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# Gut feelings: mechanosensing in the gastrointestinal tract

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## Abstract

The primary function of the gut is to procure nutrients. Synchronized mechanical activities underlie nearly all its endeavours. Coordination of mechanical activities depends on sensing of the mechanical forces, in a process called mechanosensation. The gut has a range of mechanosensory cells. They function either as specialized mechanoreceptors, which convert mechanical stimuli into coordinated physiological responses at the organ level, or as non-specialized mechanosensory cells that adjust their function based on the mechanical state of their environment. All major cell types in the gastrointestinal tract contain subpopulations that act as specialized mechanoreceptors: epithelia, smooth muscle, neurons, immune cells, and others. These cells are tuned to the physical properties of the surrounding tissue, so they can discriminate mechanical stimuli from the baseline mechanical state. The importance of gastrointestinal mechanosensation has long been recognized, but the latest discoveries of molecular identities of mechanosensors and technical advances that resolve the relevant circuitry have poised the field to make important intellectual leaps. This Review describes the mechanical factors relevant for normal function, as well as the molecules, cells and circuits involved in gastrointestinal mechanosensing. It concludes by outlining important unanswered questions in gastrointestinal mechanosensing.

Mechanical manipulation of luminal contents is required for nearly all gut functions. The gut generates a range of well-orchestrated mechanical activities that require the sensation of mechanical forces for feedback and coordination. Indeed, the importance of mechanical factors in gut function is explored in classic texts[1,2]. When Bayliss and Starling described the “law of the intestine” in 1899, they stated that the “most effective method of stimulating the intestine is the mechanical method”[3]. The gut detects forces in time and space by the process of mechanosensation. Mechanosensation relies on specialized mechanosensory cells (mechanoreceptors) that use mechanosensors to convert force into electrochemical signals. The responses detected by mechanosensors are amplified (signal amplification) and coordinated by mechanotransducers, in a process called mechanotransduction[4]. The specialized sensory cells, such as mechanosensory neurons, relay the transduced signals

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to effectors such as smooth muscle cells (SMCs) that drive physiological responses such as the peristaltic reflex. As the gut is a mechanically active organ, all cells experience and adjust their functions based on the surrounding mechanical forces. We increasingly recognize that, in mechanical organs, cells whose primary function is not sensation of force, such as SMCs, rely on force sensing for their normal operation. In other words, such cells adjust their primary functions in response to the mechanical cues that surround them. Thus, to comprehend mechanosensing by the gut, we need to define the mechanical environment of the gut and understand how both specialized and non-specialized mechanosensory cells work. By the end of this Review, we aim to have the reader appreciate the gut's crucial physical properties; the mechanical functions that it performs and the forces that it generates in the process; the known cells, molecules and circuits involved in gut mechanosensation; the limitations in translatability of discoveries from animal model studies; and the exciting new areas of research that focus on discovering unknown gut mechanosensors, defining mechanical landscapes and developing tools that probe physiological mechanical cues in animal models and humans and human diseases.

**Mechanosensors**

Proteins directly involved in converting a mechanical stimulus into an intracellular electrochemical signal, for example, mechanogated ion channels that convert mechanical forces into an ionic flow.

**Signal amplification**

Intracellular signalling steps between the primary signal generated by the mechanosensor and the final cellular output.

**Mechanotransducers**

Proteins that amplify the signals generated by the mechanosensors and conduct the downstream cellular signalling in response to force.

**Non-specialized mechanosensory cells**

Cells with a given non-mechanosensory primary function that use mechanosensors to sense mechanical stimuli and tune their own function in response to the physical state of their environment.

## Physical properties and activities

To begin thinking about how the gut senses mechanical forces, we must first consider the physical properties of the gut. These are detailed in other reviews and texts[5]. Here, we focus on aspects crucial for mechanosensing.

## Physical properties

The luminal gut is mainly a tubular structure approximately 9 m long in humans[6]. Compartment transitions are demarcated by sphincters, areas of local muscle thickening that function as imperfect one-way valves. The tube changes dimensions in its cross-section and length to disassemble, reassemble and propel luminal contents[6]. The wall of the tube is a composite, or laminated, material, made of layers with different physical properties. The layers are mucosa, submucosa, tunica muscularis and serosa[7–10] (FIG. 1). The resting physical properties of these layers, such as stiffness, resting tension and Poisson ratio, vary along the length of the gastrointestinal tract[11–14] (BOX 1). For example, mucosa and submucosa are the softest layers in the small bowel, but in the stomach, they define wall stiffness[14]. The resting mechanical properties of the layers and their arrangement define the local mechanical environment of a mechanoreceptor. Furthermore, like most soft tissues, the gut wall is viscoelastic (BOX 1), which makes the forces felt by mechanoreceptors vary over time.

In addition to the layered structure, connections between the layers have a range of physical properties. The submucosa is fluid filled and links to the muscularis layer by a fibrous connection[15]. The flowing property of the viscoelastic gut wall is due in part to this fluid layer. The high water content also makes the submucosa resistant to compressive forces[16], allowing the submucosal layer to take on the role of shock absorber, dampening forces originating from the lumen before they reach the muscle. The fluidity of the submucosal layer also allows it to function as a lubricant coat between the two adjacent layers; therefore, the mucosa could also slide over the muscle and expose intrinsic mechanoreceptors to stretch from shear forces[16]. The extent of the relative movement of mucosa over the muscularis remains poorly understood. With its hydration-dependent roles as shock absorber and lubricant, the submucosa could have a major role in detecting and dissipating light mechanical stimuli, according to experiments on the pig, guinea pig and human colon samples[16,17]. Similar to mucosa and submucosa, the tunica muscularis is layered, with circular and longitudinal layers not only having different physical properties but also allowing for sliding relative to each other[2]. Knowledge of the serosal contribution to static mechanical properties of the gastrointestinal wall is very limited. In all, the differences in physical properties and laminated arrangement lead to non-homogeneous force distributions across the gut wall in space and time. Consequently, mechanosensors in the different layers of the gut wall have different mechanical thresholds[18].

Smooth muscle, the contractile component of the muscular layers, can be approximated as a spring. At rest, smooth muscle is like a loaded spring owing to SMCs being in a state of partial contraction, which leads to a resting tone[13]. Mechanoreceptors located in this layer can be tuned to a reference point that accounts for baseline tension in the tissue. For example, mechanoreceptors in the muscular layers have higher activation thresholds than those in the mucosa[18]. As the physical parameters of tunica muscularis are fairly homogeneous, it is an optimal location to integrate length and tension sensors that report the overall state of volume and contractility of the organ[19]. An analogy can be drawn to skeletal muscle. The complementary mechanosensory functions of length and tension sensing are accomplished in the muscularis by mechanosensors that behave similarly to

muscle spindles and Golgi tendon organs in skeletal muscle[20]. Like the Golgi tendons, the muscularis in-series receptors are tension sensors that report on smooth muscle tone[21]: they are responsive to distension, especially if rapid. Muscularis in-parallel sensors are like muscle spindles and primarily detect stretching or lengthening (FIG. 2).

In all, the layered structure of the gut wall with layers of varying physical properties enables adaptations in mechanoreceptors to detect a wide range of the intrinsic and extrinsic mechanical forces in time and space.

## Mechanosensory activities

Force sensing is crucial for regulating mechanical programmes active during both digestion and the inter-digestive periods[1,22]. The mechanoreceptors encounter a balance of forces from a combination of active and passive distension balanced with wall contraction. Thus, mechanoreceptors detect the resulting wall tension due to tone, displacement or both, as well as shear from relative sliding of the layers and luminal flow generated by these activities[23] (FIG. 2).

