Microbiology

Gut pain sensors help to combat infection

Romana R. Gerner & Manuela Raffatellu

The mammalian gut must defend against a variety of infectious agents. Neurons, cells not usually thought of as first-responders during infection, are now found to aid the gut's barrier function and stop bacteria from spreading elsewhere.

The recognition and neutralization of harmful bacteria in the gut is generally thought to be orchestrated by epithelial and immune cells. Writing in *Cell*, Lai *et al.*[1] report that a subset of gut neurons also have an unexpected crucial role in the intestinal response to infection.

The gut is exposed to food, antigens (molecules that can trigger an immune response if they are recognized as 'non-self'), resident microbes that are normally harmless (commensal microbes) and harmful microbes (pathogens). Thus, gut cells have the difficult task of discerning friend from foe. Cooperative interactions between epithelial cells and immune cells are key to managing this complex balancing act, coordinating tolerance to food antigens and to commensal microbes, but initiating protective immune responses against pathogens. Nerve cells in the gut (comprising the enteric nervous system) can sense microbe-derived molecules, and these neurons interact with epithelial cells and immune cells to promote defence responses against microbes[2].

The human enteric nervous system encompasses a complex network of an estimated 10^8 neurons, which are essential for regulating many gut functions, including blood flow and the movement of the intestine's contents[3]. Moreover, certain subsets of these nerve cells interact closely with and modulate components of the gut's immune system[4]. One such type of neuron is called a nociceptor. Nociceptors elicit the perception of pain or discomfort in response to potentially harmful stimuli such as intense heat and cold, reactive chemicals or mechanical injury[5]. They also directly detect pathogens and pathogen-produced molecules, which can evoke a sensation of pain during infection[6]. Whether nociceptors contribute directly to impeding bacterial invasion of host tissues has been a matter of speculation.

Salmonella is a pathogenic bacterium that is a frequent cause of food-borne illness. It can trigger a variety of conditions, ranging from inflammatory diarrhoea (gastroenteritis) to life-threatening complications in situations in which infection spreads beyond the gut to other sites in the body[7,8]. When *Salmonella* reaches the gut, one of the major sites of tissue invasion are the dome-shaped follicles called Peyer's patches (Fig. 1). As key sensors of the gut that aid immune defences, these follicles use immune cells and specialized epithelial cells called M cells to monitor and respond to pathogens and commensal microbes. M cells can take up antigens from the lumen of the gut and transfer them to underlying immune cells[9], which then either initiate a protective immune response to the antigen or tolerate the antigen's presence.

Although Peyer's patches are important for monitoring the contents of the intestine, certain pathogenic agents, including *Salmonella*, norovirus (a common viral cause of gastroenteritis) and prions (infectious, disease-causing proteins), exploit M cells as sites of tissue entry[10,11]. Notably, although Peyer's patches are adjacent to neurons, including nociceptors, the functional consequences of

