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Intestinal Crypt Apoptosis as an Orchestrator of Necrotizing Enterocolitis: A New Mechanism?

Wei Yu
Children's Mercy Kansas City

Aparna Venkatraman
Children's Mercy Hospital

Venkatesh Sampath
Children's Mercy Hospital

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EDITORIAL

Intestinal Crypt Apoptosis as an Orchestrator of Necrotizing Enterocolitis: A New Mechanism?

Necrotizing enterocolitis (NEC) is a devastating intestinal disease in newborns, particularly premature infants. NEC pathogenesis involves a complex interplay of factors including prematurity, intestinal ischemia, dysbiosis, enteral feeding, and genetic predisposition.[1,2] It is commonly believed that inflammation and intestinal injury characteristic of NEC are triggered by aberrant activation of mucosal Toll-like receptors (TLR), specifically TLR4, which recognize endotoxin in gram-negative pathobionts.[1–3] Intestinal epithelial necrosis and apoptosis are also considered hallmarks of NEC and are among its earliest histologic findings.[3,4] However, both are considered secondary events resulting from TLR activation-mediated inflammation and endoplasmic reticulum stress within the crypt epithelium.[5] The mechanism by which primary crypt apoptosis initiates inflammatory changes within the villous epithelium, with subsequent barrier dysfunction and villous epithelial necrosis, is unknown and is an important question in the NEC field, because it potentially underpins the evolution of injury arising from risk factors, such as hypoxia and ischemia. The most commonly used experimental model of NEC uses formula milk feeding combined with hypoxia and enteral bacterial/endotoxin treatments in neonatal mice. The complexity of this model limits its ability to elucidate the potential mechanistic connections between the induction of crypt epithelial apoptosis and the subsequent villous epithelial necrosis and inflammation in NEC.

In the previous issue of *Cellular and Molecular Gastroenterology and Hepatology*, Subramaniam et al[6] created a unique neonatal mouse model to explore the link between crypt intestinal epithelial cell (IEC) apoptosis and NEC development.[6] A novel triple-transgenic(3xTg) iAP^{cIEC} mouse with epithelial-specific expression of Fasl, a type-II transmembrane protein of tumor necrosis factor family that induces apoptosis on activation, was generated using doxycycline-inducible tetO-rtTA system. Induction of FASL-driven crypt epithelial cell apoptosis triggered NEC-like intestinal injury, including inflammation and widespread villous necrosis. Rip3, a critical regulator of programmed necrosis/necroptosis and a key regulator of the inflammation, and interferon-γ (IFN-γ), were shown to be key mediators of crypt inflammation and intestinal injury in this model. Interestingly, both have been implicated in human NEC.[7,8] In addition to these findings, the authors showed that CD8$^+$ T cell infiltration, and an enrichment of gram-positive bacteria within the intestinal microbiomes contributed to the development of villous necrosis. Importantly, inhibiting any of these processes prevented intestinal injury, emphasizing their vital roles in NEC pathogenesis. Specifically, the authors showed that epithelial deletion of Rip3 or IFN-γ prevented crypt inflammation and villous necrosis. Additionally, they showed that depleting either CD8$^+$ T cells (using anti-CD8$^+$ antibodies), or luminal gram-positive bacteria (via antibiotics) attenuated NEC-like intestinal injury triggered by FASL expression. The involvement of gram-positive bacteria in the pathogenesis of NEC is a novel concept suggested by this study because it argues that TLRs other than TLR4, which sense gram-negative bacteria, can induce NEC by inducing crypt apoptosis.[9,10]

In summary, the findings presented by Subramaniam et al[6] are important because they identify a potential mechanism by which increased apoptosis in crypt IEC sets off a chain pathophysiological processes resulting in NEC. However, because FasL is not commonly expressed in IEC (it is predominantly expressed in immune cells), the transgenic model limits generalizability of results to NEC. Nevertheless, these results lay the foundation for novel research directions aimed at identifying triggers that induce IEC crypt apoptosis and potential therapeutic targets in the intestinal mucosa that could limit progression of crypt apoptosis to inflammation and subsequent necrosis in NEC. Future research centering on factors causing crypt IEC damage can offer deeper insights into the diverse altered pathways involved in NEC development. It can also serve as a foundation for understanding how other factors, such as hypoxia, genetic predisposition, diet, and environmental conditions, can program NEC vulnerability by inducing crypt apoptosis.

WEI YU
APARNA VENKATRAMAN
VENKATESH SAMPATH
Division of Neonatology
Department of Pediatrics
Children's Mercy Kansas City
Kansas City, Missouri, *and*
Neonatal Diseases Research Program
Children's Mercy Research Institute
Children's Mercy Kansas City
Kansas City, Missouri

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Correspondence
Address correspondence to: Venkatesh Sampath, MBBS, MRCPCH, Division of Neonatology, Department of Pediatrics, Children's Mercy Kansas City, 2401 Gillham Road, Kansas City, Missouri 64108. e-mail: vsampath@cmh.edu.

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