Somatosensory and autonomic neuronal regulation of the immune response

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Abstract | Bidirectional communication between the peripheral nervous system (PNS) and the immune system is a crucial part of an effective but balanced mammalian response to invading pathogens, tissue damage and inflammatory stimuli. Here, we review how somatosensory and autonomic neurons regulate immune cellular responses at barrier tissues and in peripheral organs. Immune cells express receptors for neuronal mediators, including neuropeptides and neurotransmitters, allowing neurons to influence their function in acute and chronic inflammatory diseases. Distinct subsets of peripheral sensory, sympathetic, parasympathetic and enteric neurons are able to signal to innate and adaptive immune cells to modulate their cellular functions. In this Review, we highlight recent studies defining the molecular mechanisms by which neuroimmune signalling mediates tissue homeostasis and pathology. Understanding the neural circuitry that regulates immune responses can offer novel targets for the treatment of a wide array of diseases.

Host defence
The mechanisms by which an organism protects against infection, including natural barriers, inflammatory reactions, non-specific innate immune responses and specific adaptive immune responses.

Blood–brain barrier
The barrier formed by the CNS capillary endothelium, which restricts non-selective transport of substances, including pathogens and cells, from circulating blood into the CNS extracellular fluid.

Autoimmunity
The conditions in which immune system responses are directed against normal components of an organism or self-antigens.

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https://doi.org/10.1038/s41583-021-00555-4

Both the peripheral nervous system (PNS) and the immune system are engaged in continual surveillance for external threats and internal perturbations that require complex responses to be launched to maintain homeostasis. Traditional dogma has viewed these systems as acting in a separate and parallel fashion to address disparate types of extrinsic hazard, with most clinically significant host defence viewed as being the exclusive domain of an autonomous immune system. The only interplay between these two systems was thought to occur during infection or inflammation of the nervous system, pathological conditions under which the blood–brain barrier is breached and immune cells can access, and thus interact with, the CNS. However, work starting at the turn of the twentieth century and accelerating in recent decades has challenged these assumptions, with an accumulating body of evidence demonstrating that the nervous and immune systems function in a coordinated fashion in multiple physiological and pathological contexts (BOX 1). It is now accepted that the nervous system receives input and stimuli from immune cells and that signals from the brain, via the PNS, act on immune cells to regulate inflammatory responses. Furthermore, it is increasingly clear that peripheral nerves interact closely with immune cells in the gut, lungs, skin and other peripheral organs to form neuroimmune cell units that set into motion inflammatory conditions and maintain tissue homeostasis[1,2].

These neuroimmune signalling mechanisms involve all major branches of the PNS, which can be broadly divided into motor and sensory arms. The somatic motor system provides the body's voluntary motor control and is not the focus of further discussion here. The autonomic nervous system — considered part of the motor branch of the PNS — is further organized into the sympathetic nervous system, the parasympathetic nervous system and the enteric nervous system (ENS), each of which has distinct effector functions in the involuntary control of organ physiology. It is important to note that the ENS also contains primary afferent sensory neurons, motor neurons and connecting interneurons. Somatosensory and visceral sensory neurons provide afferent input throughout the body, allowing the sensory arm of the PNS to detect both noxious and immune stimuli and to integrate these signals to drive the autonomic reflexes that coordinate inflammatory responses[3].

Neurons from each arm of the PNS communicate with tissue epithelial, endocrine and stromal cell types and with the immune system to regulate inflammation. As can be observed by browsing the website of the Immunological Genome Project (ImmGen, a consortium database of mouse immunocyte transcriptional profiling data), nearly every type of immune cell expresses receptors for neurotransmitters and neuromodulators, allowing them to respond to PNS signalling during inflammation.

In this Review, we discuss the molecular mechanisms by which peripheral sensory and autonomic neurons signal to the immune system to regulate host defence, autoimmunity and inflammatory diseases. We discuss the

Box 1 | **Peripheral nervous system regulation of immunity: historical underpinnings**

The concept of nervous system involvement in immune and inflammatory responses is quite old. As early as the first century AD, the Roman writer Celsus recognized pain — now known to be driven by activation of nociceptive sensory neurons — as one of four cardinal signs of inflammation[134]. However, it was not until the nineteenth and twentieth centuries that it was understood that activation of peripheral nerves not only accompanied inflammation but also mediated it. Work at the turn of the twentieth century demonstrated the phenomenon of neurogenic inflammation with a series of experiments that showed that electrical stimulation of sensory nerves could generate rapid vasodilation[135], whereas similar work revealed that chemical nerve stimulation could drive local inflammation[135]. Sir Thomas Lewis expanded the understanding of neurogenic inflammation by showing that the increased vascular permeability and tissue oedema that occurred in response to injury was dependent on nerves[136].