**Distension.—**The fundamental aspect of Bayliss and Starling's peristaltic reflex is that it is initiated most effectively by local distension[3]. Mechanical stimuli, such as distension, initiate several types of contractile programmes. Distension can be passive (organ filling) or active (fundic relaxation and rectoanal inhibitory reflex (RAIR))[5,24]. The gut distends, either passively or actively, as the lumen is filled by ingested and secreted materials or by gas produced via microbial fermentation. Luminal filling leads to an increase in cross-section and length, but a decrease in wall thickness[5]. The layers experience these effects non-uniformly because of differences in their Poisson ratios (BOX 1). The intestinal epithelium and mucosa experience apical compression, whereas the basal region of the mucosa stretches. In response to luminal mechanical stimuli, the physiology and shape of the mucosa are controlled through mechanosensing and mechanical activity by the muscularis mucosa[25,26]. In the locations where the tunica muscularis is the stiffest of the layers, the luminal filling should lead to small changes in circumference. In these locations, muscularis is best suited for the sensation of higher force thresholds, as higher forces are required to achieve a given displacement.

**Contraction.—**Gut smooth muscle, independently of innervation, contracts in response to stretch. This response is called the myogenic reflex[27,28]. It is particularly important for the function of sphincters, for which smooth muscle mechanosensation likely plays a crucial part. Wall stretch also initiates peristaltic contractions. The pathways that result in oral contraction and aboral relaxation are part of a broader, complex, coordinated motor programme that some experts term peristalsis and not a 'peristaltic reflex'[29]. Peristalsis depends on neuronal mechanisms and is one of the principal contractile programmes that advance intraluminal contents over large distances. As already described, mechanoreceptors in the tunica muscularis are classified as in-parallel length sensors and in-series tension sensors (FIG. 2). Both play a part in peristalsis. In the small intestine, segmentation contractions mix intraluminal contents with intestinal secretions[5]. This contractile programme typically involves the circular muscle, as it does not serve

the purpose of advancing contents through the gut tube. Segmentation is best understood as a very local response to distension. It can be evoked in a ring of circular muscle roughly a centimetre long[5]. These contractions occur in the bulging region roughly at the midpoint between two previous contractions. However, segmentation can cover large portions of the small intestine by an unknown mechanism[30]. A major limitation to progress in our understanding of these important motor activities is that the molecular identity of the mechanosensors that initiate and coordinate peristalsis and segmentation is currently unknown.

**Flow.—**Intraluminal pressure in a closed volume leads to the flow of contents along the pressure gradient. Even though the mechanical activities of the gastrointestinal tract move material in all directions, they ultimately result in the bulk transfer of ingesta aborally because of the contractile gradient. The characteristics of the intraluminal contents are not constant throughout the tract. We can generalize that the upper gastrointestinal tract encounters mostly solids, the middle mostly liquids and the lower tract encounters solids again. Sensing the physical state of the intraluminal contents would be useful, and some evidence suggests that it happens in vivo. In rats, the proximal colon will produce antiperistaltic waves if it receives soft and moist material[31]. In humans, solid diet components such as bran accelerate small bowel transit[32]. Mechanosensation should have a role in distinguishing the physical state of intraluminal contents. Solids can generate distension, and liquids are more suitable for generating shear. Finer particles and low-viscosity fluids generate light mechanical stimuli. Mucosal mechanoreceptors would be better suited for light touch sensation owing to force dissipation along the laminated tube wall. Conversely, bigger solid particles and highly viscous fluids can be aptly sensed by deeper tube layers, since the force magnitude may be large enough to penetrate through the tissue.

## Mechanosensory cells that detect forces

### Non-specialized mechanosensory cells

Given the non-stop mechanical activity of the gut, all cells in the gut wall and luminal residents, perhaps even the microbiota[33], might encounter persistent mechanical stimuli.

**Syncytium.—**As all cells in the gastrointestinal tract live in the mechanical environment, they have developed mechanisms to sense and adjust their functions in response to mechanical forces. In the gastrointestinal tract, the most numerous cell type is the SMC. SMCs are mechanosensitive and would be logical sensory elements to coordinate the myogenic reflex mentioned earlier in this Review. However, we still know little about the mechanosensitivity of SMCs. For example, are all gastrointestinal SMCs mechanosensitive or only subpopulations, as might be the case for vascular SMCs[34]? SMC express various mechanosensitive elements, such as mechanosensitive ion channels[35,36], but the mechanosensitive elements directly responsible for gastrointestinal myogenic reflex are not firmly established. Interstitial cells of Cajal (ICCs) closely associate with SMCs (FIG. 3) and coordinate the cyclical contractile activity of SMCs by generating and propagating electrical slow waves that depolarize SMCs[37]. ICCs set the frequency of gastric slow waves,

the frequency of which is responsive to force, suggesting ICC mechanosensitivity at least in this organ[37]. Similar subpopulations of mechanosensitive ICCs can be speculated in other organs. Indeed, human jejunal ICCs express mechanosensitive ion channels[38]. There are several types of ICC, classified by their location in the layered structure of the gut wall[39]: some generate slow waves, while others are involved in signal transduction, such as neuromuscular signalling. We do not yet know if all types are mechanosensitive, and if they are, whether they participate in mechanosensing in collaboration with SMCs and neurons[40]. In addition to SMCs and ICCs, fibroblast-like cells ($PDGFR^{+}$) have important roles in regulating motility, likely through purinergic signalling[41,42], but nothing is known about their responses to force.

**Glia.—**Glia are abundant and have a diverse range of physiological functions in the gut (reviewed elsewhere[43]). Although studies show that glia are mechanosensitive[44], very little is known about their mechanosensory mechanisms and functions. For instance, in vivo studies in mice and humans have implicated glia in linking immune cells and enteric neurons in the development of visceral hypersensitivity[45].

**Immune cells.—**There is three-way communication between the microbiota, immune cells and components that endow sensorimotor function, neurons[46] and myocytes[47,48] (FIG. 3). Some general immune functions, such as antigen recognition and T cell receptor (TCR) triggering, are recognized to depend on mechanical sensing[49,50] (reviewed elsewhere[51–53]), but immune cell mechanosensitivity of specific gastrointestinal immune components could also have direct physiological consequences. Studies of immune cell mechanosensitivity have gained traction in organs with mechanical function, but little is known about this topic in the gut. For example, in mouse lung macrophages, cyclic pressure regulates inflammation due to infection or fibrosis[50]. The mechanosensitive channel transient receptor potential vanilloid-type 4 (TRPV4) presumably has a central role in mechanosensation by cells of the innate immune system. TRPV4 has been implicated in neutrophil chemotaxis, macrophage phagocytosis and the formation of reactive oxygen species[54]. At the adaptive level, mechanical forces are also crucial regulators of TCR activation, which is essential for T cell activation[49,55]. Despite these advances, the field of immune mechanosensing is still in its infancy: the mechanosensitivity of and its roles for most immune cells are simply unknown. Gastrointestinal-specific advances can shed light on crucial questions, such as does immune cell mechanosensitivity contribute to the well-established concept of post-inflammatory and/or infectious mechanical hypersensitivity and dysmotility?