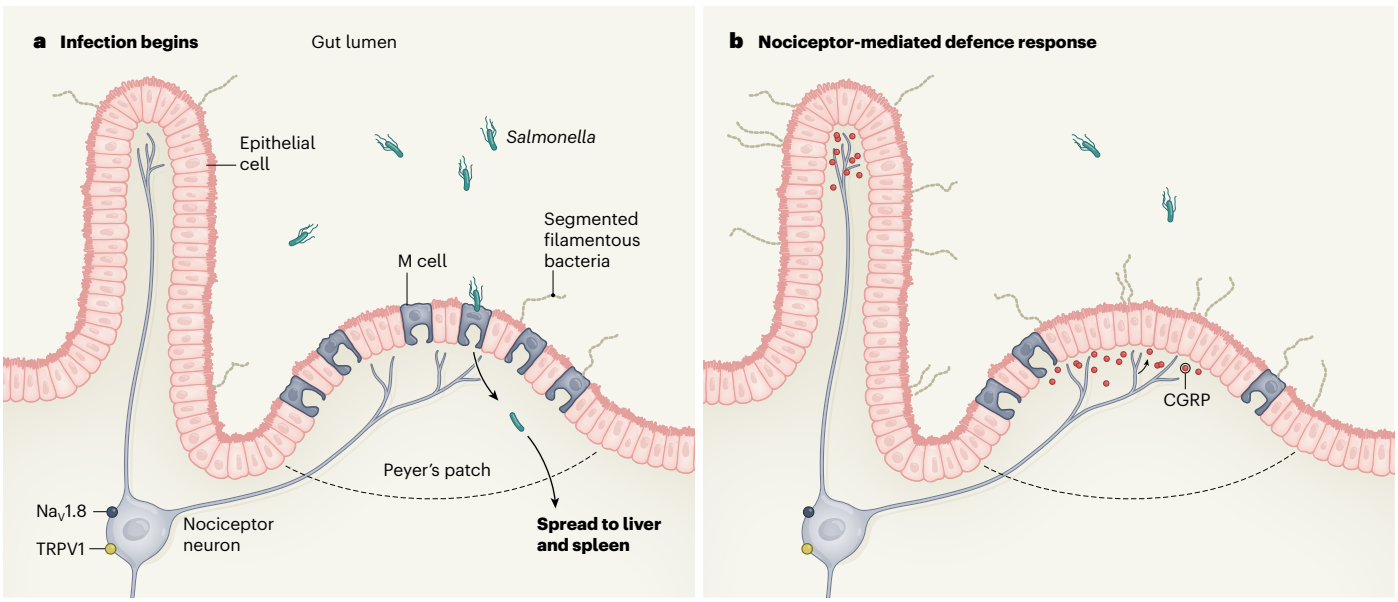

Figure 1 | Neurons in the mammalian gut help to defend against bacterial infection. Lai *et al.*[1] report that a type of gut neuron, called a nociceptor, which expresses the proteins TRPV1 and $Na_V1.8$, can thwart infection by *Salmonella* bacteria in mice. **a**, *Salmonella* can invade gut tissue by leaving the gut lumen to enter M cells — specialized epithelial cells in a region called a Peyer's patch. These microbes can then spread elsewhere. Segmented filamentous bacteria (SFB), which are normally present in the gut and can bind to M cells or other gut epithelial cells, can help to limit *Salmonella* infection[13]. **b**, The authors report that these nociceptors orchestrate a defence response to *Salmonella* infection, the hallmarks of which include a decrease in the number of M cells and an increase in SFB colonization of the gut. These changes were associated with a decrease in *Salmonella* infection and diminished spread of the bacteria beyond the gut. Lai *et al.* report that nociceptor secretion of the neuropeptide CGRP regulates the number of M cells, along with SFB levels.

this close proximity were not fully understood previously.

Lai *et al*. assessed the role of nociceptors in the gut of mice infected with the pathogen *Salmonella enterica* serovar Typhimurium. The authors report that the presence of a subset of gut nociceptors (specifically, those that express the ion-channel proteins TRPV1 and $Na_V1.8$) protect the gut against invasion by *Salmonella* and the subsequent spread of this bacterium to sites such as the liver and spleen. Intriguingly, the authors found that the protective effects of nociceptors were not mediated by well-known antimicrobial defence mechanisms, such as activation of immune cells or alterations in the levels of antimicrobial peptides that are produced by gut cells. Instead, during infection with *Salmonella*, these nociceptors orchestrated a reduction in the number of M cells. Because M cells are a key entry point for *Salmonella*, this reduction would probably have the consequence of reducing the surface area available for *Salmonella* to invade.

The authors analysed the composition of gut bacteria in the absence of *Salmonella* infection, using mice with gut nociceptors that were genetically engineered to lack either TRPV1 or $Na_V1.8$ channel proteins. Compared with animals that expressed these proteins, both types of engineered mouse had lower levels of segmented filamentous bacteria (SFB), a group of commensal microbes that attach to gut epithelial cells, and particularly to M cells[12]. Such commensal bacteria are crucial for providing resistance against gut colonization by pathogens, including *Salmonella*[13].

Lai and colleagues investigated whether there was a connection between a decrease in M cells and the extent of SFB colonization of the Peyer's patches. The authors demonstrated that M-cell depletion mediated by nociceptors, or triggered through an antibody-mediated experimental approach, led to an increase in this colonization, suggesting that the number of M cells can modulate SFB colonization in the gut (although the exact mechanisms responsible were not fully determined). This outcome was beneficial because it limited *Salmonella* infection, presumably because the higher presence of SFB and the depletion of M cells together resulted in a reduction of invasion sites available for *Salmonella*. Finally, Lai *et al*. report that when TRPV1-expressing nociceptors encountered *Salmonella*, the neurons released a neuropeptide called CGRP. This small molecule enables communication between cells. CGRP was directly able to regulate M-cell abundance and function, as well as to regulate SFB levels in the gut.

The authors have uncovered a previously unrecognized role for nociceptors in host defence against *Salmonella* infection. These remarkable findings reveal a complex loop of interactions between epithelial cells, neurons and microbes in the mammalian gut, adding another layer of complexity to our understanding of gut immunity. Whether nociceptor-mediated responses help to defend against a variety of other microbial pathogens remains to be determined. Indeed, nociceptors have been reported to protect mice during infection by the bacterial pathogen *Citrobacter rodentium*[14].

A key area for future investigation will be to determine whether Lai and colleagues' findings have relevance for human health. For example, one area that would be worth studying is whether long-term use of pain-blocking opioid drugs, such as morphine, might affect nociceptor-mediated antibacterial defence. This is of interest because nociceptors are the main target of opioids, and administering morphine to mice changes the gut's microbial composition[15,16]. Moreover, morphine use promotes the spread of certain types of microbe (Gram-negative bacteria) from the gut to elsewhere in the body, a process that can lead to sepsis, a potentially life-threatening immune response to infection[15,16]. Future research that explores interactions between neurons and immune cells during infection could uncover further exciting findings that will profoundly influence our understanding of host defence.

"These remarkable findings reveal a complex loop of interactions between epithelial cells, neurons and microbes."

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Cancer genetics

Not all driver mutations are equal

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A study of cancer-associated mutations in normal endometrial glands of the uterus has now been performed using whole-genome sequencing. The analysis sheds light on the early changes that lead to invasive disease. **See p.640**

Understanding how normal tissues give rise to cancer is crucial for improving prevention and early detection of this deadly disease. Over the past two decades, the genomic profiles of most types of invasive cancer have been catalogued; however, similar profiling of normal tissues presents a unique set of challenges. Cancer tissues are often abundantly available from biopsies or surgery, but samples from normal tissues tend to be much smaller, and specimen-collection practices are less well established, making it hard to gather high-quality material. Moore *et al*.[1] overcome these challenges on page 640, and successfully catalogue cancer-driving mutations in normal endometrial glands.

Endometrial glands are abundant in the lining of the uterus, where they secrete hormones and other substances that are essential for normal menstruation and embryonic development. Endometrial cancer is the sixth most common cancer in women worldwide, with more than 382,000 cases annually[2]. The mortality rate has increased over the past decade[3], heightening the need for prevention and early detection of this disease.