In 1934, Henry Dale postulated that transmitters secreted by sensory nerves drive neurogenic inflammation[137]. Work over the next several decades would ultimately identify substance P as one of these secreted sensory neuropeptides and show that it promotes vascular permeability and oedema via the neurokinin receptor NK1R, present on endothelial cells[30]. This discovery was followed by the finding that calcitonin gene-related peptide (CGRP) causes vasodilation by signalling through a receptor complex present on endothelial cells and vascular and lymphatic smooth muscle cells[138]. Since then, a host of other neuropeptides secreted by sensory neurons in the periphery have been identified. We now appreciate that sensory nerves act not only to sense their local microenvironment but also to secrete transmitters that actively modulate this microenvironment.

Similarly, it was appreciated for some time that long-range neural circuitry can modulate immune responses, as demonstrated by the capacity of the hypothalamic–pituitary–adrenal axis to potently suppress immune function[139]. It was also well established that the autonomic nervous system acts via long-range circuits to mediate physiological responses, such as gastrointestinal motility and secretion and cardiovascular function. More recently, we have come to recognize that the responses modulated by the autonomic nervous system include those responsible for immune function and that vagal neurons can detect cytokines and other inflammatory products[140–143]. Work starting in the 1980s revealed that immune cells express cognate receptors for various neuropeptides, establishing a common language by which these two systems can communicate. In the early 2000s, Kevin Tracey and colleagues defined a circuit whereby signalling through the efferent vagus nerve inhibits inflammatory cytokines and limits inflammation, dubbed the 'cholinergic anti-inflammatory pathway'[144]. In parallel, the molecular underpinnings through which sympathetic signalling modulates immune function have come to be understood[145]. These studies set the stage for our current mechanistic understanding of the molecular mechanisms of bidirectional neuroimmune communication.

known crosstalk between the somatosensory, sympathetic, parasympathetic and enteric neurons of the PNS and distinct immune cell types (BOX 2).

Sensory neuron regulation of immunity

Peripheral sensory neurons innervate our barrier tissues and internal organs, allowing the perception of internal state and external stimuli. In these tissues, sensory neurons can also directly signal to immune cells to modulate their function (FIGS 1 and 2). Many of the recent findings in this area have focused on somatosensory neuroimmune crosstalk in the skin, a major barrier tissue for which the types of sensory fibres have been well defined and neurobiological approaches (including optogenetics) have been optimized. In addition, some emerging studies have identified sensory neuron-mediated regulation of immune cells in mucosal barriers including the lungs and gut.

Sensory neurons include nociceptors, pruriceptors, proprioceptors, thermoreceptors and mechanoreceptors. The cell bodies of somatic sensory neurons are located in either dorsal root ganglia (DRG) or trigeminal ganglia. Visceral organs are also innervated by sensory neurons from vagal afferents whose cell bodies reside in the jugular and nodose ganglia. Sensory neurons innervate all barrier tissues of the body, including the skin, respiratory tract and gastrointestinal mucosa.

Sensory neurons express a wide variety of receptors, including transient receptor potential (TRP) channels, purinergic P2X channels, mechanosensitive ion channels, G-protein-coupled receptors and cytokine receptors. Using these receptors, sensory neurons can detect effector molecules released by immune cells (including various cytokines, chemokines and lipid mediators), which in turn modulate neuronal excitation to induce pain transduction[4] and drive thermal and mechanical pain sensitivity during inflammation. Nociceptor sensory neurons can also directly detect microbes. For example, the bacterial pathogens *Staphylococcus aureus* and *Streptococcus pyogenes* both secrete toxins that have been demonstrated to directly induce DRG neuron firing and pain-like behaviours in mice[5,6]. Nociceptors have also been demonstrated to express receptors for bacterial components, including the pathogen-associated molecular pattern (PAMP) receptors Toll-like receptor 4 (TLR4) and TLR5 (which detect lipopolysaccharides (LPS) and flagellin, respectively[7–9]), and to be able to detect fungal pathogens[10,11].

