RESEARCH HIGHLIGHT

How pain sensors make the gut weep

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Cell Research (2023) 33:339–340; https://doi.org/10.1038/s41422-022-00768-x

Nociceptors in the gut are widely known for transmitting pain signals to the spinal cord. Yang et al. now identified a novel microbiome-nociceptor-goblet cell crosstalk that protects the intestinal epithelial barrier by triggering mucus secretion.

The intestinal tract is equipped with an epithelial barrier that spatially separates the microbiome and the immune system to avoid unnecessary immune activation. Moreover, the gut epithelium itself is covered by a mucus layer providing a physical barrier to the microbiome. The major building blocks of mucus are MUC2 mucins, which are secreted by the goblet cell.[1] The mechanisms modulating and controlling goblet cell function are however poorly understood. In a recent issue of *Cell*, Yang et al. elegantly revealed that microbial-mediated activation of Nav1.8$^+$ nociceptors innervating the gut promoted MUC2 mucin secretion by goblet cells via a CGRP-Ramp1 axis during homeostasis and in the context of colitis.[2]

Initial evidence indicating a role for host goblet cell-microbiota communication in the maintenance of the mucus layer came from studies in germ-free (GF) mice. Whereas the colonic inner mucus layer of conventionally-raised mice was impenetrable to microorganisms, that of GF mice was more permeable and thinner.[3] The continuous production of mucus promotes the clearance of microorganisms to prevent colonization by pathogens. The crucial importance of the mucus layer is exemplified by the fact that MUC2-deficient mice succumb following a normally self-resolving *C. rodentium* infection and also develop spontaneous colitis.[4,5] In line with this, the inner mucus layer of ulcerative colitis (UC) patients with active disease is reduced, resulting in increased bacterial penetration.[6] Taken together, the mucus layer constitutes an important player in the context of colitis and infection; therefore new insights into the crosstalk between the microbiome and goblet cells is undoubtedly of key importance.

Previous work by Chiu et al. showed that bacterial products can directly activate sensory nerve endings, more specifically nociceptors.[7] Gut nociceptors are among the first to react against invasive pathogens and are equipped with a plethora of receptors, including transient receptor vanilloid 1 (TRPV1) and voltage-gated sodium channel Nav1.8. Bacterial products induce calcium influx and generate action potentials in these nociceptors, eliciting pain. In addition, these nociceptors regulate inflammation through release of neuropeptides such as substance P (SP, encoded by *Tac1*) and CGRP (encoded by *Calca*) at their nerve terminals.[7] Yang et al. now discovered a previously unrecognized crosstalk between the gut microbiome, nociceptors and goblet cells.[2] Chemogenetic stimulation of Nav1.8$^+$ nociceptors increased colonic mucus thickness, while genetic ablation of Nav1.8$^+$ nociceptors reduced mucus growth. Single-cell RNA sequencing revealed that goblet cells highly expressed RAMP1, the co-receptor of CGRP. Genetic deletion of the neuropeptide CGRP or its receptor showed that nociceptor-goblet cell crosstalk acted via CGRP-RAMP1 signaling. They further underscored the crucial importance of the gut microbiome-nociceptor-goblet cell crosstalk by showing that fecal transplantation from specific pathogen-free (SPF) mice into GF mice restored the colonic mucus thickness, a finding that was lost in nociceptor-deficient GF mice.[2] These findings indicate that the microbiome triggers mucus secretion, a process mediated by Nav1.8$^+$ nociceptors (Fig. 1).

In a next step, Yang et al. further attempted to unravel the interaction between the microbiome and nociceptors.[2] The authors observed that fecal supernatant from SPF mice induced more calcium influx into the dorsal root ganglion (DRG) cultures and caused more CGRP release than that from GF mice. Moreover, chemical TRPV1 denervation decreased CGRP release and mucus thickness in conventionalized GF mice. Although of great interest, it remains to be further elucidated how commensal-derived products promote the activation of gut Nav1.8$^+$ and TRPV1$^+$ nociceptors.[2] One potential mechanism could be via the production of short chain fatty acids or other mediators produced by the microbiome during the fermentation of fermentable oligo-, di-, monosaccharides and polyols (FODMAPs). Indeed, feeding of FODMAPs provoked mucus discharge, which was associated with an increased number of mast cells.[8] It however remains to be determined whether mast cells can directly communicate with goblet cells or they provoke mucus secretion indirectly via activation of TRPV1$^+$ nociceptors.