**Non-sensory enteric nerves.—**Enteric neurons form interconnected plexuses: Meissner’s in the submucosa, and Auerbach’s, sandwiched between the circular and longitudinal layers of muscularis externa (FIG. 1). The beautiful arrangement of myenteric neurons into a polygonal mesh has mechanical implications: accommodation of axial or radial change by compensating in the other direction prevents axonal tearing during gastrointestinal function[5]. Auerbach’s plexus neurons ‘float’ in loose collagen stroma, which allows them to glide during muscle activity[56]. The mechanosensitivity of neurons in the myenteric plexus of the cat small intestine was described by Mayer and Wood in 1975 based on electrical responses[57]. Using mechanical filaments or intraganglionic fluid injections

and imaging of intact plexuses, about a quarter of myenteric neurons were found to be mechanosensitive in the stomach[58], small bowel[56,59] and colon[56] of guinea pigs and mice. The highest fractions of mechanosensitive neurons were motor neurons and interneurons, which do not have an assigned mechanosensory function[56,59]. Most were rapidly adapting, but some neurons were slowly, and even ultra-slowly adapting, suggesting that myenteric neurons might be intrinsically sensitive to movement and distension[56]. Mechanosensitivity of the soma does not have a clear role. In loosely dissociated cultured guinea pig and human myenteric neurons, about half responded to mechanical deformation of the neurites, some responded to soma deformation, and they showed a range of adaptation to force, from rapid to ultra-slow. These proportions matched the findings from intact tissues, but it was unclear which subtype of enteric neuron was studied[60]. Furthermore, we still need to understand whether it is mechanosensitivity of the soma and/or the processes that drives physiological function. This process is invariably dictated by the expression of mechanosensitive proteins in distinct cellular sublocations. The hunt for mechanoreceptors and mechanotransducers in enteric nerves is ongoing. Mechanogated channel PIEZO1 is expressed in soma and neurites of human submucosal and myenteric neurons, although there is as yet no evidence that it functions as a primary mechanoreceptor in these cells[61]. Mechanosensitive channel TRPV2 expressed in gastric inhibitory motor neurons is necessary for adaptive relaxation in mice[62]. Blocking the sodium/calcium exchanger NCX1 attenuates mechanically induced $Ca^{2+}$ transients in rat and human oesophageal myenteric neurons[63]. Future studies will have to match the spatial localization of relevant molecular targets with mechanical responses.

## Specialized mechanoreceptors

The primary role of specialized mechanoreceptors is to detect mechanical stimuli and convert them into physiological responses. These cells form afferent limbs of sensory circuits. Their function is to inform the effector limbs of the circuits, which carry out the physiological end function.

**Specialized mechanoreceptors**

Cells whose primary function is the conversion of a mechanical stimulus into a physiological signal that influences the behaviour of other cells.

**Epithelial touch sensors.—**Mucosal pressure leads to a large outflow of serotonin (5-HT), suggesting that enterochromaffin (EC) cells that produce 5-HT are mechanosensitive in mice[64]. Interestingly, EC cells have developmental and functional similarities to the skin's light touch sensors, Merkel cells[65]. The mucosal layer is best suited for mechanosensing light stimuli that originate intraluminally. In both Merkel and EC cells, the mechanosensitive ion channel PIEZO2 serves as the primary mechanosensor[66,67]. EC cells are a subtype of a broad population of epithelial sensory cells called enteroendocrine cells (EECs), and several subpopulations express PIEZO2 (REF.[68]). The mechanosensitivity of channels such as PIEZO2 is affected by their localization in microdomains within the plasma membrane and cytoskeleton[69]. The rapid mechanosensitive receptor current generated by PIEZO2 leads to longer-lasting $Ca^{2+}$ signalling and 5-HT release by mechanisms that require further elucidation in tissue cultures[70]. Additionally, mechanical stimulation of EC

cell models leads to activation of G-protein-coupled receptors[71] that, in turn, leads to purine release and autocrine 5-HT release[69]. Intriguingly, both Merkel and EC cells also express the P2Y1 receptor, which contributes to touch-induced impulse generation and EC cell mechanosensitivity[69]. Mechanosensitive EECs participate in 'gut touch', which is an intrinsic mechanosensory function of the gastrointestinal mucosa that enables the intestines to sense physical properties of luminal contents, such as particulate size, similar to size and texture sensing by the fingertips and oral mucosa[72].

**Receptor current**

Ionic current generated during sensory transduction, such as the opening of the mechanogated ion channels.

**Generator potentials**

Transmembrane electrical potentials or voltage shifts due to receptor current that engage voltage-sensing transducer amplification elements.

**Intrinsic primary afferent neurons.—**The gut is unique compared with all other organs because it has an extensive built-in intrinsic, or enteric, nervous system (ENS), which has been covered in excellent previous reviews[73,74]. Some call the ENS the 'second' or 'little' brain, but others have argued that it might evolutionarily predate the central nervous system (CNS)[75]. Within the ENS, Dogiel type II intrinsic primary afferent neurons (IPANs) have cell bodies in the submucosal and myenteric plexuses along the entire length of the gastrointestinal tract. IPANs are intrinsic sensory neurons that process signals from the lumen, immune system and from within the gut wall itself[76]. In the mouse small intestine, they can be identified by the expression of calcitonin gene-related peptide (CGRP), 145 kDa intermediate molecular weight neurofilament (NF145kDa) and advillin[56,77]. IPANs are involved in responses of the gastrointestinal tissue to stretch[56,78,79]. They are not the only mechanosensitive intrinsic neurons (mechanosensitivity of the ENS has been excellently covered in detail elsewhere[80]). IPANs are specialized mechanoreceptors in the ENS because they have been formally proved with guinea pigs to initiate neural reflexes in response to physical deformation[77]. Conversely, the role of other intrinsic mechanosensitive neurons in mechanically induced reflexes needs further investigation[80]. When their processes are stretched, myenteric IPANs produce generator potentials and alter excitability[79,81]. Single-cell sequencing efforts in IPANs are beginning to identify potential mechanosensors, such as PIEZO2 (REF.[82]).

Interestingly, although distortion of IPAN processes leads to excitation, forces applied to cell bodies lead to inhibition. These findings suggest that the mechanical properties of resident cells are heterogeneous[79], just like the mechanical properties of macroscopic tissue. The molecules and mechanisms of IPAN mechanosensitivity are unclear. It is appealing to surmise that sensory cells tune the mechanosensory properties of their parts to the mechanical properties of their tissues. Examples in the interplay between static physical and

mechanosensory properties are emerging, such as the necessity for a baseline cell membrane tension in mechanosensory neurons[83].

**Extrinsic sensory neurons.—**Extensive extrinsic sensory neuronal innervation links the gut and the brain (FIG. 3). Extrinsic innervation is discussed in detail in several excellent reviews[84,85], so we focus on mechanosensing by the extrinsic sensory neurons. The abdominal and pelvic viscera are innervated by vagal, splanchnic and pelvic nerves, which originate either from the brainstem (vagal) or from the spinal cord (splanchnic and pelvic)[84] (FIG. 3). These nerves have characteristic anatomical, physiological and molecular features[86]. From the vantage of the CNS, the extrinsic gut innervation uses three anatomically distinct sensory pathways — vagal, thoracolumbar and lumbosacral. From the vantage of the gut wall, five structurally distinct types of sensory afferent ending are strategically positioned to determine the mechanical state of the gut wall: intraganglionic laminar endings (IGLEs) that surround the myenteric plexus; intramuscular arrays (IMAs); mucosal; muscular–mucosal; and vascular endings that run alongside vessel branch points[18,84] (FIG. 3). The latest discoveries point to impressive complexity and diversity of afferent ending structures. An individual extrinsic axon can have multiple sensory endings, and interestingly, individual axons can terminate as different morphological endings in different layers of the colon, including novel endings such as intraganglionic varicose endings[87,88]. Each morphological ending might correspond to a distinct mechanosensory function, but we await functional demonstration of how this structure influences mechanosensory function.

