

EDITORIAL

All Is Not Normal in “Normoganglionic” Bowel Regions of Hirschsprung Disease Model Mice



Hirschsprung disease is a congenital disorder in which neurons are missing from the distal bowel. As the enteric nervous system (ENS) is essential for propulsive gut motility, affected infants have intractable constipation. The current treatment for Hirschsprung disease involves surgical removal of the distal aganglionic region and anastomosis of the ganglionic bowel to the anus. Despite this, many patients with Hirschsprung disease

suffer from enduring motility disturbances after removal of the aganglionic bowel, some of which do not appear to be related to the surgery. In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Musser et al¹ (2015) used a mouse model of Hirschsprung disease to ask whether defects in normoganglionic regions of the bowel might account for the persistent, postoperative dysfunction experienced by many patients with Hirschsprung disease.

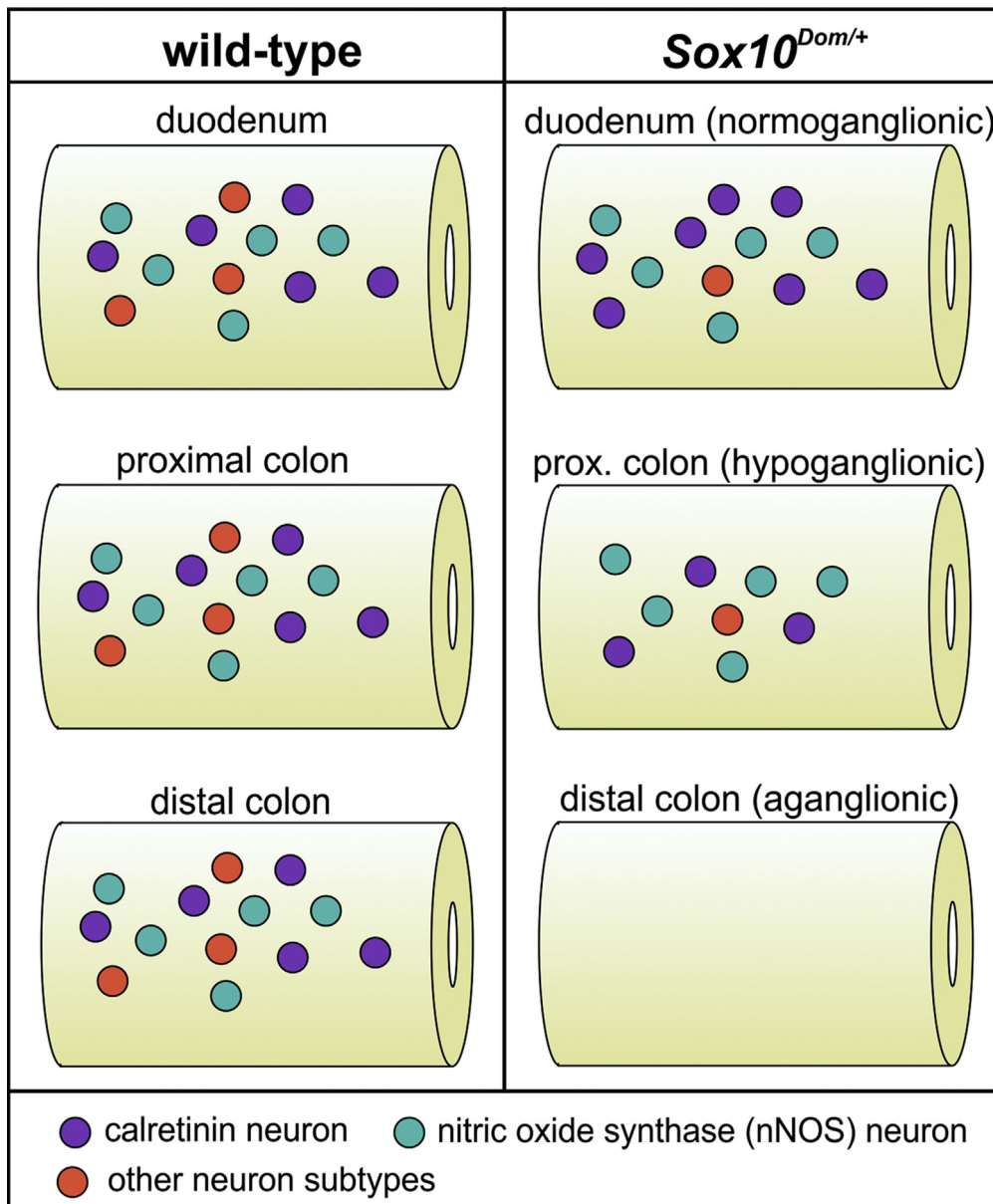


Figure 1. Changes in the major enteric neuron subtypes in different regions of bowel of *Sox10^{Dom/+}* Hirschsprung model mice. Compared with wild-type mice, *Sox10^{Dom/+}* mice have an increase in the proportion of calretinin neurons in duodenum and an increase in the proportion of nitric oxide synthase (nNOS) neurons in the colon close to the aganglionic zone.

Different functional types of enteric neurons form circuits that regulate gut motility, including excitatory motor neurons that mediate contraction and inhibitory motor neurons that are responsible for relaxation of the gut wall. For normal function, each enteric neuron subtype must be generated—and in the correct proportions—during development. Musser and colleagues investigated the presence of enteric neuron subtypes as well as the rate of transit in ganglionated regions of bowel in *Sox10^{Dom/+}* mice, a well-established Hirschsprung disease model. Although the number of enteric neurons and glial cells in the duodenum and ileum were similar in *Sox10^{Dom/+}* and *Sox10^{+/+}* mice, a greater proportion of small bowel neurons in *Sox10^{Dom/+}* mice expressed markers of excitatory motor neuron, such as calretinin (Figure 1). In contrast, numbers of inhibitory motor neurons in the small bowel of *Sox10^{Dom/+}* and *Sox10^{+/+}* mice were similar. Within the colon, closer to the distal aganglionic region, increased numbers of glia and increased proportions of inhibitory neurons expressing nNOS (neuronal nitric oxide synthase) were present, suggesting defects in both neuron/glia and neuron subtype specification. The differences between gut regions suggest that the timing of lineage segregation and specification as well as the local environment may be important for normal ENS development.

