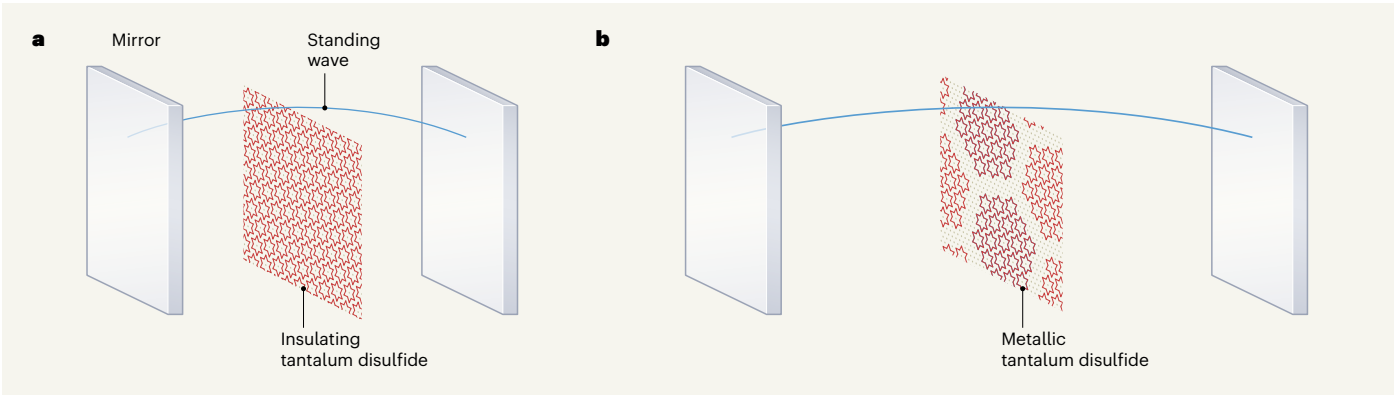

Figure 1 | Inducing an insulator-to-metal transition. The atoms in tantalum disulfide are arranged in star-shaped clusters that reorganize when temperature changes the material from being electrically insulating to metallic. **a**, Jarc *et al.*[4] placed a thin sample of insulating tantalum disulfide between two semi-reflecting metallic mirrors that were configured to generate standing waves. **b**, The authors found that they could turn the material into a metal by changing the separation (or alignment; not shown) of the mirrors, at a fixed temperature.

is isolated from its surroundings. However, according to quantum electrodynamics, the cavity is not devoid of photons. It is a vacuum, but there are electrodynamic fluctuations present, and these fluctuations manifest themselves as 'virtual' photons flitting in and out of existence. Under certain conditions, these photons can combine with excitations in the material and possibly change the energy of the states accessible to it, altering the macroscopic physical properties of matter[2]. Whereas the Purcell-like effect is known as the weak-coupling limit, the alternative is called the strong-coupling limit.

To identify the mechanism at play in tantalum disulfide, Jarc and colleagues simultaneously monitored the temperature inside and outside the cavity while changing the alignment of the mirrors. To do so, they placed a minuscule thermometer in direct contact with the material to minimize the disturbance on the cavity environment — a precise and effective means of obtaining this information. Their measurements showed that the temperature of the sample changed considerably in the cavity. This suggests that the authors' ability to tune the insulator-to-metal transition was made possible by the Purcell-like effect, in which the cavity quantum electrodynamics mediate the exchange of heat between the sample and its surroundings.

Jarc and co-workers' results serve as an exceptional proof of principle, showcasing how cavities with no artificial illumination can trigger phase transitions. However, numerous questions remain regarding the mechanism behind the detected phenomena. The Purcell-like scenario falls short of providing a quantitative explanation for the substantial changes of the sample's temperature in the cavity environment.

This raises the enthralling possibility that strong-coupling phenomena arising from the vacuum photons might also be relevant, even though the authors' cavities are not designed to operate in the strong-coupling limit. Indeed, the collective excitations that naturally arise in tantalum disulfide at gigahertz frequencies could potentially enhance the interaction between cavity and sample, driving the system to this limit. Verifying this possibility would require identification of these excitations, which are probably related to collective deformation modes associated with the star-shaped clusters of tantalum disulfide[8].

Jarc and colleagues' discovery represents a rigorous and crucial stride towards understanding the electrodynamics of complex solids embedded in an optical cavity. More generally, investigations into the effect that vacuum fluctuations have on phase transitions are ongoing[9], and could have wide-ranging implications. For example, evidence that vacuum photons affect macroscopic quantum phenomena such as long-range order, coherence and entanglement would bring into question the way in which these effects manifest in cooperative quantum matter. The search in the dark continues.