The landscape of molecular mechanosensors and mechanotransducers is not as neatly defined for extrinsic innervation of the gastrointestinal tract. It might be that a handful of molecules when placed in these specialized sensory endings can be positioned to detect unique mechanical signals. Or it could be that an equally large number of protein families is necessary to sense mechanical stimuli by each ending type. The identities of mechanosensitive proteins in extrinsic neurons remain largely unknown, although progress is ongoing. For example, extrinsic fibres projecting to the colon and originating in the nodose and dorsal root ganglia express members of the mechanosensitive acid-sensing ion channel (ASIC) family[89,90]. In mice, ASIC subtypes contribute differentially to mechanosensation by neuronal afferents depending on the target organ: *Asic1* mutations increase mechanosensation by stomach and colon afferents, whereas *Asic2* mutations increase mechanosensation by gastro-oesophageal mucosal endings[91]. As highlighted in the Future directions section of this Review, molecular candidates for mechanoreceptors and mechanotransducers in this neuronal population can be drawn from peripheral sensory neurons, particularly those that participate in pain signalling (reviewed elsewhere[92]).

The vagus nerve is an information super-highway between the gut and the brain, informing both about the interoceptive state of the body. Filling of luminal organs, such as the stomach and small intestine[93] regulates immediate satiation of hunger[94] and even thirst[94,95]. Stomach filling regulates feeding, and studies in cats show that stretch activates vagal projecting neurons[96]. Mechanical distension of the gastric wall, as would happen during feeding, is reported by vagal IGLEs[94,97]. Although the stomach is a logical location to sense filling due to food, in mice, there is a subset of vagal nerve projections that form IGLEs in

the small intestine, which could play a dominant part in the regulation of food intake by sensing intestinal filling[93]. There appears to be a pathway that integrates mechanosensory information on instantaneous volume changes in the upper gastrointestinal tract, transmits it to the parabrachial nucleus in the brainstem and translates it into appetite-suppressing signals[98]. Although the identities of the mechanoreceptors in this and many other pathways remain elusive, we describe in the Future directions section of this Review the exciting advances that are poised to identify the molecular identities of the mechanosensors involved.

IGLEs lie near the myenteric plexus and, therefore, near enteric mechanosensory neurons. The basic IGLE consists of a large diameter parent axon that bifurcates upon entering the ganglion and arborizes its laminar endings in close contact with the connective tissue capsule[99]. In the guinea pig oesophagus, IGLEs are proposed to be intrinsically mechanosensitive based on response kinetics, but mechanically induced responses were not inhibited by traditional stretch-activated ion channel blockers[97]. If intrinsically mechanosensitive, IGLEs have characteristics of in-series tension mechanoreceptors, on the basis of their location and function. Another sensory structure is the IMA, which has features of an in-parallel length mechanoreceptor[100] (FIG. 2). Vagal[101] and spinal intramuscular afferents project their fibres into the syncytium throughout the length of the gastrointestinal tract. They might be important sensory structures at two ends of the gastrointestinal tract: the oesophageal and anal sphincters[84]. They frequently run close to the ICCs, which may be mechanosensitive[37]. The arrangement of ICCs and intramuscular afferents is reminiscent of muscle spindle arrangement, as opposed to IGLEs, which are more reminiscent of Golgi tendon organs[21].

Mucosally projecting endings from the vagus and spinal nerves are involved in sensing light mechanical distortion, either by themselves[102] or in collaboration with mechanosensitive EECs that release ATP[69] and 5-HT in response to force[103]. This system has similarities to somatosensory touch, a two-mechanoreceptor system composed of a mechanosensitive epithelial Merkel cell[104] with some releasing 5-HT[105] and a mechanosensitive sensory neuron[106,107]. Another intriguing parallel between gut mechanosensing and the sensory system of the skin is the intestinal presence of structures similar to Meissner corpuscles, which are receptive to light touch in the skin[108]. There are also combined ‘muscular–mucosal’ afferents. These are low-threshold, distension-sensitive intraganglionic mechanoreceptors also activated by light mucosal distortion, according to evidence in the ferret oesophagus and stomach[109]. We do not currently know whether these sensory fibres use branching endings to detect mechanical inputs from both muscle and mucosa, or if they are strategically positioned in a subepithelial plexus that can report physical activity from both locations.

The spinal vascular afferents, which make up one-third to a half of all lumbosacral afferents to the gut[18], run along with the branch points of mesenteric vessels[110] into the submucosa[111]. Anatomically, they are divided into ‘mesenteric’ and ‘serosal’, depending on the location of their mechanosensitive sites[112]. Firm local compression of the mesentery or the gut wall activates these fibres in mice[18]. The vascular afferents are also sensitive to the dynamic phase of distension, for example, during contraction and distension during peristaltic activity[110]. These endings might be nociceptors. For example, as their position is

on vessels, they report on the mechanical aspects of blood flow, being explicitly activated in rats by a decrease in blood vessel wall tension[113]. There are two mechanosensitive populations: one with relatively high thresholds to distension plus slow firing rates, and another with lower thresholds and higher excitability[114]. The vascular afferents could serve a dual function by also controlling mechanically induced vasodilation, thereby coordinating mesenteric blood flow with changes in gut motility[115]. Some vascular afferent endings are structurally like the classic Pacinian corpuscles that detect vibration in the somatosensory system[116]. Indeed, these mechanoreceptors respond to phasic movements during the dynamic phase of distension. As the gut seldom encounters such high-frequency stimuli, they are tuned to lower frequencies[110].

**Intestinofugal afferent neurons.—**Intestinofugal afferent neurons (IFANs)[117] straddle the divide between intrinsic and extrinsic innervation of the gastrointestinal tract: IFANs have cell bodies in the myenteric ganglia and project out of the gut to prevertebral ganglia[118], where they stimulate sympathetic outflow. IFANs are arranged in parallel with circular muscle. They are active during distension but are ‘silent’ during contraction. Thus, IFANs are volume sensors that detect intestinal stretch and help maintain the wall in a relaxed condition during filling by providing a counterbalance to the myogenic reflex[117]. IFANs have been postulated as mechanoreceptors that integrate mechanical signals at the level of the prevertebral ganglia, but as they make extensive synaptic contacts, we do not definitively know that they are directly mechanosensitive[117,119]. It is worth noting that the proportion of mechanosensitive cells and neuronal endings is not fixed. So-called silent afferents are mechanically insensitive until they are ‘sensitized’, presumably by inflammatory mediators[120] or by yet to be discovered signalling cues.

## Mechanosensory circuits

Spatial and temporal integration of mechanosensory information is crucial for organizing normal physiological functions such as the well-coordinated peristaltic reflex. The mechanosensory cells discussed already assemble to form the afferent limbs of mechanosensing circuits. Specialized mechanoreceptors are at the centre of the circuits that influence physiological function. Non-specialized mechanosensory cells use mechanical feedback to regulate their function, but they likely also have auxiliary roles in dedicated mechanosensory circuits[24]. The gut is unique compared with other organs that rely exclusively on extrinsic sensory innervation; in the gut, all regions contain dual innervation from the intrinsic and extrinsic nervous systems[84].

