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RESEARCH HIGHLIGHT

# Gut nociceptors: sentinels promoting host defense

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**Gut-innervating nociceptive neurons detect noxious mechanical and chemical stimuli within our gut, constituting the start of the 'gut pain' pathway. In a recent paper in *Cell*, Lai et al. report that these nociceptors also play major roles in sensing intestinal bacterial pathogens as well as defending the host by limiting pathogen colonization and invasion.**

Our gastrointestinal tracts are incredibly dynamic signaling environments, regulated by neuronal, epithelial and immune processes.[1] Peristaltic motility is controlled by the enteric nervous system, whilst sensory information is detected and sent to the CNS by extrinsic sensory afferent pathways of vagal or spinal origin.[1] The gut is innervated by different classes of sensory neurons, which detect and convey the full repertoire of sensory information within the gut.[2] Chief amongst those neurons are nociceptors, which possess the molecular machinery to detect and transmit noxious mechanical and chemical stimuli.[3] Gut-innervating nociceptors become hypersensitive in response to inflammatory mediators and display chronic hypersensitivity in pathological conditions.[4] This hypersensitivity leads to neuroplasticity within sensory pathways, which has been implicated in chronic abdominal pain associated with prevalent gut disorder such as irritable bowel syndrome (IBS).[5] To add to the sentinel function of these nociceptors, a new study published in *Cell* by Lai et al. presents findings supporting a role for gut-innervating nociceptors in host defence in response to oral *Salmonella enterica serovar Typhimurium* (*Salmonella*) infection.[6] This is an important discovery as invading enteric pathogens, such as *Salmonella*, pose a threat to gut homeostasis by traveling through the gut to transiently colonize the distal small intestine, including the ileum. *Salmonella* invades the host predominantly through ileal Peyer's patches by exploiting microfold cells as entry points. If colonization and dissemination of *Salmonella* to systemic sites occur, there are significant risks of morbidity and even mortality for the host.[7]

Using a combination of genetic and pharmacological approaches, Lai et al. eliminated TRPV1-expressing (TRPV1+) extrinsic sensory neurons. Orally infecting these TRPV1+ neuron-ablated mice with *Salmonella* resulted in significantly greater *Salmonella* load within the ileum, wider spread of *Salmonella* to spleen and liver, and more body weight loss compared with mice with their full complement of nociceptors (Fig. 1). Using targeted ablation of either vagal or spinal TRPV1+ neurons the authors showed that only the spinal TRPV1+ neurons, those with cell bodies within the dorsal root ganglia (DRG), contributed to host defense against *Salmonella*. This difference between spinal and vagal pathways in itself is intriguing, particularly as vagal TRPV1+ neurons play a critical role in modulating innate immune responses against methicillin-resistant *Staphylococcus aureus* lethal pneumonia.[8] In contrast, spinal TRPV1+ nociceptors innervating the skin elicit a local immune response that augments host defense to both *Staphylococcus aureus* and *Candida albicans*.[9]

Interestingly, Lai et al. found that nociceptors innervating the ileum did not appear to regulate specific immune processes, or transcript abundance of epithelial tight junctions. However, the nociceptor-ablated mice had major differences in their ileal microbiome composition, particularly reduced levels of segmentous filamentous bacteria (SFB), a gut microbe that mediates resistance to *Salmonella* infection. Utilizing two different strains of mice (one lacks SFB and one with high SFB levels), Lai et al. showed that *Salmonella* infection was more severe in mice lacking SFB, confirming that SFB can protect against *Salmonella* infection. It is also shown that ablating TRPV1+ DRG neurons in SFB-lacking mice resulted in a similar severity of *Salmonella* infection compared with SFB-lacking mice with their full complement of nociceptors. In contrast, ablating TRPV1+ DRG neurons in the high-SFB mice increased *Salmonella* infection, thereby demonstrating that nociceptors regulate SFB to mediate resistance against *Salmonella* infection.

The question then arises as to how nociceptors regulate SFB. In an elegant series of studies Lai et al. showed that nociceptor ablation leads to increased numbers of microfold cells within ileal Peyer's patches, which occurs independent of SFB levels. Furthermore, specifically targeting and transiently depleting the microfold cells resulted in higher SFB levels. This suggests a cascade arrangement whereby nociceptors suppress baseline numbers of microfold cells, which correspondingly results in elevated levels of SFB. Therefore, nociceptor suppression of microfold cells protects against *Salmonella* infection via two mechanisms: (1) by reducing the number of 'entry points' (the microfold cells themselves) and (2) increasing the amount of SFB, which mediates resistance to *Salmonella* infection.