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The author declares no competing interests.

Immunology

Inflammation insights for a deadly bacterium

Klaus Aktories

Infection by the bacterium *Clostridioides difficile* can be fatal in a clinical setting. Insights into the molecular mechanisms underlying such infection might offer targets for the search to develop new treatments. **See p.611**

A key unwanted complication of antibiotic use is that disrupting the natural bacterial community in the human gut might enable infection by the harmful bacterium *Clostridioides difficile*. On page 611, Manion *et al.*[1] shed light on some of the inflammation-associated events that occur during *C. difficile* infection (CDI).

The proliferation of *C. difficile* in the gut can lead to mild to severe diarrhoea or to pseudomembranous colitis, a severe illness with potentially lethal complications such as toxic megacolon or bowel perforation[2]. Moreover, the frequency of recurrent infections and the

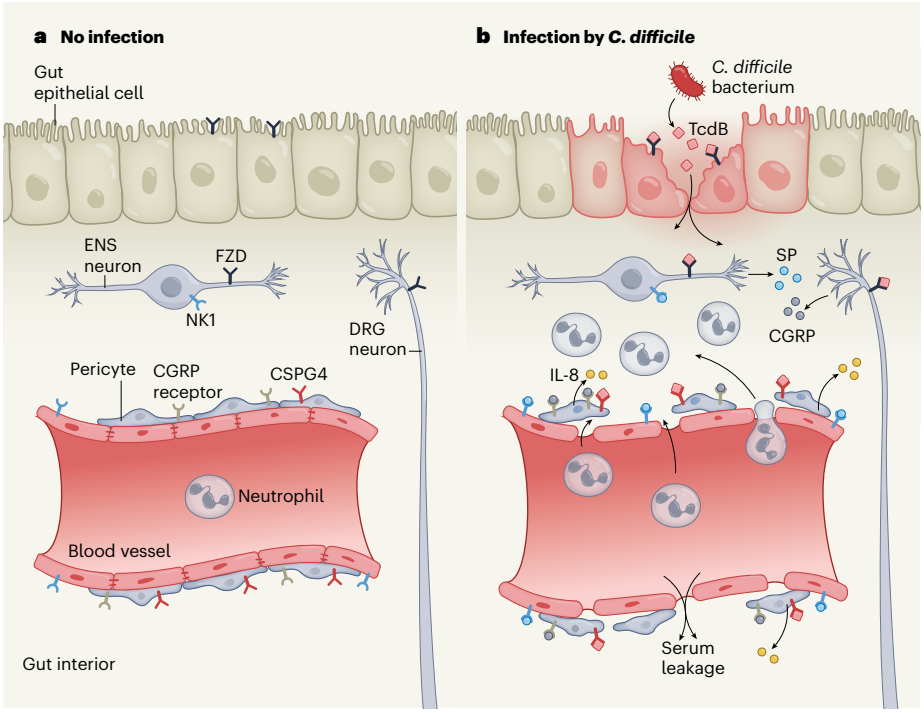

Figure 1 | How the gut bacterium *Clostridioides difficile* causes inflammation associated with sensory neurons. a, Manion *et al.*[1] examined sensory neurons called enteric nervous system (ENS) neurons and dorsal root ganglion (DRG) neurons, which have their nuclei inside and outside the gut, respectively. Both types of neuron have Frizzled (FZD) receptors, as do the epithelial cells that line the gut. ENS neurons also have NK1 receptors, as do blood vessels. The authors examined neutrophil cells of the immune system and pericytes, cells that wrap around micro blood vessels and regulate the barrier between the bloodstream and the gut. Pericytes have CGRP and CSPG4 receptors. **b**, *Clostridioides difficile* releases TcdB toxin, which binds to FZD and CSPG4 receptors. TcdB can target epithelial cells, enabling the toxin to enter internal gut tissues. There, TcdB induces inflammation mediated by neuronal release of the neuropeptides CGRP (which binds to the CGRP receptor) and substance P (SP), which binds to the NK1 receptor. During infection, pericytes release the pro-inflammatory molecule IL-8. The various inflammatory molecules increase blood-vessel permeability, enabling liquid (serum) to leave blood vessels and resulting in tissue swelling. The tissue becomes infiltrated by neutrophils — a hallmark of disease associated with *C. difficile*.

emergence of hypervirulent *C. difficile* strains make CDI one of the most threatening bacterial problems in a clinical setting.