**Neuroepithelial.—**The gastrointestinal lumen communicates with the outside environment. As such, the gut possesses mechanosensory circuits similar to those in the skin to detect luminal mechanical stimuli. For example, similar to the oral cavity and skin, which detect texture and stiffness of food, the luminal gut senses the physical properties of luminal contents[32,72,121]. Intriguingly, structures similar to Meissner and Pacinian corpuscles, which are specialized mechanosensory endings in the skin, are found in the gut[108,110,116]. Although structural similarities suggest that these might respond to light touch and high-frequency stimuli, respectively, the roles of these structures are currently unclear.

The gut also has a neuroepithelial connection akin to the Merkel cell — a sensory neuron connection involved in sensing skin light touch[122]. Mechanical stimulation of epithelial EC cells, which are similar to Merkel cells, leads to activation of IPANs[123]. This neuroepithelial connection regulates local secretory[66,124] and extrinsic sensory neurons[94], which inform the gut–brain axis. In light touch sensation in the mouse skin, neuroepithelial mechanosensory circuits rely on synaptic transmission[105,122]. In the mouse gut, neuroepithelial sensory connections couple epithelial mechanosensitive EECs with neurons, either modulating[94] or directly activating the latter[66]. There has been major progress in elucidating neuroepithelial synaptic communication between a group of EECs called neuropods and extrinsic sensory neurons[125], which can mediate sensory transduction for direct input to the CNS in mice[126]. It remains unknown whether mechanotransduction takes the same route or requires refinement before relay to the CNS (discussed later). Moreover, the proportion of EECs that participate in such synaptic communication with extrinsic neurons is unclear. With respect to intrinsic neurons, the mode of communication between EECs and IPANs remains unresolved[65,123]. Notably, there is no distinct requirement for the neurons synapsing with epithelial mechanoreceptors to be mechanoreceptors themselves. Although peristalsis can be initiated in animal models by stroking the mucosa[127,128], peristalsis-like activity can also be elicited in mice by mechanical stimulation of the tunica muscularis[129]. Thus, mechanosensitivity of both mucosa and tunica muscularis are likely involved in peristalsis. This observation is reminiscent of the two-receptor arrangement in skin touch sensing[107], in which both the epithelial and neuronal cells are mechanosensitive, and, a similar two-receptor arrangement is possible in gastrointestinal neuroepithelial circuits.

**Interstitial or glial–neuron.—**An important intrinsic mechanosensory reflex is the RAIR, which is used in the diagnosis of Hirschsprung disease (BOX 2). RAIR is a nitric oxide-mediated relaxation of the anal canal in response to even small mechanical stimuli in the rectum[24]. Interestingly, ICCs have been implicated in RAIR mechanotransduction[24], suggesting an ICC–neuron communication in mechanotransduction. Even though subpopulations of ICCs elsewhere are mechanosensitive, we do not know whether in RAIR ICCs are mechanoreceptors or downstream recipients of signals generated by bona fide mechanoreceptors. In the stomach, ICCs reside very close to another presumably mechanosensitive structure, the IMA of the vagal projections[40]. But, as discussed, although structure suggests function, we do not currently know whether ICC–IMA connections are functional mechanoreceptors or indeed how they work. Glia mechanosensitivity in the gut remains understudied[44]. Nevertheless, glia also reside near enteric and extrinsic neurons, and ample communication between glia and neurons in the gut has been demonstrated in vivo[130], suggesting the possibility of glia–neuron mechanosensing units. There is a growing possibility that mechanosensing by immune cells such as macrophages might control physiological gut function, specifically through their connections with neurons[46,130], smooth muscle[48] and ICCs[131].

**Neuron–neuron.—**There are several types of mechanosensitive neuron in the gut wall, including IPANs, extrinsic sensory neurons, interneurons, muscle motor and secretomotor neurons. Structurally, these neurons are often near each other, such as the IGLEs formed by extrinsic neurons that serve as mechanosensory endings[93]. We still do not know

how the ENS and extrinsic neurons communicate: is there a role for ENS modulation of mechanosensory signals carried by extrinsic primary afferents? The discovery of mechanosensitive interneurons and other intrinsic neurons raises the possibility, especially given that there is already bidirectional flow of information between the ENS and CNS[132]. Interestingly, IGLEs signal during both distension and contraction[133], suggesting structural and functional specialization. The spatial arrangement is suggestive of interaction, and indeed neuron–neuron mechanosensory connections might give the ENS the ability to refine mechanosensory responses before sending signals to the CNS.

## Future directions

Impressive progress has been made in our understanding of mechanosensation in the gut. We propose that many more exciting discoveries lie ahead. Here, we focus on some emerging areas, both technical and intellectual, that will bear fruit in our understanding of gut mechanosensation. These areas include discoveries of mechanosensors, definition of the landscape of mechanical energy distribution in the gut wall and development of novel approaches to test gut mechanosensation.

First, it is worth emphasizing that many of the studies referenced up to now have used a variety of model organisms. We have attempted to highlight the organisms on which gastrointestinal mechanosensation has been studied because interspecies developmental and dietary differences pose important confounders. Future efforts to understand gut mechanosensation in humans will need to include some validation that the discoveries made in these other species translate to human physiology. A 2020 study that identified mechanosensitive neurons in the porcine submucosal plexus validated its animal observations with human studies[16]. The common features of mechanosensitive neurons were interpreted as evidence of conserved mechanosensory pathways and strengthened the use of this animal model, which has been proposed to share important anatomical, nutritional and physiological similarities with humans[16]. Tools such as voltage and calcium dyes, as well as ultrafast neuroimaging techniques, allow researchers to study neurons in large animals and in fields with more cells[16]. Although labour-intensive, challenged by the availability of human samples, and limited by lack of refined diagnostic techniques to study mechanosensing in humans (when compared with fields such as neurology), these types of comparative studies are more necessary than ever as mechanosensation becomes clinically recognized for its role in human disease (BOX 2).

### Identifying mechanosensors and pathways

Acute cellular mechanosensation depends on mechanosensors, which are molecules that convert mechanical stimuli into chemical and electrical signals. Cytoskeletal proteins[134–136], cell–cell junctions[137] and cell–extracellular matrix junctions[138–140] are mechanosensors potentially expressed in cells of the gastrointestinal tract. These proteins vary in response kinetics to mechanical stimuli. An important type of mechanosensor that allows rapid force sensing is the mechanosensitive ion channel. Previous reviews have aptly described the mechanosensitive ion channels broadly[141], in the gut[142,143] and in nociception[92]. To be considered a mechanosensor channel, the transmembrane protein must fulfil four

