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Disordered enterocyte signaling and intestinal barrier dysfunction in the pathogenesis of necrotizing enterocolitis

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Necrotizing enterocolitis (NEC) is the leading cause of death from gastrointestinal disease in neonates, and is characterized by the development of diffuse intestinal necrosis in the stressed, pre-term infant. Systemic stress causes a breakdown in the intestinal mucosal barrier, which leads to translocation of bacteria and endotoxin and the initiation of a signaling response within the enterocyte. This review summarizes recent evidence defining a clear role that defective enterocyte signaling plays in the pathogenesis of NEC through the following mechanisms: 1) The localized production of nitric oxide by villus enterocytes results in an increase in enterocyte apoptosis and impaired proliferation; 2) The translocation of endotoxin results in a PI3K-dependent activation of RhoA-GTPase within the enterocyte leading to decreased enterocyte migration and impaired restitution; 3) Dysregulated sodium-proton exchange within the enterocyte by endotoxin renders the enterocyte monolayer more susceptible to damage in the face of the acidic microenvironment characteristic of systemic sepsis; and 4) Endotoxin causes a p38-dependent release of the pro-inflammatory molecule COX-2 by the enterocyte, which potentiates the systemic inflammatory response. An understanding of the mechanisms by which disordered enterocyte signaling contributes to the pathogenesis of barrier failure and NEC—through these and other mechanims—may lead to the identification of novel therapeutic approaches for this devastating disease.

Necrotizing enterocolitis (NEC) is the leading cause of death from gastrointestinal disease in neonates.[1] Complications related to NEC represent the major indications for surgical intervention in neonates, and NEC remains a leading cause of intestinal failure in the pediatric population.[2] The high incience of NEC in premature infants[3] and the lack of effective treatment strategies suggest that novel therapeutic approaches are required to improve the survival of infants afflicted with this disease. Elucidation of the molecular mechanisms contributing to the pathogenesis of NEC is essential to derive new treatment modalities.

Studies from our laboratory and the laboratories of others have indicated a clear role for defective enterocyte signaling in the pathogenesis of NEC. Rather than serving as a mere absorptive surface for nutrients, the enterocytes form a tight epithelial barrier that restricts the passage of microbial pathogens and regulates mucosal antigen sampling. The dynamic interface between the enterocyte monolayer and the intestinal microbial flora has profound implications for the host immune system. The enterocytes are capable of functioning as immune effector cells because they can sense the presence of pathogenic organisms, and when stimulated

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Clinical observation		Biologic relevance
• Premature infant	→	• Susceptible host
• Systemic stress	→	• Gut barrier damage
• Pneumatosis	→	• Bacterial translocation
• Systemic inflammation	→	• Cytokine release

Figure 1 Clinical and biological correlates in the pathogenesis of NEC.

by such microbes, can mount an immune response resulting in the release of pro-inflammatory cytokines and other mediators. This cascade must be tightly regulated, as perturbations in enterocyte signaling can lead to disruption of the epithelial barrier, bacterial translocation and activation of the inflammatory cascade resulting in systemic sepsis and full-blown NEC. An understanding of the mechanisms governing enterocyte signaling in the neonate, and the effects of disordered enterocyte signaling on intestinal function, are critical in the elucidation of the mechanisms of NEC. This review will explore the mechanisms by which disordered enterocyte signaling can lead to the early steps resulting in intestinal inflammation, mucosal necrosis and systemic sepsis—the hallmark of NEC. We will begin by listing a variety of clinical observations that implicate various putative factors in the development of NEC. Subsequently, we will propose a model whereby disordered enterocyte signaling can lead to a breakdown of the mucosal barrier, and suggest possible therapeutic approaches to combat this devastating disease.

