Published in final edited form as:

Gastroenterology. 2017 December ; 153(6): 1473–1475. doi:10.1053/j.gastro.2017.10.029.

Enteric Glia: The Origin of Duodenal Gastrinomas?

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Multiple endocrine neoplasia 1 (MEN1) is a rare autosomal-dominant disorder characterized by the development of tumors in endocrine glands and the duodenum. Duodenal gastrinomas (gastrin-secreting neuroendocrine tumors) are frequently associated with *MEN1* mutations, but their natural history is poorly understood. This limits the development of new therapies for serious complications such as ulcers and severe diarrhea caused by hypergastrinemia in these individuals. New findings in this issue of *Gastroenterology* by Sundaresan et al¹ have the potential to overcome this roadblock by providing important new insight into the mechanisms that produce *MEN1*-associated duodenal gastrinomas. Surprisingly, these findings suggest that *MEN1*-associated duodenal gastrinomas arise from an unexpected source, enteric glia.

Gastrinomas were originally described as pancreatic neuroendocrine tumors by Zollinger and Ellison,² but since then it has become clear that most gastrinomas are located in the duodenum.³ Duodenal and pancreatic gastrinomas are now recognized as being developmentally and functionally distinct and perhaps share nothing more in common than their ability to produce gastrin.⁴ Likewise, subtypes of duodenal gastrinomas, themselves, are distinct in their development and biological functions. For example, sporadic gastrinomas are typically solitary tumors whereas *MEN1* gastrinomas are usually multicentric,⁵ and *MEN1*-associated, but not sporadic, duodenal gastrinomas are associated with proliferative gastrin cell changes that precede tumor development.⁶

In the setting of MEN1, mutations in the *MEN1* gene contribute to tumor development by decreasing the production of a protein called menin. Menin normally acts to suppress tumor development by directly interacting with JunD and inhibiting its transcriptional activity.⁷ However, other unknown mechanisms contribute to the loss of menin protein beyond genomic changes because less than one-half of *MEN1* gastrinomas exhibit loss of heterozygosity.^{8,9}

In this issue of *Gastroenterology*, Sundaresan et al¹ use a mouse model of gut endocrine tumors to study the cellular origin of *MEN1*-associated duodenal gastrinomas and the mechanisms responsible for the loss of menin protein. This model relies on the conditional deletion of *Men1* in epithelial cells in mice with a somatostatin null background concomitant

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Conflicts of interest

The author discloses no conflicts.

with the suppression of gastric acid secretion (omeprazole) to produce features of the early stages of MEN1 gastrinomas such as hypergastrinaemia.¹⁰ Interestingly, the authors found that omeprazole treatment in this model reversibly induced gastrin expression by a subset of cells within the duodenal lamina propria that co-express markers of enteric glial cells, but lack expression of markers for epithelial cells, neurons, endothelial cells, and myofibroblasts. Human MEN1 gastrinomas also express the same panel of glial markers, suggesting that they also arise from neural crest cells. The appearance of gastrin-expressing glia seems to primarily reflect a change in glial phenotype rather than proliferation or influx because no change in glial number was observed in vivo and the phenotype could be reproduced in vitro by treating glial cultures with gastrin. Thus, the gastrin-expressing glial phenotype is paradoxically driven by gastrin in a feed-forward signaling loop that results in the loss of glial menin protein and the de-repression of gastrin messenger RNA. The authors go on to show that the mechanisms responsible for the gastrin-driven loss of glial menin protein involve the activation of cholecystokinin B receptors that signal through protein kinase A-dependent intracellular pathways to induce the export of menin from the nucleus to the cytoplasm where it is subsequently degraded by the proteasome (Figure 1).

These are exciting observations that suggest novel roles for enteric glia in both health and disease. Enteric glia are a class of peripheral glia that reside within the intestine and display functional specializations that reflect their unique microenvironments. Subpopulations of myenteric and sub-mucosal glia in the colon and ileum have reciprocal interactions with enteric neurons that contribute to the coordination of motility and secretomotor reflexes,^{11–13} whereas glia at the level of the mucosa influence the development and maturation of epithelial cells.^{14–17} Very little is known about glia in the duodenum, but findings in this study suggest they may play important roles in normal hormonal signaling and tumorigenesis. Mucosal glia are likely the main population that contributes to *MEN1*-associated gastrinomas, because these cells express cholecystokinin B receptors and menin in wild-type animals. Mucosal glia in the duodenum, therefore, seem primed to detect gastrin, but the functional significance of this observation is unclear. The ability of glia to synthesize and release gastrin certainly suggests that they could contribute to hormonal signaling in the duodenum under certain circumstances. Hypergastrinemia seems to drive tumor development in MEN1 by hijacking these pathways, but this hypothesis only explains *MEN1*-associated gastrinomas. Hypergastrinemia alone does not seem to be sufficient to induce tumorigenesis from enteric glia, because it is also present in sporadic forms of duodenal gastrinomas and pancreatic gastrinomas where tumors arise from other sources. The cellular origin of these other types of gastrinomas is not clear, but some evidence points towards a neural, or additional neural crest, contribution because 80% to 100% of duodenal neuroendocrine tumors stain positive for neuron-specific enolase.³ Additional work with advanced methods such as mosaic analysis with double markers would be very beneficial to more thoroughly understand the cellular origin of these tumors.