requirements[144] (BOX 3). Drawing conclusions on ion channels being mechanoreceptive without all criteria being fulfilled can lead to misidentification. For example, transient receptor potential (TRP) proteins comprise a large family of channels that are gated by a range of chemical and physical stimuli, including mechanical force. Several TRP channels, such as TRPA1 (REF.[145]), were proposed to be mechanosensitive. Nevertheless, rigorous testing[146] ruled out the majority, and now only some remain viable candidates. For example, TRPV2 is demonstrably mechanosensitive, expressed in inhibitory motor neurons of the gastric myenteric plexus and seems to have a role in gastric adaptive relaxation in mice[62]. Another noteworthy example is the search for mechanosensors in the IGLEs. If IGLEs are mechanosensitive, their mechanosensors remain unknown. As mechanosensors can be lowly expressed but have major downstream effects, their discovery is akin to looking for a small needle in a haystack. Often, promising molecular candidates are involved in signal transduction instead of in sensing primary stimuli. For example, ASICs, candidate mechanosensors, are expressed by IGLEs, yet stomach stretch responses were reduced but not eliminated in individual *Asic2* and *Asic3* knockout mice. Interestingly, mechanosensitivity was increased in *Asic1* knockouts[91]. The incomplete elimination of mechanosensitivity in these cases suggests that TRP channels and ASICs might not be mechanosensors, but could instead play a part in mechanotransduction. Force might be the first stimulus that membrane-residing proteins sense[147]. We are discovering that many ion channels gated by stimuli other than force, such as voltage, are frequently mechanosensitive[35,36,148]. These channels can contribute substantially to cell mechanosensation in vitro, especially in electrically excitable cells[149,150]. However, we still do not know whether the voltage-gated ion channels serve as mechanosensors or mechanotransducers. In addition to mechanosensitive ion channels, mechanosensitive G-protein-coupled receptors are emerging as sensors of acute forces in endothelial cells and SMCs[151,152]. It will be crucial for future research to determine which proteins serve as mechanosensors and which as mechanotransducers. The identity of the primary mechanosensors has not been established in most established mechanoreceptors in the gut. As these molecules are attractive drug targets[153], there is an ongoing intense hunt for their identities.

Technical advances are poised to answer these questions. Circuit tracing using viruses[125,154] and transgenic animal models, single-cell RNA sequencing (RNA-seq)[155] and connecting omics with function using techniques such as patch-seq[156,157] will drive functional dissection of enteric circuitry and provide molecular resolution in the hunt for mechanoreceptors and mechanotransducers. For example, traced and examined at the single-cell level, colon-projecting sensory neurons from the thoracic and pelvic levels form seven clusters, with multiple of these clusters expressing the mechanogated ion channel PIEZO2 (REF.[155]). Efforts to decode the human ENS at single-cell resolution are already under way[158].

## Visualizing forces

Distension and contraction powerfully activate visceral pain pathways[84]. The arrangement of mechanoreceptors in series or in parallel allows the tissue to sense both contraction and distension. Yet, at the molecular level, mechanosensors can only detect force through

displacement. Visceral sensory mechanisms are studied by isolating mechanoreceptors, applying different kinds of stimuli and studying the resulting responses. The responses might be conscious visceral sensations, physiological reflexes and electrophysiological responses. A problem that arises from this approach is that common forms of stimuli, such as organ filling and peristaltic movement, have the potential to activate more than one cell[112]. Another challenge is that mechanosensory signals are likely integrated in brain–gut signalling. A single cell type can be activated by what we perceive as different stimuli. Leek[112] drew an analogy to visual sensory systems: detection of the colour 'yellow' follows from the stimulation of red and green retinal cones, and detection of the colour 'magenta' follows from the stimulation of red cones again, but this time in conjunction with blue cones. Similarly, he posited, what we perceive as 'fullness' may follow from the stimulation of tension and serosal mechanoreceptors, whereas 'flow' may follow from the stimulation of serosal mechanoreceptors in conjunction with mucosal ones[112]. Studies connecting structure and function in real time, therefore, are highly revealing. For example, connecting mechanical stimulation of the gut wall with a recording of electrical activity and mechanoreceptor visualization, although technically demanding, is poised to bear fruit[111]. Intravital colonic imaging has seen major progress in mice[159]. It might one day be possible to simultaneously and directly observe how multiple mechanoreceptors are activated in response to various stimuli. For example, intravital calcium imaging of traced neurons with reporters of historical activity, such as CaMPARI[160,161], could shed light on neuronal reflexes initiated by luminal distension. To determine how forces activate mechanosensory elements, we need to visualize the force distribution in cells[162] and tissues[163]. This spatial information needs to be related to direct measurements of mechanosensor activation.

## New and relevant techniques

Mechanosensation is a tissue property tightly controlled in space and time. To effectively study mechanosensitivity, stimuli must be as physiological as possible. Reductionist approaches and highly reproducible mechanical stimuli applied to cells and tissues, such as poking and shear stress in cells, infusing fluids into ganglia[59], and von Frey hairs and intraluminal balloons in tissues, are crucial to determining the molecular and cellular basis of mechanosensation. Indeed, understanding gut mechanosensing at the cellular and molecular levels is unambiguous and poised to provide molecular targets. However, given the importance of mechanosensation by the gut, the gut's mechanosensory system is highly redundant. The result, per Bozler, is that "variability in the responses obtained is partly due to the use of abnormal, crude stimuli"[164], suggesting that, even in the golden age of physiology more than 70 years ago, more physiologically relevant mechanical stimuli were required. Innovative technical approaches to model mechanical stimuli in the gut will be mechanistically revealing. For example, varying the physical properties of intraluminal contents to deliver physiologically relevant mechanical stimuli in vivo could be highly revealing[32,121,165], especially as the physical properties of food still serve as some of the best therapies for gastrointestinal sensorimotor disorders, such as gastroparesis and constipation[165]. An additional consideration is that mechanoreceptors do not live in isolation. Some of them, such as subpopulations of EECs, multitask by having dual roles as mechanosensors and chemosensors[166,167]. Further improvements in technical approaches to best reflect physiological stimuli are required.

## Conclusions

Mechanosensing is important for normal gut function, yet it remains superficially understood. In this Review, we focus on the physical properties of the gut, and on the molecules, cells and circuits involved in gut mechanosensing. Mechanosensation depends on the ability of the gut to feel mechanical stimuli, as determined by its mechanical properties and as elicited by activity during digestion. Given the vibrant mechanical world in the gut, normal function requires the engagement of specialized mechanoreceptors that are arranged in mechanosensing circuits, as well as of non-specialized mechanosensory cells that tune their behaviour in response to surrounding forces. The mechanosensing and mechanotransduction mechanisms, which vary in time and space, are accomplished by a range of molecules (mechanosensors and mechanotransducers) in these cells, but their identities remain mostly undiscovered. Technological advances and discoveries of novel mechanosensors are poised to substantially advance this field.

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**Key points**

- Mechanosensation is the ability to sense mechanical forces and transduce them into physiological responses.
- The gut is a mechanically active organ in which all cells must sense the forces emanating from the digestion of intraluminal contents and organ activity, such as motility.
- All cells reside in tissue at a baseline mechanical state; the gastrointestinal tract is a layered (composite) organ in which the baseline mechanical state varies by spatial localization.
- Non-specialized mechanosensory cells sense force to adjust their function; specialized mechanoreceptors are mechanosensory cells that guide physiological organ responses to mechanical stimuli.
- Gastrointestinal mechanoreceptors share similarities with mechanoreceptors in other sensory and non-sensory organs; leveraging these similarities helps in understanding the purpose and function of mechanoreceptors in the gastrointestinal tract.
- Mechanosensory circuits built into the gastrointestinal wall allow for spatial and temporal integration of mechanical stimuli into a coordinated physiological response (for example, peristaltic reflex), and connections to the extrinsic mechanosensory circuits are crucial for brain–gut communication (for example, sense of fullness).
- Areas with research potential include the discovery of unknown mechanosensors, quantification of the baseline mechanical state of the gastrointestinal wall, and the development of novel tests for gut-specific mechanosensation.

**Box 1 |**

## Physical properties of the intestine

**Viscoelasticity**

Property describing a material that exhibits viscous and elastic qualities. Pure elastic objects behave like a spring: force and deformation are linearly related and the release of force returns the object to its original shape. In viscoelastic materials, the viscous components, such as interstitial liquids in the gut wall, make it such that parts of the material 'flow'. Consequently, the gut shows stress relaxation: force dissipates over time when tissue remains deformed for a period of time.