Whereas nociceptors can be directly activated by pathogens in painful pyogenic bacterial and fungal infections, recent work has shown that nociceptors can also detect pathogens outside traditionally painful contexts. In a guinea pig tuberculosis infection model, *Mycobacterium tuberculosis* glycolipid sulfolipid-1 (SL-1) activated vagal sensory neurons in the respiratory tract to induce a cough reflex[12]. Furthermore, studies in mice demonstrated that nasal nociceptor neurons mediate the sneezing reflex (sneezing represents a prominent defence mechanism against respiratory viruses and other environmental irritants) via signalling through the neuropeptide neuromedin B to postsynaptic central neurons[13], implicating nociceptors in host defence in protective reflexes beyond pain.

The integration of sensory signals from the environment in the CNS can alert us to important stimuli; however, sensory neurons also have efferent functions that can quickly influence the local tissue environment via axonal reflexes[14]. Activation of sensory neurons leads to the propagation of action potentials to the CNS. However, when these action potentials reach axonal branch points, they can also propagate back to peripheral nerve terminals[14]. This causes calcium influx that results in the rapid release of neuropeptides from both the affected and the surrounding nerve terminals into a localized area of affected tissue. Immune cells within these tissues express receptors for many types of neurotransmitter and neuropeptide, including substance P, calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP) and neuromedin U (NMU). This process was first appreciated in the context of neurogenic inflammation, in which neurons act directly on the vasculature to initiate an acute inflammatory reaction[14] (BOX 1). However, we now know that sensory

Barrier tissues
The bodily tissues that interface with the external world and represent both a physical and an immunological barrier between the host and the environment.

Optogenetics
Experimental techniques that allow the modulation of excitable cells using light via genetically specified expression of opsins, or light-activated proteins, in the cellular population of interest with resulting cellular excitation or silencing upon stimulation with light.

Cytokines
A category of small proteins expressed by various cells; cytokines have immunomodulating roles and include chemokines, lymphokines, interferons and interleukins.

neurons interact with and influence immune cells in multiple contexts.

Sensory regulation of antimicrobial host defences. In the skin, sensory nociceptor neurons, which preferentially express the voltage-gated sodium channel Nav1.8 and the transient receptor potential cation channel subfamily V member 1 (TRPV1), can directly detect microbes and signal back to the innate immune system to influence the outcome of infection. For example, Nav1.8-expressing (Nav1.8$^+$) neurons release CGRP to suppress the recruitment of monocytes and neutrophils in *S. aureus* subcutaneous infection in mice[5]. Similarly, in a mouse model of necrotizing fasciitis due to *S. pyogenes*, CGRP release from neurons decreased neutrophil recruitment and inhibited their bacterial killing capability (FIG. 1b). Depleting TRPV1-expressing (TPRV1$^+$) nociceptors through genetic ablation or treatment with the TRPV1-binding toxin resiniferatoxin led to increased recruitment of neutrophils and improved control of infection, as did botulinum toxin-mediated blockade of peripheral neuropeptide release and CGRP receptor antagonism[6]. In the lungs, vagal TRPV1$^+$ neurons drove suppression of neutrophil function during *S. aureus*-induced pneumonia in mice[15] (FIG. 2). The neurons released CGRP into the bronchoalveolar lavage fluid, which suppressed production of the proinflammatory cytokines tumour necrosis factor (TNF) and C–X–C chemokine ligand 1 (CXCL1). Inhibition of CGRP signalling increased neutrophil recruitment and bacterial clearance, with benefits for survival and host defence[15].

In other scenarios, sensory neuron modulation of immune cells has protective roles in infection. For example, ablation of nociceptive neurons increased susceptibility to fungal infection in mice with epicutaneous *Candida albicans* infection, whereas the activation of TRPV1$^+$ neurons led to interleukin-23 (IL-23) production by dendritic cells, downstream IL-17A production by γδ T cells and resistance to cutaneous candidiasis[10] (FIG. 1b). Optogenetic activation of cutaneous TRPV1$^+$ neurons also elicited a local response involving IL-17-secreting T helper cells (T_H17 cells) without pathogen inoculation or tissue damage and reduced susceptibility to subsequent infection with *C. albicans*, showing that this pathway could mediate an anticipatory immune response to prepare the host for pathogen exposure[16]. Optogenetic activation of cutaneous TRPV1$^+$ neurons also reduced susceptibility to subsequent epicutaneous *S. aureus* infection. CGRP drives dermal dendritic cell production of IL-23 and IL-17 in this paradigm of anticipatory immunity[16]. Given the differential inhibitory and activating actions of CGRP in different contexts of cutaneous immunity[15,16], it is possible that its role depends on the threshold of neural activation, its immune cell targets (neutrophils versus dendritic cells) and its skin localization (epicutaneous versus subcutaneous).

