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Interoception: Spinal sensory neurons that innervate the intestines

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The gut is innervated by sensory neurons that relay mechanical and chemical signals to the brain. Two new studies characterize the spinal sensory neurons that innervate the intestines and reveal a role for Piezo2 in these cells in sensing colonic distension and regulating gastrointestinal motility.

The gastrointestinal (GI) tract is essential for digesting and absorbing nutrients from food, eliminating waste, and promoting satiety in response to chemical and mechanical signals during a meal[1–4]. Mechanosensation in the gut is mediated by two distinct classes of extrinsic sensory neurons: vagal afferents, which have cell bodies in nodose ganglia and are involved in homeostatic gut–brain signaling[1,3,4], and spinal afferents, which have cell bodies in dorsal root ganglia (DRG)[2,4] and are known for sensing noxious distension, inflammation and other painful visceral stimuli[5–7] (Figure 1A). While recent studies have identified molecular markers for the vagal sensory neurons that sense stretch in the upper GI tract[1,3], less is known about the DRG neurons that detect mechanical signals in the gut and how this regulates GI physiology. Two new studies from Servin-Vences *et al.* and Wolfson *et al.* in *Cell*[8,9] uncover the functional subtypes of spinal sensory neurons that sense colon distension and reveal that the mechanosensor Piezo2 is involved in controlling gut motility.

A genetic atlas of spinal sensory neurons that innervate the colon

DRG neurons innervate both the skin and internal organs. Previous studies of skin-innervating sensory neurons revealed molecular markers — such as TrkB, TH, and Bmpr1b — that label functionally distinct cell types[10]. These cell types are distinguished by the specific cells and tissue layers that they innervate, the types of sensory endings that their axons form, and how they respond to different kinds of sensory stimuli, ranging from gentle stroking to noxious touch. Viscera-innervating DRG afferents also exhibit distinct innervation patterns and morphologies[11], but how these anatomic properties relate to cell types is not well defined. Wolfson *et al*. therefore used the genetic toolkit of skin-innervating sensory neurons as a starting point to investigate the cell types that innervate the colon[9].

The authors first characterized the anatomy of DRG neurons by performing anterograde tracing using a panel of Cre and Flp drivers that intersectionally label distinct cell types[9]. This revealed that all DRG subtypes densely innervate the myenteric plexus, which is a network of enteric neurons that are responsible for producing the peristaltic activity that propels food through the intestine[12] (Figure 1B). Some cell types also innervated the circular muscle layer (TH) or the submucosal plexus (Sstr2+ and Adra2a+) whereas others exclusively innervated the myenteric plexus (TrkB and Bmpr1b). These differences in innervation targets were accompanied by differences in axon terminal morphology. For example, TrkB neurons formed intraganglionic varicose endings that wrapped extensively around myenteric cell bodies, whereas TH neurons innervating the circular muscle layer formed intramuscular arrays. Thus genetically defined DRG cell types have distinct sensory endings and innervation patterns across layers of the intestine.

The authors next asked how these molecular and anatomical differences correlate with functional responses[9]. Responses to touch stimuli are traditionally classified along several dimensions, including the force threshold for activation, the response latency, which depends on whether the neurons contain myelinated A-delta fibers or unmyelinated C fibers, and the rate of adaptation to sensory stimuli[10]. The authors therefore measured these properties in response to colonic distension, using a combination of electrophysiological recordings and *in vivo* imaging. This revealed that DRG subtypes collectively tile force space in the colon, with TrkB neurons having the lowest force threshold for activation and Bmpr1b neurons the highest. Characterization of response latencies and rates of adaptation revealed that TrkB-, TH-, Bmpr1b-, and SStr2-expressing sensory neurons correspond to four distinct classes of mechanoreceptors: the A-delta low-threshold, C-fiber low-threshold, A-delta high-threshold, and C-fiber high-threshold mechanoreceptors, respectively[10]. Of note, although the individual DRG neurons that responded to colonic distension were distinct from those that responded to pinching of the skin (with the exception of a subset of TrkB neurons), as a class, TrkB-, TH-, and Bmpr1b-expressing neurons responded to skin touch and colonic distension with similar functional properties. Thus the genetic signature of DRG neurons dictates how they respond to both external and visceral sensory cues.

