Cellular models of fetal intestinal tissue may help combat deadly neonatal disease

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Cellular models of fetal and adult intestinal tissues generated by investigators from the Mucosal Immunology and Biology Research Center (MIBRC) at MassGeneral Hospital for Children (MGHfC) have identified differences in the immune response to natural intestinal bacteria at different developmental ages. The findings, described in a paper published online in *Cellular and Molecular Gastroenterology and Hepatology*, support the use of this model to investigate conditions including necrotizing enterocolitis (NEC), a dangerous gastrointestinal disease affecting premature infants.

NEC can destroy an infant's intestinal wall, leading to perforation, overwhelming infection and possibly death. The condition adversely affects the smallest infants, with a mortality rate of 30 to 50 percent in very low and extremely low birthweight children. Even if a child survives, complications may require surgery to remove damaged bowel sections, which can affect many aspects of a child's development and lead to a compromised quality of life for many children.

Decades of research have not resulted in effective treatment for or prevention of NEC, although feeding premature infants exclusively on breast milk can reduce the risk. Studies in animal models have not completely unlocked the cellular and molecular mechanisms leading to NEC's onset, but research suggests that an abnormal response to gut-colonizing bacteria might play a role in creating conditions for its development.

"The lack of human models has hampered research into NEC," says Alessio Fasano, MD, director of the MGHfC MIBRC, a professor of Pediatrics at Harvard Medical School, and co-senior author of the current report on a promising new model to study intestinal infant development.

Using human intestinal samples, MIBRC scientists have cultivated intestinal "organoids" at varying stages in fetal and adult development. These multicellular clusters, made up of epithelial cells from the small intestine, allow researchers to study the "mini-gut's" response to colonizing bacteria at different periods of development. And timing seems to be crucial in the development of NEC.

"In the most premature infants, we think that the immature intestinal epithelial cells create an exaggerated immune response to commensal gut bacteria, contributing to the pathogenesis of NEC," says Stefania Senger, PhD, first author of the study. She and her colleagues analyzed patterns of gene expression in the fetal and adult intestinal organoids and found that the fetal organoids clustered roughly into two groups according to their developmental age: early (roughly 14 to 15 weeks) and late (roughly 17 to 22.5 weeks). When exposed to gut-colonizing bacteria or their endotoxins, the two groups had different immune reactions based on the developmental age.

"This suggests that only fetal organoids from mature fetuses would be likely to react to bacteria as a premature infant would," says Senger. "So drawing conclusions from analyzing younger fetal tissue might be misleading."

Allan Walker, MD, former MIBRC director and co-senior author of the study, says, "NEC is a disease best dealt with by prevention, as the intestine of the premature infant is not equipped to deal with bacteria outside the mother's womb." A prominent pediatric gastroenterologist

and investigator into the field of NEC research, Walker calls this a "breakthrough moment" into the causes of the devastating disease.

"This work moves us closer to developing a patient-derived, in vitro model. The advantage of this approach is that we can build a repository of tissues from various stages of fetal and infant development. Once you make an observation, you can go to the biorepository and use the organoid tissue to test that observation," says Walker, who is the Taff Professor of Pediatrics at Harvard Medical School.

The novel research model has potential for broader applications. "Not only does this promising new model of human intestinal organoids allow us to study this devastating disease, it also provides new tools to learn about infant gut development," says Senger, who is a geneticist with a background in stem cell and mucosal biology and an instructor in Pediatrics at Harvard Medical School. The team now plans to culture intestinal organoids from infant tissue damaged by NEC to determine the mechanisms of inflammation that lead to the disease.

"This important work was only possible thanks to the highly collaborative environment at MIBRC," Senger adds. "Dr. Walker's group provided us with guidance and expertise in fetal intestinal development and NEC pathogenesis. The work to stop this disease is so important. Our hope is to develop strategies to prevent the expression of NEC before it can gain a foothold in any infant's intestine."

More information: S. Senger et al, Human fetal-derived enterospheres provide insights on intestinal development and a novel model to study Necrotizing Enterocolitis (NEC), *Cellular and Molecular Gastroenterology and Hepatology* (2018). DOI: 10.1016/j.jcmgh.2018.01.014

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