Two toxins made by the bacterium, TcdA and TcdB, are the major factors that drive disease associated with CDI. These toxins function by inactivating certain Rho-family proteins through a modification process called glucosylation[2]. Although much progress has been made in the analysis of these toxins and their receptors[3], the mechanisms that trigger intestinal inflammation associated with the infection are still largely mysterious.

Manion and colleagues report that *C. difficile* TcdB (which seems to be the main toxin) attacks neurons and cells called pericytes that attach to the walls of blood vessels. This attack causes neurogenic inflammation[4], a disease-associated process in which local release of inflammatory mediator molecules — such as the neuropeptides CGRP and substance P (SP) — from sensory neurons contributes to inflammation and causes blood-vessel dilation, release of plasma from blood vessels, tissue swelling and infiltration by immune cells called neutrophils (Fig. 1).

Examining a mouse model, Manion *et al.* report that animals lacking a functional copy of the genes *Tac1* (encoding the peptide precursor needed to produce SP), *Nk1r* (encoding the SP receptor NK1) or *Calcb* (encoding a form of CGRP called CGRPβ) show a markedly reduced inflammatory response to TcdB compared with that in animals that had functional copies of the genes. Accordingly, the administration of SP to mice lacking a functional copy of *Tac1* restored TcdB-induced inflammation.

Manion and colleagues show that sensory neurons that innervate the mouse colon and that have their nucleus either inside the gut (enteric nervous system (ENS) neurons) or outside the gut (dorsal root ganglion (DRG) neurons) possess the receptor Frizzled (FZD), which is a TcdB receptor[5]. The authors examined DRG neurons grown *in vitro* and found that exposure to TcdB resulted in SP release, whereas mutant versions of TcdB that are unable to glucosylate Rho proteins or to bind to FZD did not induce SP secretion.

Another known receptor for TcdB is CSPG4 (ref. 6), which is not expressed in neurons but is highly expressed on pericytes, as shown by Manion and colleagues. These cells decisively regulate blood-vessel function and control the migration of immune cells from blood vessels into tissue through the release of inflammatory molecules called cytokines, such as IL-8 (ref. 7).

The authors carried out microscopy analysis which revealed that pericytes and intestinal neurons establish a tightly connected network in the gut. Efforts to culture gut pericytes from mice failed, so the authors tested human-brain pericytes instead. TcdB exposure resulted in IL-8 release and, crucially, CGRP exposure also drove release of IL-8 from these cells. Thus, CGRP released from sensory neurons that are targeted by TcdB enhances IL-8 release from pericytes. Accordingly, TcdB injection into the gut of mice resulted in secretion of the mouse version of IL-8.

To further verify the interplay of neurons and pericytes in neurogenic inflammation induced by TcdB, the researchers used a mouse footpad injection model that measures inflammation through the assessment of swelling. TcdB injection under mouse skin led to rapid swelling. However, blockade of SP using an inhibitor of the NK1 receptor prevented swelling, and TcdB did not induce swelling in mice lacking a functional version of the gene *Tac1*. Because the swelling was still observed in mice lacking a functional version of CSPG4, the authors conclude that targeting neurons through TcdB is sufficient to induce neurogenic inflammation, and that pericytes are probably acting downstream of sensory neurons. In line with this view is the finding that mutant versions of TcdB that do not interact with FZD receptors do not cause inflammation, whereas mutants that are unable to interact with CSPG4 do.

The authors carried out experiments aimed at determining the role of the toxin-induced neurogenic inflammation by transporting the TcdB catalytic domain — the part that enables its toxicity — into peripheral neurons but not into other cells. The authors used a fusion-protein approach, bringing together segments of TcdB and diphtheria toxin (DT). Manion *et al.* generated a fusion toxin containing the catalytic domain of TcdB needed for toxicity and full-length, but non-toxic, catalytically inactive DT, which contained a functional binding and translocation domain that enabled the fusion toxin to enter cells bearing the DT receptor.

Injection of this fusion toxin into the footpads of control mice had no effect (mice normally lack the toxin-sensitive DT receptor[8]), whereas injection of the fusion toxin into mice that express the DT receptor only in peripheral neurons developed the typical signs of neurogenic inflammation. Moreover, although the injection of full-length TcdB into the body cavity of these mice is lethal, injection of the fusion toxin had no effect in

control mice. However, in mice expressing the DT-receptor in peripheral neurons, the fusion toxin induced diarrhoea and colonic tissue damage. In addition, the authors show that the expression of the DT receptor in DRG neurons is sufficient for the fusion toxin to induce neurogenic inflammation in the gut and other hallmarks of CDI.

