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EDITORIAL

# Human Fetal Enterospheres: New Tools for the Study of Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is a serious and often life-threatening disorder that affects the gastrointestinal tract of premature infants. The disease develops in seemingly stable infants, who, after receiving formula feeds, suddenly develop abdominal distention and feeding intolerance, which often progresses to systemic sepsis and death. At laparotomy, which is required in approximately half of all babies with NEC, patchy regions of intestinal necrosis are encountered, necessitating intestinal resection in an attempt to save the infant's life. Specific therapies for NEC are currently lacking, which explains in part why the survival rate in patients with NEC has remained largely unchanged over the past several decades. One of the major reasons for the lack of forward progress in unraveling the biological underpinnings of NEC has been a lack of readily available in vitro experimental model systems, which are required to enable reductionist approaches. Barriers to the development of useful cellular systems for NEC study include the fact that NEC occurs in the intestines of premature infants, making the study of mature intestinal tissue of uncertain relevance, and the requirement for enteric bacteria to model NEC accurately, given the essential role played by Toll-like receptor 4 (TLR4) signaling in the pathogenesis of NEC. Experimental systems that use intestinal cells that are derived from premature human infants, and that also combine bacterial/TLR4 signaling, are likely to be of significant impact in closing this knowledge gap in the field.

The current study by Senger et al[1] provides an important step forward in closing this knowledge gap. Specifically, Senger et al[1] have developed an elegant and simple experimental system that is derived from human fetal enterospheres—clusters of intestinal stem cells that are maintained in tissue culture, and that provide a platform for the evaluation of genetic pathways potentially involved in the pathogenesis of NEC. To do so, Senger et al[1] focused on the responsiveness of fetal enterospheres to lipopolysaccharide and commensal bacteria as compared with adult enterospheres, and assessed genetic pathways that are induced, as well as effects on barrier function and morphology. Strikingly, and in support of work from a variety of laboratories, they determined that the TLR4 receptor was up-regulated in the fetal intestine compared with the mature gut, whereas its negative regulators were down-regulated, consistent with an essential role for exaggerated TLR4 signaling in NEC pathogenesis.

The major strength of their work lies in the establishment of an experimental model for understanding NEC biology using human intestinal cultures, during the window of time in which NEC development occurs using fetal tissue as a rational surrogate for the premature host. These studies also establish a biorepository of banked fetal intestinal tissue, thus offering an off-the-shelf platform for NEC studies, without the need to rely on complex animal studies or the need to obtain resected specimens. That said, the study did have several limitations, including the relatively small sample size, and the fact that studies were performed on tissue that was not derived from patients with NEC. Furthermore, it is possible that the aborted fetuses from which the enterospheres were derived had intrinsic properties unique to their particular disease state that resulted in their early delivery, and that may not be directly relevant to the study of NEC.

Despite these potential pitfalls, the current experimental platform provides a superb opportunity to address important unanswered questions related to the pathogenesis of NEC. Such questions include how does breast milk protect against NEC? What explains the protective role of probiotics against NEC? Can NEC outbreaks be explained at the genetic or cellular level within the premature intestine? Moreover, the addition of stool from patients with NEC to the fetal enterospheres may enhance the translational significance. More excitingly, a feeding formula design could be developed using the enterosphere platform, with an eye to assessing the presence or absence of an inflammatory response in the fetal tissue.

It is through studies such as these from Senger et al,[1] using this exciting novel and elegant platform, that doors to the pathogenesis of NEC will be unlocked, and important advances for this devastating disease eventually will be discovered.

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## Reference

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**Conflicts of interest**
The author discloses no conflicts.

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