Musser et al also found defects in gastric emptying and small intestinal transit in *Sox10^{Dom/+}* mice. Interestingly, these phenotypes varied with age and gender, which may relate to the well-known gender bias, 3:1 male:female, in Hirschsprung disease.

The study by Musser and colleagues is important for many reasons. Previous studies had reported defects in motility in the proximal and midcolon of Hirschsprung model mice, where the density of enteric neurons is also reduced. However, this is the first report of altered motility in the stomach and duodenum, where there are normal numbers of enteric neurons. Moreover, the data indicate defects in neuron subtype specification within normoganglionic small bowel. The data therefore suggest that ENS defects may also be present in the stomach and proximal, normoganglionic bowel of patients with Hirschsprung disease.

Like all good studies, the data also raise several interesting questions. Do defects in the brainstem or in the

gastric ENS underlie the intriguing observation of accelerated emptying in mature male *Sox10^{Dom/+}* mice? Are the perturbations in neuron subtype specification responsible for the observed small bowel motility defects? Are the additional calretinin-positive neurons in the small bowel cholinergic (excitatory) motor neurons? Is the density of circular muscle innervation by axons expressing calretinin increased in the small bowel? As total neuron numbers and proportions of inhibitory neurons within the duodenum of *Sox10^{Dom/+}* and *Sox10^{+/+}* mice were not detectably different, does the increased number of calretinin-positive neurons in *Sox10^{Dom/+}* mice reflect reductions in other neuron subtypes? Finally, given that Hirschsprung disease is multigenic, do variants in other genes that cause aganglionosis result in similar region-specific changes in lineage specification and motility to those seen in *Sox10^{Dom/+}* mice?

Understanding the functional defects and the cellular mechanisms that underlie abnormal motility in proximal, normoganglionic intestine in patients with Hirschsprung disease is the critical first step in devising treatments for those patients with persistent bowel problems after surgery.

HEATHER M. YOUNG, PhD

Department of Anatomy and Neuroscience
University of Melbourne
Melbourne, Victoria, Australia

Reference

1. Musser MA, Correa H, Southard-Smith EM. Enteric Neuron Imbalance and Proximal Dysmotility in Ganglionated Intestine of the *Sox10^{Dom/+}* Hirschsprung Mouse Model. *Cell Mol Gastroenterol Hepatol* 2015;1:87–101.

Conflicts of interest

The author discloses no conflicts.

© 2015 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/3.0/>).

2352-345X

<http://dx.doi.org/10.1016/j.jcmgh.2014.11.001>