**Compression**

Application of an inwardly directed force on an object, colloquially known as 'pushing' on the object.

**Tension**

Application of an outwardly directed force on an object, colloquially known as 'pulling' on the object. It can be considered the opposite of compression.

**Strain**

Upon application of force, the resulting change in length of an object normalized to its original length.

**Poisson ratio**

A dimensionless quantity that describes how much sideways expansion an object that is being squeezed undergoes. Calculated as a change in object length in directions that are perpendicular to the direction of applied force.

**Residual strain**

- Baseline strain of tissue when the gastrointestinal lumen is empty and no external forces are acting on the tissue. Residual strain can be quantified as the deformation when all intrinsic forces acting on the tissue are removed. Gregersen and Kassab[168], and others[8,11]:
  - pig duodenum, inner surface: compression (−0.13 to −0.06)
  - pig duodenum, outer surface: tension (0.05–0.14)
  - guinea pig jejunum with villi, inner surface: compression (−0.33 ± 0.06)
  - guinea pig jejunum without villi, inner surface: compression (−0.05 ± 0.030)
  - rat colon and rectum, serosa: tension (0.1–0.25, 0.07–0.16)
  - rat colon and rectum, mucosa: compression (−0.06 to −0.1 and −0.16 to −0.09)

- For comparison, Vaishnav and Vossoughi[169] used a similar method to determine residual strains in the pig aortic segments:
  - intima: compression (−0.117 to −0.057)
  - adventitia: tension (0.056–0.120)

**Box 2 |**

### Pathologies with known or suspected disruption of gastrointestinal mechanosensation

- Hirschsprung disease
- Irritable bowel syndrome
- Functional dyspepsia
- Diverticula
- Ulcerative colitis
- Nausea
- Obesity
- Centrally mediated abdominal pain syndrome
- Dyssynergic defaecation
- Achalasia
- Functional dysphagia
- Crohn’s disease
- Visceral hypersensitivity

**Box 3 |**

### Four criteria of a mechanosensitive channel

- Spatial and temporal expression in a mechanosensory organ.
- Must be required for the response to mechanical stimuli. Hence, channel removal must eliminate the response to a mechanical stimulus.
- Molecular alteration of the channel must change the nature of the mechanical response.
- Heterologous channel expression must demonstrate mechanical gating.

According to REF.[144]

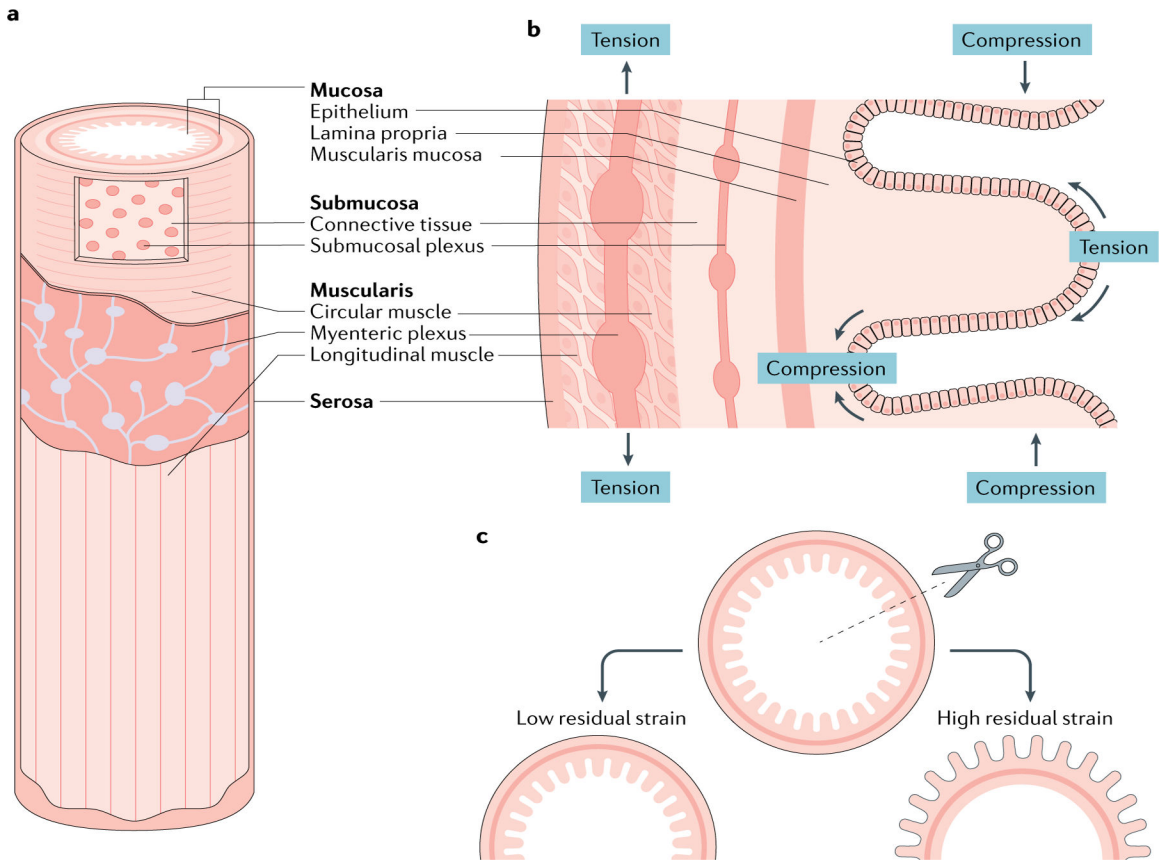


**Fig. 1 |. Static mechanical properties of the gut wall.**

**a** | An oblique view to show the layers needed to understand the composite nature of the wall. **b** | Longitudinal cross-section showing a different view of the laminated structure and enteric nervous system organization. The layers closest to the lumen are under a constant state of compression, whereas those further away are in a state of tension (stretch). The four layers of the gut wall are identified in both cross-sections for orientation. **c** | Experiments to determine residual strain (BOX 3) and other passive mechanical properties of the gut wall. A radial cut on a gut segment causes it to open. Some segments have small opening angles (left) and others turn completely ‘inside out’ (right). The opening angle correlates with the balance of compression and tension between the tissue layers.

