

EDITORIAL

A Promising Genetic Target for a Deadly Disease: Single Immunoglobulin Interleukin 1 (SIGIRR) Mutations in Necrotizing Enterocolitis



Necrotizing enterocolitis (NEC) is a deadly disease that primarily affects premature infants, but the precise etiology is not well understood. Premature infants are predisposed to NEC because of their immature intestinal epithelium and host defenses, as well as bacterial dysbiosis that precedes disease onset. Data from mouse models suggest that NEC arises from activation of the innate immune receptor, Toll-like receptor 4 (TLR4), by its ligand lipopolysaccharide derived from gram-negative bacteria in abundance after dysbiosis occurs. Several recent lines of investigation into the underlying causes of NEC have focused on identifying genetic predispositions to the disease. A promising genetic target includes a negative regulator of TLR4 signaling, called single immunoglobulin interleukin 1 (SIGIRR), mutations of which have been identified previously in infants with NEC.¹ How mutations in SIGIRR affect the development of NEC has remained undefined.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Yu et al² explore how SIGIRR mutations contribute to NEC pathogenesis and induce TLR hyper-responsiveness in the postnatal intestine. Toward this end, Yu et al² generated a transgenic mouse line with clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) encoding a novel SIGIRR mutation (p. Y168X) that was discovered in an infant who died from a severe form of NEC.¹ Interestingly, the *SIGIRR*^{Tg} mice showed exaggerated inflammation within the intestine along with nuclear factor- κ B activation, a hallmark of TLR4 signaling. In further mechanistic studies, using RNA interference, *SIGIRR* was knocked down in human intestinal epithelial cells, which led to the decreased expression of small noncoding RNAs called microRNAs, specifically, microRNA146a and microRNA155, which have been shown previously to be anti-inflammatory. In seeking to determine the signaling pathways mediating this effect, Yu et al² further showed that the phosphorylation of signal transducer and activator of transcription 3 (STAT3) was reduced in the SIGIRR-knockdown human intestinal epithelial cells. Yu et al² also showed that STAT3 could bind directly to the promoters of the microRNAs and activate expression in a manner dependent on SIGIRR. These results suggest that SIGIRR can regulate the expression of microRNAs in intestinal epithelial cells in association with the phosphorylation of STAT3, uncovering a novel signaling pathway involved in the neonatal intestine. Through immunoprecipitation, SIGIRR overexpression, and the use of an interleukin Receptor Associated Kinase (IRAK) inhibitor, they were able to

conclude that regulation of STAT3 phosphorylation is mediated through its interaction with IRAK1. Furthermore, expression levels of microRNAs decreased with IRAK1 inhibition in a dose-dependent manner. Yu et al² showed in human intestinal epithelial cells that SIGIRR inhibition of the proinflammatory response induced by the TLR5 ligand flagellin is dependent on STAT3-microRNA activation. They also showed that, in vivo, *SIGIRR*^{Tg} mice showed a spontaneous level of intestinal inflammation together with decreased intestinal microRNA expression, decreased STAT3 phosphorylation, and increased IRAK1 compared with wild-type littermates. Taken together, these data suggest that in the neonatal intestine the SIGIRR-IRAK1-STAT3 pathway can regulate microRNA expression, impacting intestinal inflammation.

The findings presented by Yu et al² detail the mechanistic pathway of SIGIRR, an important negative regulator of TLR4, and how mutations can lead to exaggerated intestinal inflammation. Interestingly, this research team and others, also showed other contributing factors that impact the expression levels of SIGIRR in the preterm infant including the microbiome.^{3,4} Collectively, not only have these data shed light on the potential for genetic predisposition to NEC in the premature infant population, but also how multiple factors independently may disrupt the same regulatory pathways that lead to disease. The latter emphasizing the need for multiple concurrent therapeutic strategies to mitigate the development of this complex multifactorial disease. Studies focusing on identifying additional mutations can further delineate the various altered pathways in NEC pathogenesis and serve as a basis to determine how other modifiable factors, such as nutrition and the environment, can impact these pathways. Successful determination of modifiable factors will lead to practice change at the bedside and identification of therapeutic targets for future clinical trials to ultimately curtail this devastating disease.

MISTY GOOD, MD, MS

Division of Newborn Medicine, Department of Pediatrics
Washington University School of Medicine
St. Louis, Missouri

CAMILIA R. MARTIN, MD, MS

Department of Neonatology
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, Massachusetts

References

1. Sampath V, Menden H, Helbling D, Li K, Gastonguay A, Ramchandran R, Dimmock DP. SIGIRR genetic variants in premature infants with necrotizing enterocolitis. *Pediatrics* 2015;135:e1530–e1534.
2. Yu W, Haque I, Venkatraman A, et al. SIGIRR mutation identified in human necrotizing enterocolitis (NEC) disrupts STAT3-dependent microRNA expression in neonatal gut. *Cell Mol Gastroenterol Hepatol* 2022;13:425–440.
3. Cuna A, Yu W, Menden HL, Feng L, Srinivasan P, Chavez-Bueno S, Ahmed I, Umar S, Sampath V. NEC-like intestinal injury is ameliorated by *Lactobacillus rhamnosus* GG in parallel with SIGIRR and A20 induction in neonatal mice. *Pediatr Res* 2020;88:546–555.
4. Wu W, Wang Y, Zou J, Long F, Yan H, Zeng L, Chen Y. *Bifidobacterium adolescentis* protects against necrotizing enterocolitis and upregulates TOLLIP and SIGIRR in premature neonatal rats. *BMC Pediatr* 2017; 17:1.

Correspondence

Address correspondence to: Camilia R. Martin, MD, MS, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Brookline, Massachusetts 02215. e-mail: cmartin1@bidmc.harvard.edu.

Conflicts of interest

The authors disclose the following: Misty Good receives research support from Takeda Pharmaceuticals and Evive Biotech. Camilia R. Martin is on the scientific advisory boards of Plakous Therapeutics and Lactalogics, Inc. Dr. Martin receives research support from Feihe International, Inc., Shire, and Mead Johnson Foundation.

Funding

Misty Good is supported by the National Institutes of Health grants R01DK118568, R01DK124614, and R01HD105301, the St. Louis Children's Hospital Foundation, the Children's Discovery Institute of Washington University and St. Louis Children's Hospital, and the Department of Pediatrics at Washington University School of Medicine, St. Louis. Camilia Martin is supported by the National Institutes of Health grant R01HD106359,



Most current article

© 2022 The Authors. Published by Elsevier Inc. on behalf of the AGA Institute. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

2352-345X

<https://doi.org/10.1016/j.jcmgh.2021.10.011>