

Breast milk may be protective against devastating intestinal disorder

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Dr. Mark Frey. Credit: Saban Research Institute

Premature infants are at increased risk for a potentially lethal gastrointestinal disease called necrotizing enterocolitis, or NEC. Studies conducted by researchers at Children's Hospital Los Angeles demonstrate that a protein called neuregulin-4 (NRG4)—present in breast milk, but absent from formula—may be protective against the



intestinal destruction caused in NEC. Their results will be published online on September 9 in advance of the print edition of the *American Journal of Pathology*.

Thirty percent of babies with NEC die from their disease, and even survivors can face lifelong consequences that may include removal of part of their intestine and dependence upon intravenous nutrition. Formula feeding is a known risk factor for the disease.

"Our research suggests that without the NRG4 protein found in breast milk, a normal protection mechanism for the immature gut may be missing," said Mark R. Frey, PhD, the study's principal investigator at The Saban Research Institute of Children's Hospital Los Angeles. "If a baby on formula encounters an NEC trigger such as <u>intestinal infection</u> or injury, he or she may be at increased risk for a life-threatening condition."

The investigators conducted a series of studies using rodent models, as well as in vitro analysis and examination of <u>human breast milk</u> and infant intestinal tissue. Formula-fed rats developed a condition similar to NEC, but those receiving formula plus the NRG4 were protected against intestinal damage, as were cultured intestinal <u>cells</u> challenged with bacteria related to strains that may induce NEC in humans. These experiments suggest that NRG4 binds specifically with a receptor found in the intestine, ErbB4, to block inflammatory intestinal damage. In addition, NRG4 was present in human breast milk samples but not formula.

Human NEC is characterized by a loss of specialized intestinal cells, called Paneth cells. Located throughout the small intestine, these cells protect the organ from microbial damage. The Paneth cells also sustain <u>intestinal stem cells</u> that are required for ongoing renewal of the intestinal lining. In a mouse model of NEC, the investigators



demonstrated that NRG4 prevented loss of Paneth cells.

"We're finding a protective protein in <u>breast milk</u>, with its receptor in the intestine," says Frey, who is also an assistant professor of Pediatrics and Biochemistry & Molecular Biology at the Keck School of Medicine of the University of Southern California. "Given that NEC is a significant clinical problem without an effective treatment, we plan to evaluate NRG4 for its therapeutic potential in this disease."

More information: "The ErbB4 Ligand Neuregulin-4 Protects against Experimental Necrotizing Enterocolitis," by Steven J. McElroy, Shannon L. Castle, Jessica K. Bernard, Dana Almohazey, Catherine J. Hunter, Brandon A. Bell, Denise Al Alam, Larry Wang, Henri R. Ford, and Mark R. Frey. (dx.doi.org/10.1016/j.ajpath.2014.06.015). The article appears online ahead of The *American Journal of Pathology*, Volume 185/Issue 4 (October 2014)

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