cmgh
CELLULAR AND MOLECULAR
GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Formation of Giant Lysosome in Neonatal Ileal Enterocytes Requires Endotubin

Enterocyte maturation involves the development of a highly sophisticated brush border, tight junctions, and an intracellular membrane network pivotal for the intestinal barrier and absorptive functions. Genetic or environmental factors that disrupt the enterocyte's proper development can severely impact growth and survival. Interestingly, the developing enterocytes in the ileum of neonates have a transient but distinct morphologic feature: the presence of giant lysosomes in the subapical cytoplasmic region.[1] These enlarged endocytic compartments emerge at late gestation and persist through the suckling period, with a proposed function for degrading endocytosed milk products during the neonatal stage. It was postulated that the formation of these giant lysosomes might result from fusion of multiple apical lysosomes, however, the molecular mechanism contributing to the development of these highly specialized endocytic membrane structures has been unclear.

In this issue, Cox et al[2] investigated the in vivo contribution of a scaffold protein, endotubin (EDTB), to the enterocyte development in neonatal mouse ileum. By using both a conditional gene ablation model in mice and a CRISPR-Cas9–edited EDTB-deficient Caco2 cell line, the Cox et al provided convincing evidence to support the conclusion that EDTB, as a component found in the apical endocytic complex (AEC), plays a critical role in the proper morphogenesis of neonatal enterocytes. Inducible removal of EDTB at late gestation in mouse intestinal epithelia resulted in a disrupted formation of the characteristic giant lysosomes as well as the AEC. The EDTB-deficient epithelia also showed a reduction of tight junction proteins, a previously described phenotype by the same group,[3] that was consistent with disrupted membrane trafficking. In addition, loss of EDTB occasionally caused microvillus defects that resembled some features of the microvillus inclusion diseases. These abnormalities appeared to be accompanied by disorganization of apical membrane proteins, an observation that bears similarities to the cellular defects reported for enterocytes lacking *Myo5b*,[4] *Syntaxin 3*,[5] *Rab8a*,[6] *Rab11a*,[7] or *Cdc42*.[8,9] The study collectively suggested that EDTB contributes to the development of multiple aspects of ileal enterocytes, potentially through coordinating several endocytic processes (eg, endosomal maturation, targeting, and fusion).

However, at the molecular level it remains unclear how EDTB engages in the diverse array of endocytic events related to apical and basolateral protein sorting, lysosome formation from AEC, and its maintenance. Future elucidation of the EDTB-associated protein partners in the giant lysosomes or in AECs may shed lights on its functional contribution toward the evolution of these compartments. In addition to endocytic trafficking, whether EDTB also directly controls the delivery of apical membrane to brush border in developing enterocytes also may be interesting for further investigation. EDTB is highly expressed in ileal enterocytes at late embryonic and neonatal stages. Its level decreases by half in postweaning mice. How the level of EDTB is up-regulated and down-regulated at transcriptional or post-translational levels in the developing ileum is important to follow up. Such information may be useful for understanding the developmental signals that control the spatial and temporal induction of distinct endocytic structures in the gastrointestinal tract during a specific developmental window. Knowledge gained about the molecular evolution and adaptation of endocytic compartments may be harnessed to modulate the endocytic states of enterocytes or in other cell types. The study by Cox et al on EDTB opens a door to beginning to understand the intracellular network that controls the dynamic organization of endocytic membrane compartments in development and disease.

XIAO ZHANG
NAN GAO, PhD
Department of Biological Sciences
Rutgers University
Newark, New Jersey

References

1. Wilson JM, Whitney JA, Neutra MR. Biogenesis of the apical endosome-lysosome complex during differentiation of absorptive epithelial cells in rat ileum. J Cell Sci 1991;100:133–143.
2. Cox CM, Lu R, Salcin K, Wilson JM. The endosomal protein endotubin is required for enterocyte differentiation. Cell Mol Gastroenterol Hepatol 2018;5:145–156.
3. McCarter SD, Johnson DL, Kitt KN, Donohue C, Adams A, Wilson JM. Regulation of tight junction assembly and epithelial polarity by a resident protein of apical endosomes. Traffic 2010;11:856–866.
4. Weis VG, Knowles BC, Choi E, Goldstein AE, Williams JA, Manning EH, Rolant JT, Lapierre LA, Goldenring JR. Loss of MYO5B in mice recapitulates microvillus inclusion disease and reveals an apical trafficking pathway distinct to neonatal duodenum. Cell Mol Gastroenterol Hepatol 2016;2:131–157.
5. Wiegerinck CL, Janecke AR, Schneeberger K, Vogel GF, van Haaften-Visser DY, Escher JC, Adam R, Ce Thoni, Pfaller K, Jordan AJ, Weis CA, Nijman IJ, Monroe GR, van Hasselt PM, Cutz E, Klumperman J, Clevers H, Nieuwenhuis EE, Houwen RH, van

Haaften G, Hess MW, Huber LA, Stapelbroek JM, Muller T, Middendorp S. Loss of syntaxin 3 causes variant microvillus inclusion disease. Gastroenterology 2014;147:65–68 e10.

6. Sato T, Mushiake S, Kato Y, Sato K, Sato M, Takeda N, Ozono K, Miki K, Kubo Y, Tsuji A, Harada R, Harada A. The Rab8 GTPase regulates apical protein localization in intestinal cells. Nature 2007; 448:366–369.
7. Knowles BC, Weis VG, Yu S, Roland JT, Williams JA, Alvarado GS, Lapierre LA, Shub MD, Gao N, Goldenring JR. Rab11a regulates syntaxin 3 localization and microvillus assembly in enterocytes. J Cell Sci 2015; 128:1617–1626.
8. Sakamori R, Das S, Yu S, Feng S, Stypulkowski E, Guan Y, Douard V, Tang W, Ferraris RP, Harada A, Brakebusch C, Guo W, Gao N. Cdc42 and Rab8a are critical for intestinal stem cell division, survival, and differentiation in mice. J Clin Invest 2012; 122:1052–1065.
9. Zhang X, Gao N. RAB and RHO GTPases regulate intestinal crypt cell homeostasis and enterocyte function. Small GTPases 2016;7:59–64.

Correspondence
Address correspondence to: Nan Gao, PhD, Department of Biological Sciences, Rutgers University, 195 University Avenue, Boyden Hall, Suite 206, Newark, New Jersey 07102. e-mail: ngao@rutgers.edu.

Conflicts of interest
The authors disclose no conflicts.

Funding
This work was supported by National Institutes of Health grant DK102934, Research Scholar grant (RSG-15-060-01-TBE) from the American Cancer Society, and an Initiative for Multidisciplinary Research Teams award from Rutgers University.

Most current article

2352-345X
https://doi.org/10.1016/j.jcmgh.2017.11.002