Further evidence underscoring a crosstalk between the microbiome and nociceptors was provided by the observation that chemical and chemogenetic ablation of Nav1.8$^+$ or TRPV1$^+$ nociceptors induced microbial dysbiosis.[2,9] Yet, how nociceptors exactly alter the gut microbiome composition remains an enigma. Possibly, the reduced thickness of the mucus layer impacts on nutrient availability for the commensal bacteria, thereby causing changes in microbiome composition. Nonetheless, microbial dysbiosis is a key feature of several intestinal diseases including IBD. Interestingly, Zhang et al. showed that mucosal biopsies of IBD patients have a dysregulated pattern of TRPV1, suggesting that defective nociceptors could be a possible cause of microbial dysbiosis and mucus defects observed in IBD patients.[9] Conversely, increased mucus secretion is one of the clinical hallmarks of irritable bowel syndrome (IBS) patients. Notably, an increase in both number and sensitization of TRPV1$^+$ nociceptors has been reported in gut biopsies of IBS patients.[10,11] To what extent these observations can be explained by the nociceptor-goblet cell axis remains to be studied.

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Published online: 10 January 2023

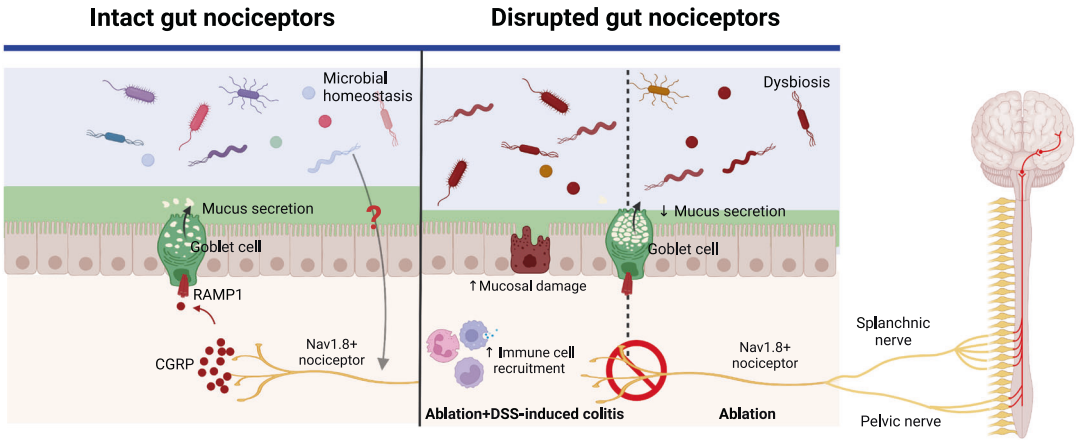

Fig. 1 Nociceptors possess tissue-protective properties during homeostasis and intestinal inflammation. (Left) Microbial products activate Nav1.8$^+$ nociceptors, causing the release of CGRP. This neuropeptide in turn acts on goblet cells expressing RAMP1, the CGRP co-receptor, provoking the secretion of mucin. (Right) Ablation of Nav1.8$^+$ nociceptors alters the microbiome composition in the gut during homeostasis and aggravates mucosal inflammation in a model of DSS-induced colitis.

Besides dietary and bacterial products, Nav1.8$^+$ and TRPV1$^+$ nociceptors also sense immunological cues and regulate inflammation accordingly. In particular, chemical or chemogenetically silencing of Nav1.8$^+$ and TRPV1$^+$ nociceptors increased mucosal inflammation in a model of chemically-induced colitis. Administration of SP or CGRP reversed disease severity in nociceptor-deficient, *Calca*- and *Tac1*-deficient mice, highlighting that nociceptor-derived CGRP and SP have tissue-protective properties during colitis.[2,9] These studies are in line with previous work showing that CGRP participates in mucosal immunity. Whether the immunoregulatory function of nociceptors is limited to SP and CGRP remains to be elucidated, as other neuropeptides such as VIP and galanin can be released. Notably, nociceptors are not the sole source of SP and CGRP in the intestine. Cholinergic vagal and enteric neurons also produce SP and CGRP,[12] but it remains to be elucidated whether they participate in neuron–goblet cell crosstalk.

Taken together, Yang and colleagues discovered a novel and exciting tissue-protective role of nociceptors.[2] These nerves maintain the mucus barrier via their close interaction with goblet cells involving the CGRP-Ramp1 axis and seem to closely monitor the composition of the microbiome. This insight may be of great importance to better understand immune-mediated diseases such as IBD and IBS and pave the way for further research on the microbiome–nociceptor–goblet cell axis.

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ACKNOWLEDGEMENTS

This work was supported by the European Research Council (ERC) Advanced Grant (ERC-833816-NEUMACS) to G.E.B. N.S. is supported by a postdoctoral research fellowship of FWO (12V3619N).

ADDITIONAL INFORMATION

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