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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Another Brick in the Wall: Discovering the Role of Necroptosis in Neonatal Necrotizing Enterocolitis

Neonatal–perinatal medicine and the care of preterm infants is a relatively new field in the world of medicine. Neonates were not generally considered patients until the mid-20th century and the terms *neonatology* and *neonatologist*, as well as the opening of the first neonatal intensive care unit (NICU) in the United States in New Haven, CT, did not occur until 1960.[1] Despite this short timeline, neonatal medicine has made great strides in the past 6 decades in both therapeutic treatments and in pushing the limits of viability lower and lower. One of the hallmarks of premature infants is that almost all of their organ systems are immature, including the intestinal tract. Therefore, it is not surprising that one of the earliest diseases to plague neonatology was necrotizing enterocolitis (NEC).[2] However, despite decades of research, NEC remains one of the leading causes of morbidity and mortality in the NICU.[3] Risk factors associated with development of NEC include prematurity, low birth weight, formula feeding, intestinal ischemia, prolonged antibiotic use, and anemia. However, the exact etiology and pathophysiology of NEC remain unclear. To complicate matters, the NEC phenotype actually may be the result of a final common pathway starting from multiple inciting events that result in an imbalance between mucosal injury and epithelial defense and repair, with activation of an unchecked proinflammatory cascade.[4]

One of the defining characteristics of NEC is the rapid development of inflammation and subsequent death of the bowel. However, a mechanistic understanding of the death of intestinal epithelial cells in NEC is incomplete. Interestingly, cellular death is not a single process and is known to occur through several different mechanisms. The first is an accidental death after a chemical or physical injury to the cell resulting in passive cellular loss known as *necrosis*.The hallmarks of necrosis are cellular swelling followed by cellular rupture. However, not all cellular death is caused by accidental injury. Apoptosis is a second type of cellular death that is a highly regulated process used in normal development and maintenance of homeostasis. This programmed cellular loss is dependent on caspase signaling and leads to nuclear condensation followed by membrane blebbing and cellular loss. Induction of excessive apoptosis has long been thought to play a role in NEC and has been seen both in human[5] and animal studies of NEC.[6,7]

However, a third type of cellular death exists, known as *necroptosis*, which is also a highly regulated programmed death that is caspase-independent and results in a phenotype that more resembles necrotic death.[8] Necroptotic cellular death occurs through activation of receptor-interacting serine/threonine protein kinases. In their article "A novel role for necroptosis in the pathogenesis of necrotizing enterocolitis," Werts et al[9] describe a role for necroptosis in both clinical and experimental NEC. In their article, they describe up-regulation of necroptosis genes in both human NEC surgical specimens and in a well-established rodent model of NEC. The degree of intestinal injury was associated positively with the degree of necroptotic gene up-regulation, and inhibition of necroptosis pathways using genetic or chemical methodology reduced the severity of intestinal injury, suggesting that necroptosis plays a significant role in the intestinal damage that occurs with NEC. Finally, Werts et al[9] provide evidence that the human milk oligosaccharide 2-fucosyl lactose is able to prevent the development of necroptosis gene activation, which may explain in part why infants fed human milk have lower rates of NEC than those fed bovine-based formula, which lacks 2-fucosyl lactose.

Taken together, these data by the Hackam laboratory help to shed some additional mechanistic light on how the intestinal epithelium dies after induction of NEC.[9] An important point to remember about cellular death is that there is overlap in all 3 mechanistic pathways so that any of the 3 pathways can be stimulated by the same originating signal such as tumor necrosis factor.[10] This is important because a single insult can result in cellular death through multiple mechanisms, which can greatly impact the effectiveness of therapeutic targets.

Because neonatologists, pediatric surgeons, neonatal nurses, and all the various providers who care for these tiny fragile patients still struggle with NEC, this is an important work that helps better define the mechanisms of cellular death. Understanding these mechanisms will allow novel approaches of both detection and treatment of a disease that still remains one of the leading causes of death in the NICU.

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Conflicts of interest
The author discloses no conflicts.


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