Could glia be responsible for tumorigenesis in other regions of the intestine, such as the colon? Very little is known regarding the roles of enteric glia in diseases such as colon cancer, but the likelihood of a glial contribution, if not a central role, is very high. Considering that glia are the main source of tumors in the brain, it is easy to speculate that enteric glia display similar potentials in the gut. Understanding these, and other, roles of

enteric glia will be an exciting avenue for future research and has great potential to identify new therapeutic targets to benefit debilitating human diseases such as illustrated here for MEN1 gastrinomas.

Acknowledgments

Funding

Dr Gulbransen's research is supported by grants from the Crohn's and Colitis Foundation (CCF Senior Research Award to BDG), the National Institutes of Health (NIDDK RO1DK103723 to BDG), and the Department of Defense (CDMRP W81XWH1610631 to BDG).

References

Author names in bold designate shared co-first authorship.

1. Sundaresan S, Meininger CA, Kang AJ, et al. Gastrin induces nuclear export and proteasome degradation of menin in enteric glial cells. *Gastroenterology*. 2017; 153:1555–1567. [PubMed: 28859856]
2. Robert M, Zollinger EHE. Primary peptic ulcerations of the jejunum associated with islet cell tumors of the pancreas. *Ann Surg*. 1955; 142:709. [PubMed: 13259432]
3. Hoffmann KM, Furukawa M, Jensen RT. Duodenal neuroendocrine tumors: Classification, functional syndromes, diagnosis and medical treatment. *Best Pract Res Clin Gastroenterol*. 2005; 19:675–697. [PubMed: 16253893]
4. Fendrich V, Ramerth R, Waldmann J, et al. Sonic hedgehog and pancreatic-duodenal homeobox 1 expression distinguish between duodenal and pancreatic gastrinomas. *Endocr Relat Cancer*. 2009; 16:613–622. [PubMed: 19240184]
5. Pipeleers-Marichal M, Somers G, Willems G, et al. Gastrinomas in the duodenum of patients with multiple endocrine neoplasia type 1 and the Zollinger-Ellison syndrome. *N Engl J Med*. 1990; 322:723–727. [PubMed: 1968616]
6. Anlauf M, Perren A, Meyer CL, et al. Precursor lesions in patients with multiple endocrine neoplasia type 1-associated duodenal gastrinomas. *Gastroenterology*. 2005; 128:1187–1198. [PubMed: 15887103]
7. Agarwal SK, Kester MB, Debelenko LV, et al. Germline mutations of the MEN1 gene in familial multiple endocrine neoplasia type 1 and related states. *Hum Mol Genet*. 1997; 6:1169–1175. [PubMed: 9215689]
8. Anlauf M, Perren A, Henopp T, et al. Allelic deletion of the MEN1 gene in duodenal gastrin and somatostatin cell neoplasms and their precursor lesions. *Gut*. 2007; 56:637–644. [PubMed: 17135306]
9. Debelenko LV, Zhuang Z, Emmert-Buck MR, et al. Allelic deletions on chromosome 11q13 in multiple endocrine neoplasia type 1-associated and sporadic gastrinomas and pancreatic endocrine tumors. *Cancer Res*. 1997; 57:2238–2243. [PubMed: 9187127]
10. Sundaresan S, Kang AJ, Hayes MM, et al. Deletion of Men1 and somatostatin induces hypergastrinemia and gastric carcinoids. *Gut*. 2017; 66:1012–1021. [PubMed: 26860771]
11. McClain JL, Fried DE, Gulbransen BD. Agonist-evoked Ca(2+) signaling in enteric glia drives neural programs that regulate intestinal motility in mice. *Cell Mol Gastroenterol Hepatol*. 2015; 1:631–645. [PubMed: 26693173]
12. McClain JL, Grubišić V, Fried D, et al. Ca²⁺ responses in enteric glia are mediated by connexin-43 hemichannels and modulate colonic transit in mice. *Gastroenterology*. 2014; 146:497–507. e1. [PubMed: 24211490]
13. Grubišić V, Gulbransen BD. Enteric glial activity regulates secretomotor function in the mouse colon but does not acutely affect gut permeability. *J Physiol*. 2017; 595:3409–3424. [PubMed: 28066889]

14. Neunlist M, Aubert P, Bonnaud S, et al. Enteric glia inhibit intestinal epithelial cell proliferation partly through a TGF- β 1-dependent pathway. *Am J Physiol Gastrointest Liver Physiol*. 2007; 292:G231–G241. [PubMed: 16423922]
15. Savidge TC, Newman P, Pothoulakis C, et al. Enteric glia regulate intestinal barrier function and inflammation via release of S-nitrosoglutathione. *Gastroenterology*. 2007; 132:1344–1358. [PubMed: 17408650]
16. Van Landeghem L, Mahé MM, Teusan R, et al. Regulation of intestinal epithelial cells transcriptome by enteric glial cells: impact on intestinal epithelial barrier functions. *BMC Genomics*. 2009; 10:507. [PubMed: 19883504]
17. Neunlist M, Rolli-Derkinderen M, Latorre R, et al. Enteric glial cells: recent developments and future directions. *Gastroenterology*. 2014; 147:1230–1237. [PubMed: 25305504]

Figure 1.

Proposed glial mechanisms contributing to the development of *MEN1*-associated duodenal gastrinomas. Gastrin, derived from G cells, glia and other sources, acts on glial cholecystikinin B (CCKB) receptors to stimulate a protein kinase A (PKA)-dependent translocation of menin from the nucleus to the cytoplasm, where it is degraded by the proteasome. The decrease in menin releases the suppression of gastrin gene expression and triggers a feed-forward loop that contributes to hypergastrinemia.