Piezo2 mediates responses to colon distension

Piezo2 is a mechanosensitive ion channel that is essential for touch and proprioception as well as sensing

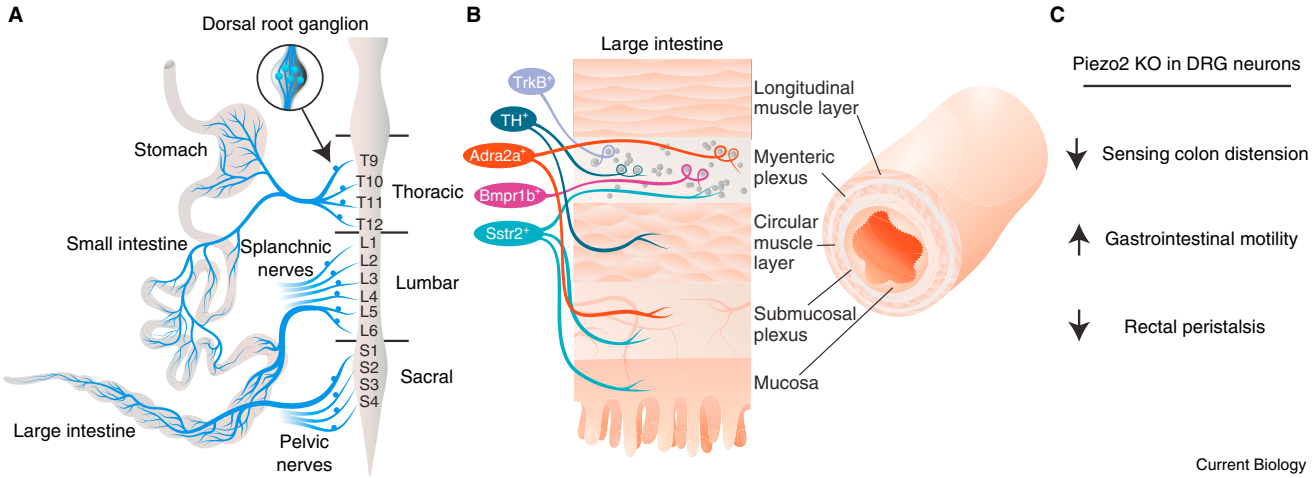

Figure 1. Spinal sensory neurons that innervate the intestines.
(A) Spinal sensory neurons in the dorsal root ganglion (DRG) innervate the gastrointestinal tract — from the stomach to the small and large intestines. The sensory neurons that innervate the large intestine (also known as the colon) have cell bodies in the lumbar and sacral segments of the spinal cord. (B) DRG neurons expressing the genetic markers TrkB, TH, Adra2a, Bmpr1b, or Sstr2 innervate different tissue layers of the large intestine and tile force space. (C) Loss of the mechanosensitive channel Piezo2 in DRG neurons results in impaired sensing of colon distension, accelerated GI motility, and impaired rectal peristalsis or defecation. (Illustrations by Julia Kuhl.)

mechanical signals arising from several internal organs, including changes in blood pressure, lung inflation, and bladder stretch[13,14]. Consistent with this, knocking out the Piezo2 gene resulted in a reduction in the behavioral and autonomic responses to colon distension[8,9] (Figure 1C). Moreover, both groups showed that Piezo2-expressing DRG neurons were activated by supraphysiologic distension of the colon, and, using 2-photon imaging, Servin-Vences *et al.* showed that sacral DRG neurons have greatly reduced responses to colon distension in Piezo2 -knockout animals[8]. This reveals that Piezo2 is a major sensor for colonic stretch, adding to the list of important physiologic functions for this protein. However, the loss of Piezo2 did not completely eliminate the behavioral responses to supraphysiologic colon distension[9], suggesting that there is another sensor that detects either high-threshold stretch or tissue damage.

