

Letter to the Editor

One gut microbiota, *Fusobacterium nucleatum* aggravates Neonatal necrotizing enterocolitis by induction of IRF5 expression through lncRNA ENO1-IT1/miR-22-3p axis

Dear Editor,

we have recently read "One gut microbiota, *Fusobacterium nucleatum* aggravates Neonatal necrotizing enterocolitis by induction of IRF5 expression through lncRNA ENO1-IT1/miR-22-3p axis" by Lin et al¹ that was published in the European Review for Medical and Pharmacological Sciences. The topic is quite interesting because of the clinical level implications the results of this study may have regarding new prospects for therapeutic treatment for necrotizing enterocolitis (NEC). Necrotizing enterocolitis (NEC) is a serious inflammatory bowel disease of the newborn that recognizes a multifactorial etiopathogenesis. Prematurity, low birth weight, intestinal hypoxic-ischemic insult, enteral feeding with formulas and intestinal colonization by pathogenic bacteria, represent the main risk factors that predispose the newborn to this pathology^{2,3}. The importance of bacterial colonization in the development of NEC was recognized by Santulli et al⁴ as early as 1975. Though only recently, studies³ regarding the genomic sequencing of the gut microbiota have made it possible to confirm the significant role bacterial colonization plays in the development of this pathology. In fact, some studies^{4,5} have shown the fundamental role of bacteria in its pathogenesis as germ-free mice do not develop NEC. The studies published so far have shown a state of intestinal dysbiosis characterized by a generalized microbial imbalance of the gut microbiota since clear evidence of the involvement of a specific bacterial species are still lacking^{6,7}. A specific pathogenic bacterial species that satisfied Koch's postulate in the development of NEC could not be identified because of the reduced biodiversity and significant individual differences of the gut microbiota during the first years of the child's life. Recently, a meta-analysis by Pammi et al⁸ showed a significant alteration of the biodiversity of the gut microbiota in subjects with NEC that was characterized by a higher relative abundance of Proteobacteria and decreased relative abundance of Firmicutes and Bacteroidetes. Studies⁸⁻¹⁰ have shown that the specific gut microbiota profile depended on the age of the subject at the onset of the disease. Infants who develop NEC early (within 10 days of life) have shown a dominance of the Firmicutes phylum, in particular the Clostridia class. Concurrent with this increase in Firmicutes, a decrease in Gammaproteobacteria was observed in these early onset cases. Late-onset NEC (after 10 days of life) has been associated with an increase in Gammaproteobacteria with an associated decrease in Firmicutes (especially Negativicutes)¹¹. According to the various authors of these studies, the presence of intestinal dysbiosis in patients with NEC seems to be responsible for inducing inflammation of the intestinal mucosa due to an excessive response of Toll like receptors 4 (TLR4) to lipopolysaccharides (LPS) of pathogenic intestinal bacteria. TLR4 is, in fact, up-regulated in the premature gut compared to the gut of the term newborn¹². The intestinal colonization by numerous gram-negative bacteria would be responsible for the excessive activation of TLR4 with consequent inflammatory cascade due to the hyperactivation of

the nuclear factor Kappa- β , which is involved in the transcription of various pro-inflammatory cytokines and chemokines, an increase in apoptosis of enterocytes and impairment of mucosal healing^{13,14}. Recently, Hui et al¹⁵ have demonstrated increased TLR4 expression and increased pro-inflammatory cytokines in resected intestinal samples from 28-29-week-old infants with NEC. Furthermore, bacterial translocation through the intestinal mucosa activates TLR4 on the endothelium of the intestinal vascular system, resulting in reduced blood flow and the development of intestinal ischemia and necrosis¹⁶. The study you published undoubtedly represents a major step forward in the research on this matter as it confirms on one hand, the correlation between intestinal dysbiosis, mucosal inflammation and necrotizing enterocolitis and on the other hand, demonstrates for the first time the existence of a potential specific bacterial fingerprint represented by the increased presence of *Fusobacterium nucleatum* (FN) related to the onset of NEC. Previous work has already shown that FN – an opportunistic anaerobic Gram-negative microorganism that is ubiquitous in the oral cavity and implicated in periodontal disease – can spread to other sites in the body¹⁷. Evidence shows that fusobacteria from the oral cavity can translocate, for example, to the colon by descending through the digestive tract, or by using the hematogenous pathway during frequent transient bacteremia caused by chewing, daily hygiene activities or dental procedures¹⁸. There is also significant evidence¹⁹⁻²² that shows FN can generate a pro-inflammatory environment in the intestine by promoting the proliferation of colon cancer (CRC) cells FN has also been isolated from the amniotic cavity, the placenta and the chorioamniotic membranes of women who give birth prematurely and its presence has been correlated to a high prevalence of intrauterine infection²³⁻²⁶. Recent studies^{27,28} have examined the association between FN and preterm birth, emphasizing the ability of FN to disseminate throughout the body by adhering to, and invading, the endothelium through the link with vascular endothelial cadherin (VE) (CDH5). The pathogen's ability to colonize the placenta can be determined by its ability to adhere to and invade the host's epithelial and endothelial cells via adhesin FadA, a virulence factor, which may be involved in the pathogenesis of intrauterine infection²⁹. Classically, the fetal environment was considered sterile. However, recent studies suggest that colonization of the gastrointestinal tract may have already begun in utero. Therefore, it can be hypothesized that FN could colonize the fetal-placental environment during intrauterine development and be responsible for NEC in preterm infants. Considering the results of your study, in the future it could be useful to conduct research of the oral and gut microbiota of pregnant women for the presence of FN, especially if the women are suffering from periodontal disease. It also seems suitable that future prevention and treatment of NEC could also include the manipulation of the gut microbiota through probiotics, prebiotics and fecal microbiota transplantation in order to correct intestinal dysbiosis, in particular the increased presence of FN.

Conflict of Interest

The Authors declares that he has no conflict of interests.

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