The final questions arise as to how TRPV1+ DRG nociceptors detect *Salmonella* and how they regulate microfold cell function. Lai et al. showed that TRPV1+ DRG nociceptor cell bodies, in isolation of other epithelial or immune components, are directly activated by *Salmonella*. Whilst activation of these nociceptors will result in 'alarm' signals being sent to the CNS, in the context of the current study this will also result in the release of calcitonin gene-related peptide (CGRP) from nociceptor peripheral terminals within the wall of the ileum. This is important as mice lacking CGRP, particularly the CGRPα isoform expressed by nociceptors, have significantly reduced SFB levels in ileal mucosa at baseline compared to their wild-type counterparts.[6] Correspondingly, *Salmonella* infection in mice lacking CGRPα results in significantly higher *Salmonella* loads in the ileum, spleen and liver. Therefore, CGRP, probably via local diffusion rather

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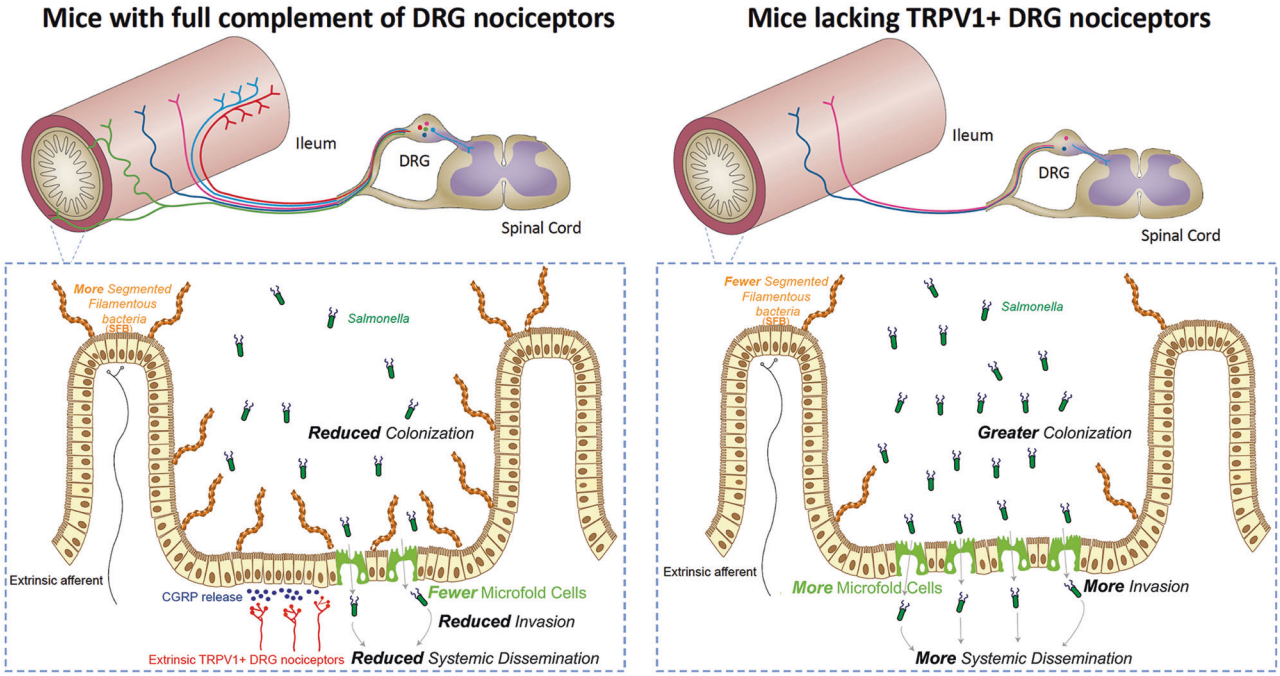


**Fig. 1 Spinal gut-innervating nociceptors play a crucial role in detecting *Salmonella* infection and regulating host defense.** *Salmonella* activates TRPV1+ nociceptors within the ileum resulting in the release of CGRP from nociceptor terminals. Increased levels of CGRPα reduces the density of Peyer's Patch microfold cells, limiting the ability of *Salmonella* to invade. Reducing the number of microfold cells reciprocally increases the levels of SFB, a gut microbe residing on villi within the ileum that mediates resistance to *Salmonella* infection. Therefore, gut-innervating nociceptors are crucial components of a sentinel system that 'batten down the hatches' in response to enteric pathogens. (Figure adapted from Lai et al.[6]).

than direct neuronal cell synaptic connections as seen in other intestinal signaling processes,[10] appears to be the key integrator between nociceptors and microfold cells. This key interaction governs ileal homeostasis and SFB levels to impact the susceptibility of the host to *Salmonella* infection.

Overall, the study by Lai et al. shows that nociceptors innervating the ileum detect *Salmonella*, presumably at the initial onset of infection, and release the neuropeptide CGRP from their peripheral terminals. CGRP, via a mechanism which remains to be determined, suppresses the density of microfold cells in ileal Peyer's patches and increases SFB within the ileum to resist *Salmonella* infection. Therefore, gut-innervating nociceptors are crucial components of a sentinel system that 'batten down the hatches' (Peyer's patches) in response to enteric pathogens. As nociceptor hypersensitivity is linked to chronic disorders such as IBS, in light of the current findings, it is intriguing to postulate that such changes might also be a host response to limit future enteric infections in these afflicted patients. Lastly, as CGRP is implicated as the crucial integrator in nociceptor-mediated host defense to *Salmonella* infection in the ileum, manipulation of CGRP levels may have the potential to therapeutically regulate the host susceptibility to the infection.

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