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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Insights From the Crypt: Regionalization, Adaptation, and Renewal of the Intestinal Epithelium

The current issue of *Cellular and Molecular Gastroenterology and Hepatology* presents 3 important studies that further our understanding of intestinal epithelial regionalization, adaptation, and maintenance by using both rare human pediatric ileal samples and advanced mouse genetic models.

Regionalization of the gastrointestinal tract is essential to its function and to organismal survival. Dozens of studies in genetically tractable models have delineated many of the key transcriptional regulators and control networks that ensure that an initially undifferentiated epithelial tube derived from embryonic endoderm can take on the diverse functions of esophagus, stomach, and small and large bowel. Among the key DNA-binding transcription factors that impact patterning of the gut tube is GATA4. It was noted years ago that this zinc-finger transcription factor was expressed in enterocytes of the duodenum and jejunum but absent from ileum and colon.[1,2] Strikingly, removal of GATA4 from the mature intestine by using mouse genetic models caused a shift in jejunal identity toward an ileal phenotype, which was reflected in a dramatically altered gene expression pattern and resulted in severe defects in lipid absorption.[1,2] In the current work by Thompson et al,[3] the opposite hypothesis was tested: Is misexpression of GATA4 in the ileum enough to shift its identity and gene expression pattern toward the anterior fates of duodenum and jejunum? By using an elegant new genetic mouse model, they found exactly that: Using comprehensive expression profiling, they discovered that many genes typically expressed preferentially in the proximal small intestine were induced in the GATA4-expression ileum, whereas conversely, multiple ileal-enriched transcripts were reduced in abundance. Among the GATA4-regulated genes were several known to function in ileal absorption of bile acid, suggesting that GATA4 helps to regionalize the activity of this important pathway. By repressing bile acid absorption in the duodenum and jejunum, GATA4 helps to ensure that levels of bile acid stay sufficiently high to enable lipid emulsification and uptake before they enter the enterohepatic recirculation in the ileum.

The intestine not only effectively subdivides its functions but also adapts to changing nutritional and metabolic states. Thus, it had been established in rodent models more than 40 years ago that nutrient availability affects proliferation rates in intestinal crypts and villus length.[4,5] However, simple fasting-refeeding studies are confounded by massive changes in hormonal and metabolic status. In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Wieck et al[6] address this question systematically in a rare set of human pediatric samples. They collected pediatric ileal tissue samples from both proximal and distal margins at the time of intestinal anastomosis after at least 7 weeks of ileostomy. Thus, the proximal sample, considered "fed," had been continuously exposed to luminal contents and mechanical stress, whereas the distal sample, considered "unfed," had experienced mechanoluminal deprivation but not systemic nutrient deprivation as in standard fasting models. Thus by using paired samples for the expression profiling, the authors could dramatically limit confounding factors, in particular the nutritional, developmental, and hormonal status of the individual. The unfed ileum was characterized by shortened villi with fewer replicating crypt cells but no shift in distribution among absorptive and secretory cell types. Correspondingly, the number of LGR5 and OLFM4 positive stem cells was reduced in the ileum that had not been under mechanoluminal stimulation. Conversely, multiple brush border enzymes and transporters were upregulated in the unfed part of the ileum. Thus, even though the children studied received adequate calories and nutrients and exhibited normal weight gain, the distal fragment of the ileum exhibited many features seen in animal models of caloric restriction, suggesting that the ileum responds locally to luminal contents.

Maintenance of the intestinal crypt is critical to intestinal homeostasis and organismal survival. Smith et al[7] investigated the contribution of the cell adhesion model CD166, also known as activated leukocyte cell adhesion molecule, in this process by using a mouse loss-of-function model. They report that CD166 is produced at high levels in Paneth cells and rapidly cycling LGR5-positive stem cells but not in slow-cycling BMI1-positive stem cells. Strikingly, the distribution of replicating cells in small intestinal crypts was perturbed in the absence of CD166, with more proliferating cells residing in the middle and fewer in the base of the crypt. Concomitantly, there was a change in cell lineage allocation among the differentiated progeny of intestinal stem cells, with more goblet cells overall and a redistribution of these cells into the crypt and a dramatic increase in Paneth/goblet cell "hybrid" cells. The authors argue that the differences in the location of proliferating cells can be attributed to altered Paneth cell signaling to the neighboring Lgr5 stem cell. However, because a cell adhesion molecule was ablated, it is difficult, strictly speaking, to prove whether direct signaling activity is perturbed, or whether defective cell retention in and/or migration from the crypt is the primary defect in this model. This is especially relevant because of multiple recent reports that crypt health can be maintained in the absence of Paneth cells,[8,9] their main Wnt product, Wnt3,[10] and that subepithelial cells are absolutely required for crypt survival.[11]

Together, these 3 articles provide new insight into the factors that regulate intestinal epithelial differentiation and function to promote overall health. They also use state-of-the-art approaches to further our understanding of intestinal development, function, and health, as has become typical of the fascinating articles published in *Cellular and Molecular Gastroenterology and Hepatology*.

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References

1. Battle MA, Bondow BJ, Iverson MA, et al. GATA4 is essential for jejunal function in mice. Gastroenterology 2008;135:1676–1686.e1671.
2. Bosse T, Piaseckyj CM, Burghard E, et al. Gata4 is essential for the maintenance of jejunal-ileal identities in the adult mouse small intestine. Mol Cell Biol 2006; 26:9060–9070.
3. Thompson CA, Wojta K, Pulakanti K, et al. GATA4 is sufficient to establish jejunal versus ileal identity in the small intestine. Cell Mol Gastroenterol Hepatol 2017; 3:422–446.
4. Aldewachi HS, Wright NA, Appleton DR, et al. The effect of starvation and refeeding on cell population kinetics in the rat small bowel mucosa. J Anat 1975;119:105–121.
5. Altmann GG. Influence of starvation and refeeding on mucosal size and epithelial renewal in the rat small intestine. Am J Anat 1972;133:391–400.
6. Wieck MM, Schlieve CR, Thornton ME, et al. Prolonged absence of mechanoluminal stimulation in human intestine alters the transcriptome and intestinal stem cell niche. Cell Mol Gastroenterol Hepatol 2017; 3:367–388.
7. Smith NR, Davies PS, Levin TG, et al. Cell adhesion molecule CD166/ALCAM functions within the crypt to orchestrate murine intestinal stem cell homeostasis. Cell Mol Gastroenterol Hepatol 2017;3:389–409.
8. Durand A, Donahue B, Peignon G, et al. Functional intestinal stem cells after Paneth cell ablation induced by the loss of transcription factor Math1 (Atoh1). Proc Natl Acad Sci U S A 2012;109:8965–8970.
9. Kim TH, Escudero S, Shivdasani RA. Intact function of Lgr5 receptor-expressing intestinal stem cells in the absence of Paneth cells. Proc Natl Acad Sci U S A 2012; 109:3932–3937.
10. Farin HF, Van Es JH, Clevers H. Redundant sources of Wnt regulate intestinal stem cells and promote formation of Paneth cells. Gastroenterology 2012;143:1518–1529. e1517.
11. Aoki R, Shoshkes-Carmel M, Gao N, et al. Foxl1-expressing mesenchymal cells constitute the intestinal stem cell niche. Cell Mol Gastroenterol Hepatol 2016;2:175–188.

Conflicts of interest
The author discloses no conflicts.

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2352-345X
http://dx.doi.org/10.1016/j.jcmgh.2017.03.001