What are the key DRG neuron subtypes that use Piezo2 for sensory transduction? Wolfson *et al.* showed that genetic ablation of Piezo2 in Bmpr1b-expressing DRG neurons reduced the behavioral responses to colon distension[9]. They also showed that optogenetic stimulation of these cells was sufficient to recapitulate the behavioral and autonomic responses to supraphysiologic distension. Responses of colon-innervating DRG afferents are modulated by inflammation[15], and Wolfson and colleagues showed that Bmpr1b neurons were also necessary for behavioral over-reactivity to colon distension after chemically-induced inflammation by the compound dextran sodium sulfate[9]. Thus Bmpr1b cells appear to be a particularly important node for responses to noxious stimuli in the colon.

Loss of Piezo2 impairs GI motility

The discovery that Piezo2 is critical for responses to noxious visceral stimuli raises the question of whether this channel is also involved in normal aspects of GI function. In support of this, Servin-Vences *et al.* found that humans with loss-of-function mutations in Piezo2 report difficulty in sensing their bowel movements, relying instead on sound, smell or vision[8]. Piezo2-deficient humans also reported an increased frequency of both watery stools and constipation, suggesting a potentially complex role for this channel in controlling GI motility.

To determine where Piezo2 acts to control GI motility, Servin-Vences *et al.* ablated the Piezo2 gene from cell classes that could sense mechanical signals from the gut — vagal afferents, spinal afferents, intestinal epithelial cells, and enteric neurons — and then measured how this affected the amount of time required for ingested food to be excreted[8]. Surprisingly, only the loss of Piezo2 in DRG neurons had an effect on GI transit, which was accelerated. Piezo2 DRG knockout mice also had watery stools, which mirrors the human phenotype and may be secondary to the more rapid passage of food through the gut, which allows insufficient time for water absorption[8].

The finding that Piezo2 acts in DRG neurons to control GI transit was unexpected, in part because the control of GI motility is traditionally associated with enteric and vagal rather than spinal pathways. As stated above, enteric neurons generate the peristalsis that propels food through the intestine, whereas the vagus nerve controls gastric accommodation and emptying via vagovagal reflexes[16–18]. Both of these processes involve mechanosensation, and the fact that loss of Piezo2 in vagal and enteric neurons has no effect on GI transit times suggests that other, unidentified mechanosensors operate in these cells to control gut motility. An additional unanswered question regards how mechanosensing by Piezo2 in DRG neurons functions to modulate GI motility — i.e. what is the relevant mechanosensory stimulus and downstream circuitry. Servin-Vences *et al.* showed that loss of Piezo2 independently accelerates GI transit in the

stomach, small intestine, and colon, indicating that this effect is not restricted to a single tissue[8]. Interestingly, loss of Piezo2 accelerated GI transit in fed but not fasted animals, suggesting that DRG neurons may sense the presence of food in the gut via Piezo2 and then signal to globally decelerate GI transit. This could occur through a reflex loop involving the activation of sympathetic neurons that innervate the myenteric plexus, which are known to inhibit GI motility, or through a longer loop that passes through the central nervous system. Given how little is known about the role of spinal afferents in regulating gut motility, elucidation of these pathways is likely to be an active area of future research.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Regeneration: Signaling superhighways

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Regeneration requires the collective effort of multiple organ systems. A recent study of planarian whole-body regeneration finds that Erk kinase activity propagates rapidly across the entire animal through longitudinal muscle cells to coordinate animal-wide wound responses and that this signal propagation is required for regeneration.

Regeneration is traditionally investigated as a local process, with analyses focused on spared tissue that borders the injury and provides cellular sources, signals, and scaffolds to functionally reconstruct an organ, appendage, or animal that has been damaged. Notably, recent studies have revealed that injuries have a broader impact on animals, as they elicit changes at molecular, cellular, and physiological levels in organs distant from the wound site[1–4]. Producing such remote responses requires signals induced by injury that can quickly travel long distances and reach uninjured tissues[5–7]. Correspondingly, distant structures and