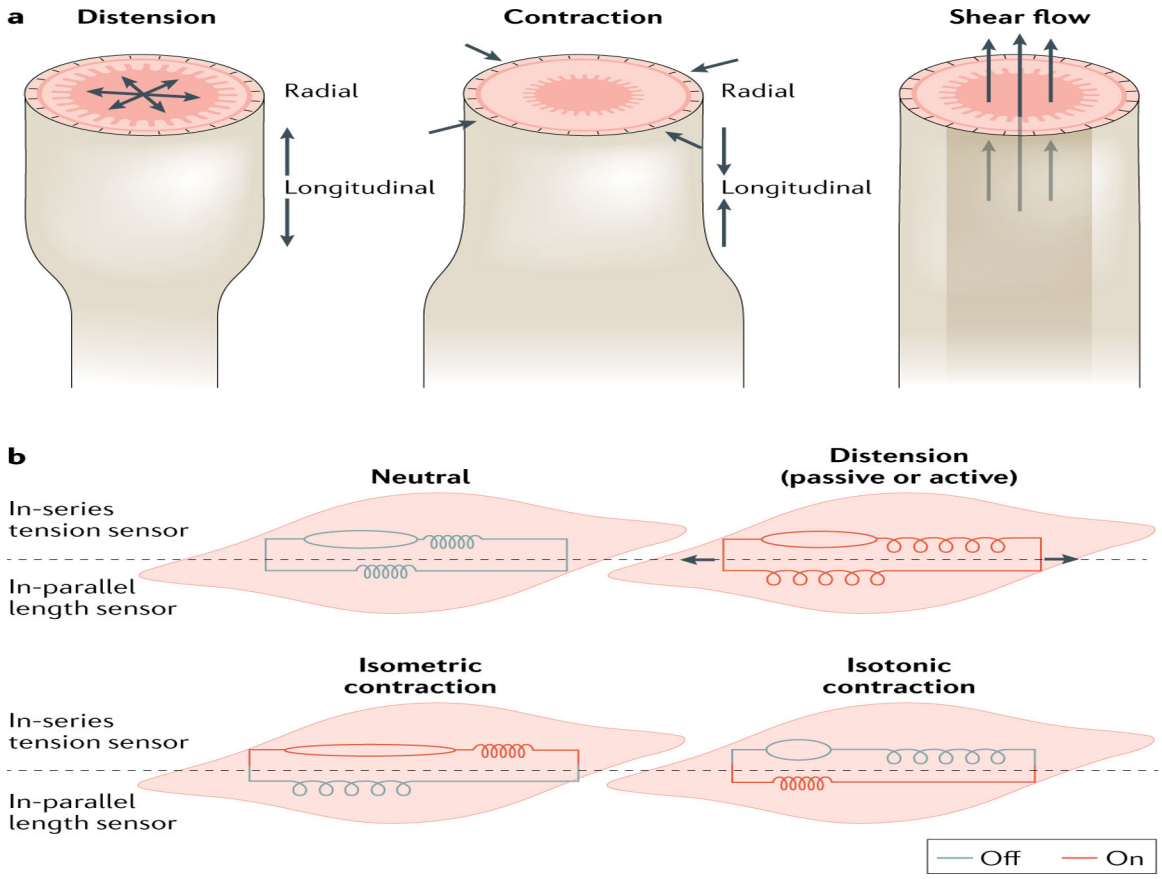


**Fig. 2 |. Dynamic activities of the gut wall.**

**a** | Mechanosensation by gut wall tissues enables the organ to respond to three types of physical activity: distension, contraction and flow (shear). Distension and contraction have longitudinal and radial components. **b** | Inseries and in-parallel mechanoreceptors are differentially activated depending on the gut activity. Red colour means that the mechanoreceptors are engaged as a result of the activity; grey colour means that they are not engaged.

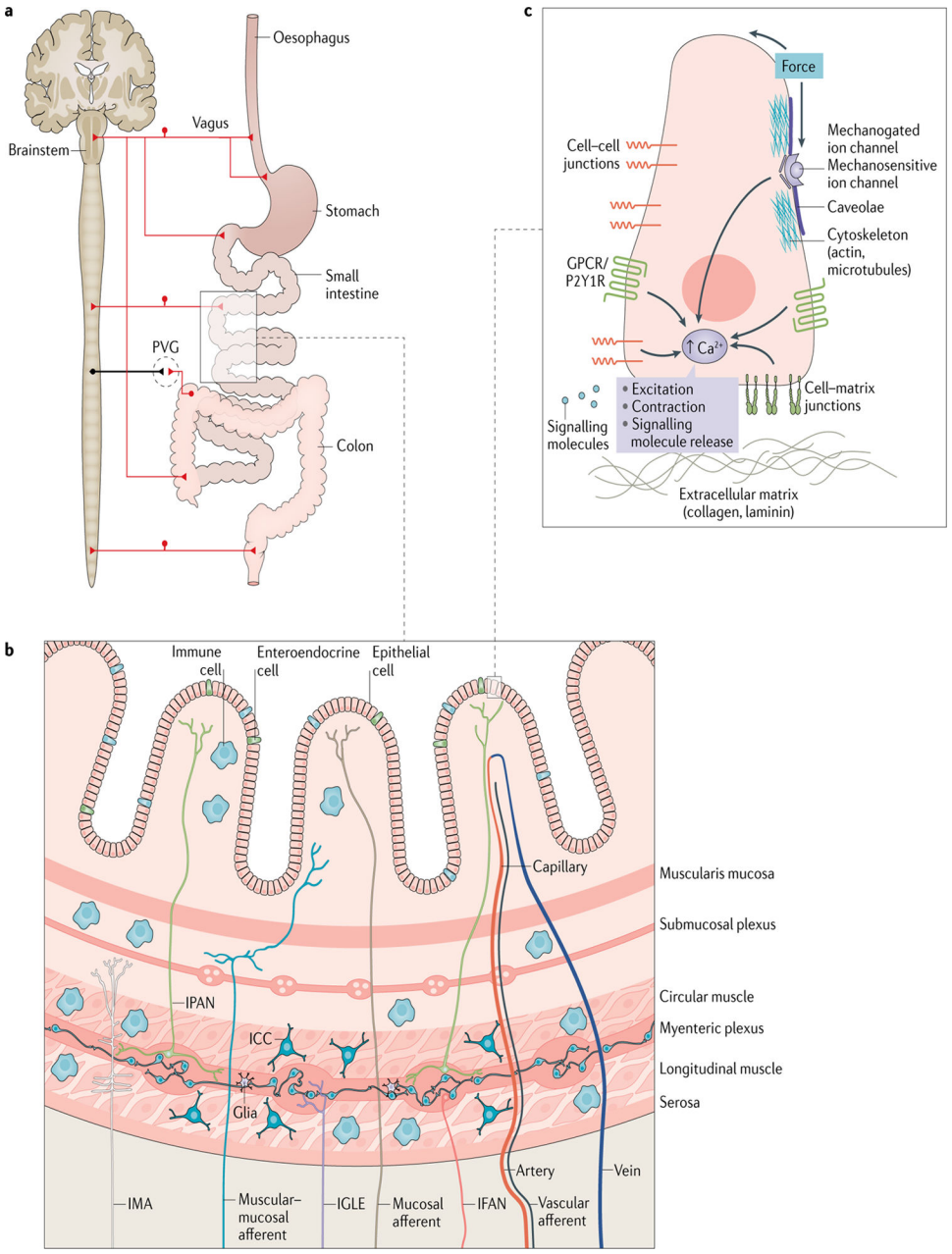


**Fig. 3 |. Circuits, cells and molecules involved in gut mechanosensation.**

**a** | Extrinsic innervation of the gastrointestinal tract. From the vantage of the central nervous system, vagal, thoracolumbar and lumbosacral pathways innervate distinct regions of the gastrointestinal tract. There are three prevertebral ganglia (PVGs): coeliac, superior mesenteric and inferior mesenteric. **b** | Constituent cells of mechanosensory circuits in a section of the gut wall. All highlighted cell types are discussed in the main text. **c** | Mechanosensors in a generic mechanoreceptor. Mechanical force gets transduced by several proteins in the mechanoreceptor, including mechanogated ion channels, integrins and cytoskeletal filaments, among others. Mechanotransducers such as purine receptor P2Y1R and mechanosensitive G-protein-coupled receptors (GPCRs) amplify pathways initiated

by mechanosensors. Mechanotransducers carry out their amplification role by activating secondary messengers such as intracellular calcium ($Ca^{2+}$). ICC, interstitial cell of Cajal; IFAN, intestinofugal neuron; IGLE, intraganglionic laminar ending; IMA, intramuscular array; IPAN, intrinsic primary afferent neuron.