From clinical observations to scientific investigation

A variety of clinical features of NEC have shed light on possible mechanisms contributing to this disease. These are listed in Figure 1, and are summarized below. First, NEC, by its very definition, occurs predominantly in premature infants. The premature infant represents a vulnerable host in whom disordered enterocyte signaling can be expected to exert dramatic effects, not observed in older children and adults. Second, NEC is known to develop after a systemic stress, such as systemic hypoxia, which may result from a nuchal cord, or from associated congenital heart disease. Such a hypoxic insult can lead to direct damage to the intestinal mucosa. Third, NEC is characterized by the finding of pneumatosis within the wall of the involved intestine in the vast majority of cases. Pneumatosis results from the release of bacterial gases within the wall of the intestine and illustrates both the importance of bacterial colonization, and the potential consequences of bacterial-enterocyte interactions in the pathogenesis of this disease. Finally, advanced NEC is associated with profound systemic sepsis. The systemic inflammatory response that characterizes NEC reflects the release of pro-inflammatory cytokines and other mediators, and underscores the importance of understanding the signaling cascades, within the enterocyte and within other immune cells, that lead to NEC.

Each of these clinical observations and biological correlates reflects the importance of enterocyte signaling and the development of intestinal barrier failure in the pathogenesis of this disease. We will now describe our general approach to understanding how barrier failure leads to NEC, then explore various signaling cascades that lead to barrier dysfunction in NEC.

Hypothesis: Intestinal barrier failure results in the development of NEC

We and others have proposed the following unifying hypothesis regarding the pathogenesis of NEC (see Figure 2). In the setting of an episode of perinatal stress, such as respiratory distress syndrome or systemic hypoxia, the premature infant suffers a period of intestinal ischemia that

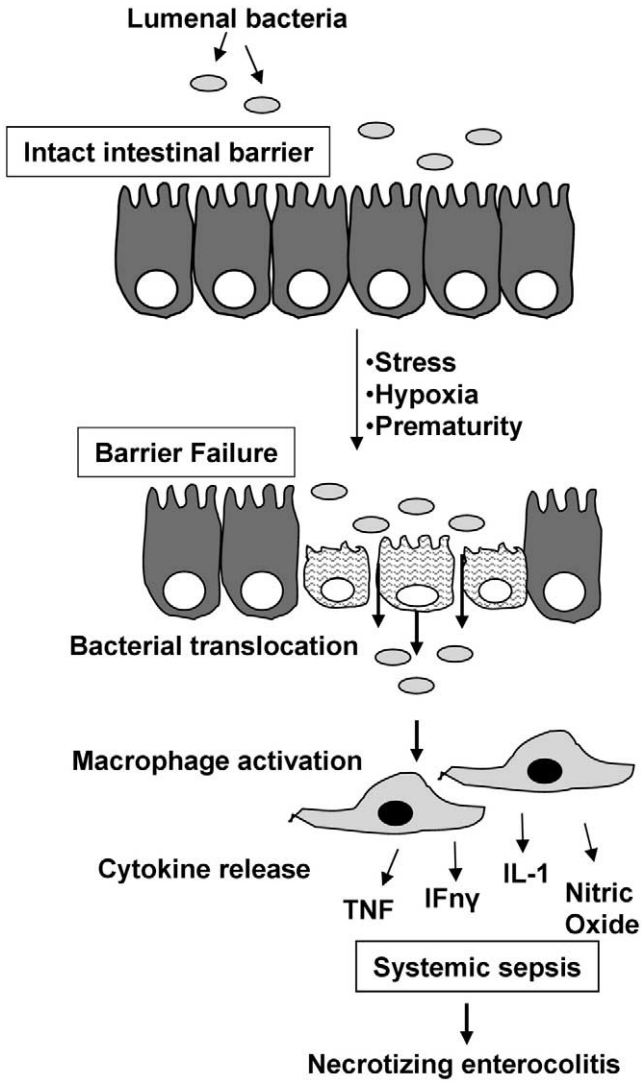

Figure 2 The role of intestinal barrier failure in the pathogenesis of NEC.