NEUROGASTROENTEROLOGY

A role for nociceptor neurons in gut defence

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A new study published in *Cell* has revealed that gut-innervating nociceptors, which have roles in mediating pain responses, also play a part in host mucosal protection and limiting invasion against enteric pathogens in mice. These findings could lead to novel targets to treat infectious and inflammatory diseases of the gut.

The gastrointestinal tract is a heavily innervated organ. Among the sensory neurons that innervate the gut are nociceptors, which detect noxious stimuli and disturbances and then mediate protective sensations and neural reflexes such as visceral pain and diarrhoea. However, the role of nociceptors in enteric infections is unclear, as is whether these neurons can crosstalk with microorganisms and intestinal cells to facilitate host mucosal defences.

Prior work by the researchers and others had shown that sensory neurons can detect microorganisms and their products. Notably, in skin, nociceptors could be directly activated by bacteria to produce pain, also releasing neuropeptides to affect inflammation and an immune response. However, whether a similar type of signalling exists in the gut was not fully appreciated. "We were excited to launch this project because we wanted to ask whether the nervous system played a role during gut infections and inflammation," explains lead author Isaac Chiu. "We focused on the major gut pathogen *Salmonella enterica* serovar Typhimurium (STm) and the role of neuroimmune interactions during enteric pathogen infection."

The investigators performed a range of experiments targeting gut-innervating nociceptors in mice using genetic and pharmacological approaches, and then examined the responses to STm gut infections. For example, neurons positive for TPRV1 (a nociceptive ion channel that detects heat and capsaicin) from both vagal ganglia and dorsal root ganglia (DRG) were specifically targeted using differential injections of drugs. "We adopted this approach because we wanted to understand for the first time how neural input from gut-extrinsic sensory neurons affected infection," says Chiu.

For their model of infection, mice were orally gavaged with STm, which invade intestinal tissues before spreading to other organs. The major site of STm invasion in the gut is through microfold (M) cells in Peyer's patches. Thus, following experimentation, the small intestine, Peyer's patches and peripheral organs were examined for bacterial load, and microscopy was performed to inspect for variation in the locations of nerves.

"We found that gut-innervating nociceptor neurons have a major role in protecting mice from STm infection," reports Chiu, adding that this process occurs by two mechanisms. In the first mechanism, nociceptors were found to regulate the density of M cells on the top of Peyer's patches through release of the neuropeptide calcitonin gene-related peptide (CGRP). By suppressing numbers of M cells in response to the presence of STm and limiting the entry point of infection, nociceptors protected against STm colonization and dissemination from the gut. In the second mechanism, DRG nociceptors were found to be required to maintain levels of segmented filamentous bacteria (SFB), which are normally resident in the mouse gut and protective against STm. Levels of SFB were substantially decreased in mice in the absence of nociceptor neurons, and levels of SFB were also regulated by CGRP.

"These findings are very exciting and we are interested in further understanding how peripheral neurons regulate gut immunity," concludes Chiu. Looking ahead, the researchers would like to investigate whether neuronal regulation of M cells could play a part in other immunological processes and in infections by other bacterial or viral pathogens that utilize M cells as entry points.

The researchers are also interested in whether nociceptors crosstalk with other types of immune or epithelial cells in the gut. "Is there biogeographical specificity so that neurons talk to different types of immune cells in different regions of the gastrointestinal tract?" asks Chiu, adding that they are also interested in determining whether this neuro-immune crosstalk has a role in colitis or other inflammatory conditions.

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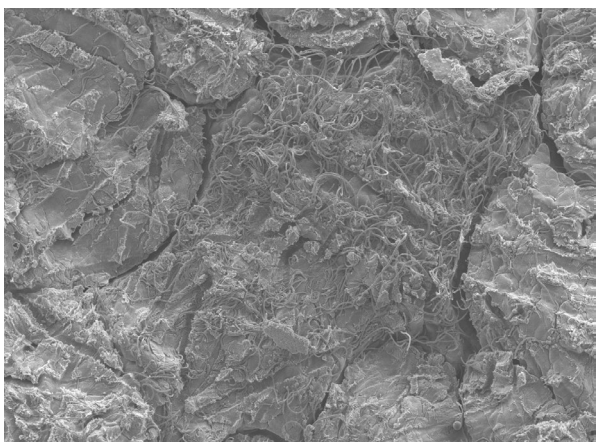

Scanning electron microscopy image shows a dense population of segmentous filamentous bacteria attached to a follicle of a Peyer's patch from the ileum of a mouse. Nociceptor neurons regulate levels of these bacteria, which are protective against *Salmonella* invasion. Image courtesy of I. M. Chiu, Harvard Medical School, USA.

ORIGINAL ARTICLE Lai, N. Y. et al. Gut-innervating nociceptor neurons regulate Peyer's patch microfold cells and SFB levels to mediate *Salmonella* host defense. *Cell* https://doi.org/10.1016/j.cell.2019.11.014 (2019)