Proteobacteria* and a concomitant underrepresentation of*Firmicutes* and *Lactobacillus* [4]. To determine whether members of genus *Lactobacillus* affect

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Paneth cell formation during NEC onset, Kim et al. treated pregnant females and their pups with selected *Lacticaseibacillus rhamnosus* (Lr) strain in the presence or absence of NEC experimental conditions. They found that Lr transplantation corrected the impaired development of the mesenchymal niche and Paneth cell differentiation and consequently partially rescued the NEC-like phenotypes (Figure 1)[4].

Previous studies in germ-free mice and mice with Toll-like receptor knockout have highlighted the key relationship between the microbiome and NEC development[5]. Probiotic administration has been suggested as a potential strategy to prevent NEC. In general, probiotic bacteria, including *Lactobacillus* species, modulate microbiota composition, intestinal epithelial barrier function, and cytokine secretion. Kim et al. showed that transplantation of Lr restored the amount of *Lactobacilli* resulting in an improvement of NEC-like phenotypes. We have recently shown that administration of*Lactiplantibacillus plantarum* WJL also increased the proliferation of intestinal epithelial stem cells in chronically undernourished juvenile mice, resulting in improved growth of the young. This effect was strictly bacterial strain-dependent, and NOD2 signaling in intestinal epithelial cells was essential for the bacteria-mediated beneficial effect[6]. A growing body of evidence suggests that the strain specificity of probiotic microbes and their efficacy in alleviating specific diseases are crucial aspects that are often overlooked when selecting the best probiotic microbes[7]. Therefore, it would be important to determine whether all probiotic bacterial species or even different Lr strains promote the stem cell niche development by the same mechanism. Further, as it has been shown that NOD2 signaling plays a crucial role in epithelial stem cell proliferation, the role of this receptor in the NEC prevention and development should be probed.

To sum up, the study by Kim et al. provides another important contribution to the understanding of the mechanism of NEC pathogenesis. However, more research is needed to fully understand the role of*Lactobacilli* and other probiotic bacteria in the prevention of NEC and to strengthen their potential as therapeutic agents to combat this serious disease.

KEYWORDS

necrotizing enterocolitis (NEC), *Lacticaseibacillusrhamnosus* , microbiota, intestinal stem cells, Paneth cells

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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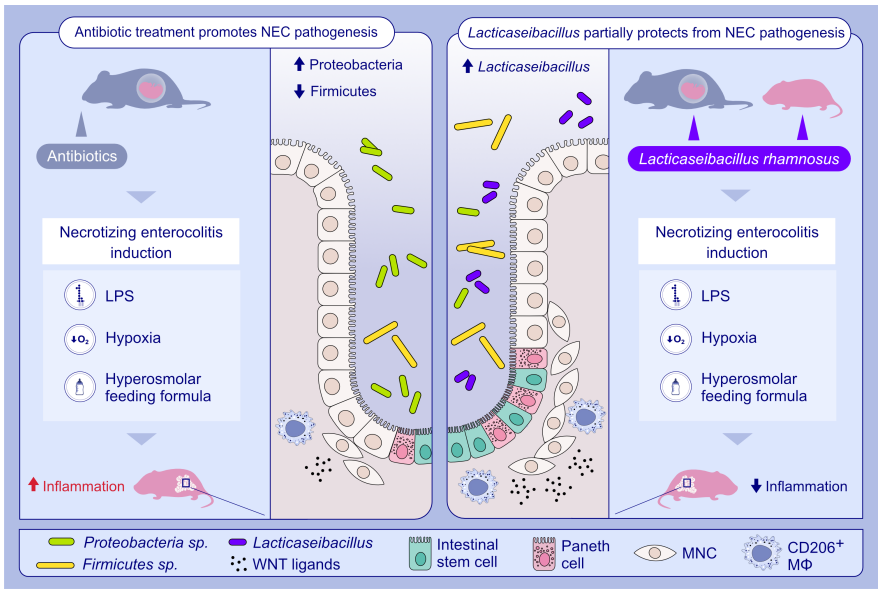
Figure 1 Summarized view of the article by Kim et al. (doi: 10.1016/j.immuni.2022.11.003). Treatment of Lacticaseibacillus rhamnosus (Lr) partially rescues from necrotizing enterocolitis-like phenotypes in a murine model. Lr transplantation corrected the impaired development of the mesenchymal niche and Paneth cell differentiation. As a result of exposure to the gut microbiota in early life, intestinal stem cells differentiate into Paneth cells by regulating CD206+ macrophages associated with epithelial Wnt signaling, which sustains the proliferation of mesenchymal niche cells. NEC, necrotizing enterocolitis; LPS, lipopolysaccharides; MNC, Mesenchymal niche cell; WNT, Wingless-related integration site; MΦ, macrophage; CD, the cluster of differentiation.



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