Clostridioides difficile exploits changes in the host's gut metabolism that occur during CDI to enhance its own proliferation and colonization[9]. Consistent with this, levels of *C. difficile* were reduced in mice lacking a functional copy of *Tac1* compared with those in animals with a functional copy of the gene. Similarly, in mice lacking a functional copy of the gene *Calcb*, levels of *C. difficile* were reduced compared with those in animals with a functional copy of the gene.

Finally, the researchers address the therapeutic implications of their findings. Selective NK1 receptor inhibitors, which block SP signalling, are available to counteract severe vomiting induced by anticancer drugs, for example. In addition, antibodies against CGRP (such as fremanezumab) or inhibitors of CGRP receptors (such as olcegepant) have been developed for the treatment of migraine. All of these drugs, the authors found, greatly reduced signs of disease in the case of TcdB gut injection and also in the CDI mouse model.

Although FZD receptors have a key role in infection mediated by many subtypes of TcdB, some hypervirulent strains of *C. difficile* exist, such as ribotype 027. These strains are characterized by the toxin TcdB2, which does not bind to FZD. However, the injection of TcdB2 and also TcdA induced footpad swelling that can be blocked by an NK1 receptor inhibitor, suggesting a crucial role for neurogenic inflammation regardless of the specific toxin subtype and receptor type.

This study fills a key gap in our knowledge of the disease underlying CDI and offers new perspectives on treatment options to explore. It is worth noting, too, that the experiments provide good support for previous findings[10] regarding the importance of SP for the effects mediated by TcdA.

Many questions remain unanswered. Investigating the precise role of intestinal pericytes is an exciting topic for future research. The question of why and how *C. difficile* toxins, which inactivate Rho proteins by glucosylation, prompt the release of SP and CGRP should be investigated. Understanding the interactions of the many toxin-sensitive cell populations in the gut over the course of toxin action remains a major challenge to address.

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Photonics

The compact accelerator that confines as it drives

Yelong Wei

A silicon-based device uses laser light to accelerate electrons and simultaneously shape them into a narrow beam. The principle could be used to build microchip accelerators that do away with bulky conventional designs. **See p.476**

Whether they're used for cancer treatment or testing the fundamental tenets of physics, particle accelerators are designed to drive narrow beams of charged particles to extremely high speeds and energies — and they typically take up a lot of space. But what if these speeds and energies could be achieved on a microchip no bigger than a fingertip? One way to do so involves increasing the rate of energy transfer so that the particles can be propelled to high energies over very short distances. On page 476, Chlouba *et al.*[1] report an accelerator that can increase the energy of particles by 43% in just 500 micrometres. Realizing a

From the archive

Studies of behaviour grab the limelight, and Charles Darwin shares ideas about how organ loss might evolve.

50 years ago

The award last week of a Nobel Prize to three animal behaviourists ... marks the full emergence of the study of animal behaviour from one of the less respectable corners of natural history to the forefront of the biological sciences.

From *Nature* 19 October 1973

150 years ago

My father finds that in his letter ... he did not give with sufficient clearness his hypothetical explanation of how useless organs might diminish, and ultimately disappear. I therefore now send you, with his approval, the following further explanation of his meaning. If one were to draw a vertical line on a wall, and were to measure the heights of several thousand men ... against this line, recording the height of each by ... a pin, the pins would be densely clustered about a certain height, and ... their distribution would diminish above and below ... Supposing ... that a race of cattle becomes exposed to unfavourable conditions, my father's hypothesis is that, whilst the larger proportion of the cattle have their horns developed in the same degree as though they had enjoyed favourable conditions, the remainder have their horns somewhat stunted ... If .. horns are useless organs, the cattle with stunted horns have as good a chance of leaving offspring (who will inherit their peculiarity) as their long-horned brothers. Thus, after many generations under the poor conditions, with continual intercrossing of all the members, the symmetry of distribution will be ... restored, but it will have come about through the general removal of *all* the pins downwards, and this will ... have shifted the central cluster. Thus, supposing the hypothesis to be supported by facts (and my father intends to put this to the test ...), there is a tendency for useless organs to diminish and finally disappear, besides those arising from disuse and the economy of nutrition. GEORGE H. DARWIN

From *Nature* 16 October 1873