Nav1.8$^+$ sensory neurons were also recently shown to attenuate herpes simplex virus 1 (HSV-1) cutaneous infections. In a mouse model of HSV-1 infection, ablation of Nav1.8$^+$ neurons increased skin lesions and neutrophil accumulation and decreased draining lymph node CD8-expressing (CD8$^+$) T cell and antiviral dendritic cell responses[17].

Sensory regulation of skin allergic and inflammatory responses. Emerging evidence indicates that regulation of dendritic cell, macrophage and T cell responses by sensory neurons has roles in autoimmune and allergic skin conditions. The circuitry described above — whereby

Box 2 | **Overview of immune cell types that interact with the nervous system**

The highly complex mammalian immune system comprises a wide array of cell types and is broadly divided into the innate and adaptive immune systems. Here, we briefly introduce the major cell types of the immune system that have been demonstrated to interact with peripheral neurons; as such, this is not an exhaustive compendium of all immune cells.

Innate immune cells

Innate immune cell responses are non-specific and entrained from birth to allow rapid sensing of pathogens and tissue injury. Innate immune cell function can be triggered by pattern recognition receptors, which recognize broadly conserved components of microbes — called pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) — that are present in injured or stressed cells and tissues[146].

Monocytes, macrophages and dendritic cells are mononuclear phagocytes with important innate immune functions[147,148]. Macrophages are tissue-resident leukocytes that are found throughout the body and serve as scavengers, pathogen-recognition cells and antigen-presenting cells, as well as being an important source of chemokines and cytokines during the initiation of inflammation. Macrophages with a 'M1-like' phenotype are skewed towards pro-inflammatory and microbicidal functions, whereas those with a 'M2-like' phenotype are important for tissue repair and resolving inflammation. Dendritic cells are bone marrow-derived phagocytic cells that are found in most tissues and have a predominant antigen presentation function, taking up antigens in the periphery and then migrating to peripheral lymphoid tissues to stimulate T cell responses. Langerhans cells are a specialized tissue-resident macrophage found in the epidermis of the skin and display several properties similar to those of dendritic cells[149].

Neutrophils are circulating phagocytes that are recruited to the site of tissue injury, where they act to amplify inflammation via release of cytokines and can directly eliminate pathogens via mechanisms including phagocytosis and the formation of neutrophil extracellular traps[150].

Mast cells, eosinophils and basophils are granulocytes which quickly respond to allergic and immune stimuli (particularly parasites) by rapidly releasing granules containing inflammatory mediators. Mast cells are found in the connective tissues of the epithelium and mucosa and release various bioactive molecules, including histamine, lipid mediators, proteases and cytokines[151].

Innate lymphocytes are critical for the initiation of antimicrobial defences and tissue immunity and include natural killer cells and innate lymphoid cells (ILCs). Natural killer cells are large granular cytotoxic lymphocytes that play an important role in killing virus-infected cells, intracellular pathogens and cancer cells. Their granules contain apoptosis-inducing molecules such as granzymes and perforins. ILCs, which belong to the lymphoid lineage but lack specific antigen receptors, encompass four groups: type 1 innate lymphoid cells (ILC1s), ILC2s, ILC3s and lymphoid tissue inducer cells[152]. ILCs are largely tissue-resident cells and are particularly abundant at barrier mucosal surfaces.

Adaptive immune cells

The adaptive immune system recognizes specific non-self antigens to allow the generation of responses tailored to distinct pathogens or abnormal host cells. The adaptive immune system also maintains the ability to mount these specialized responses via memory cells to provide long-lasting immunity. The cells of this system are lymphocytes known as B cells and T cells[153]. B cells are responsible for generating a humoral antibody response and can also have immunomodulatory roles[154]. T cell subtypes, including cytotoxic T cells (CD8-expressing (CD8$^+$) T cells) and helper T cells (CD4-expressing (CD4$^+$) T cells), mediate antigen recognition and cell-based immunity[153]. Within the CD4$^+$ T cell lineage, distinct subsets — including T helper 1 cells (T_H1 cells), T_H2 cells, T_H17 cells and regulatory T cells (T_{reg} cells) — mediate distinct types of downstream adaptive immunity that are tailored towards distinct types of tissue inflammation and antimicrobial defences[155]. Natural killer T cells and γδ T cells are subsets of T cells that express more invariant T cell receptors, and are thus considered to be a hybrid between innate and adaptive immune cells[156].

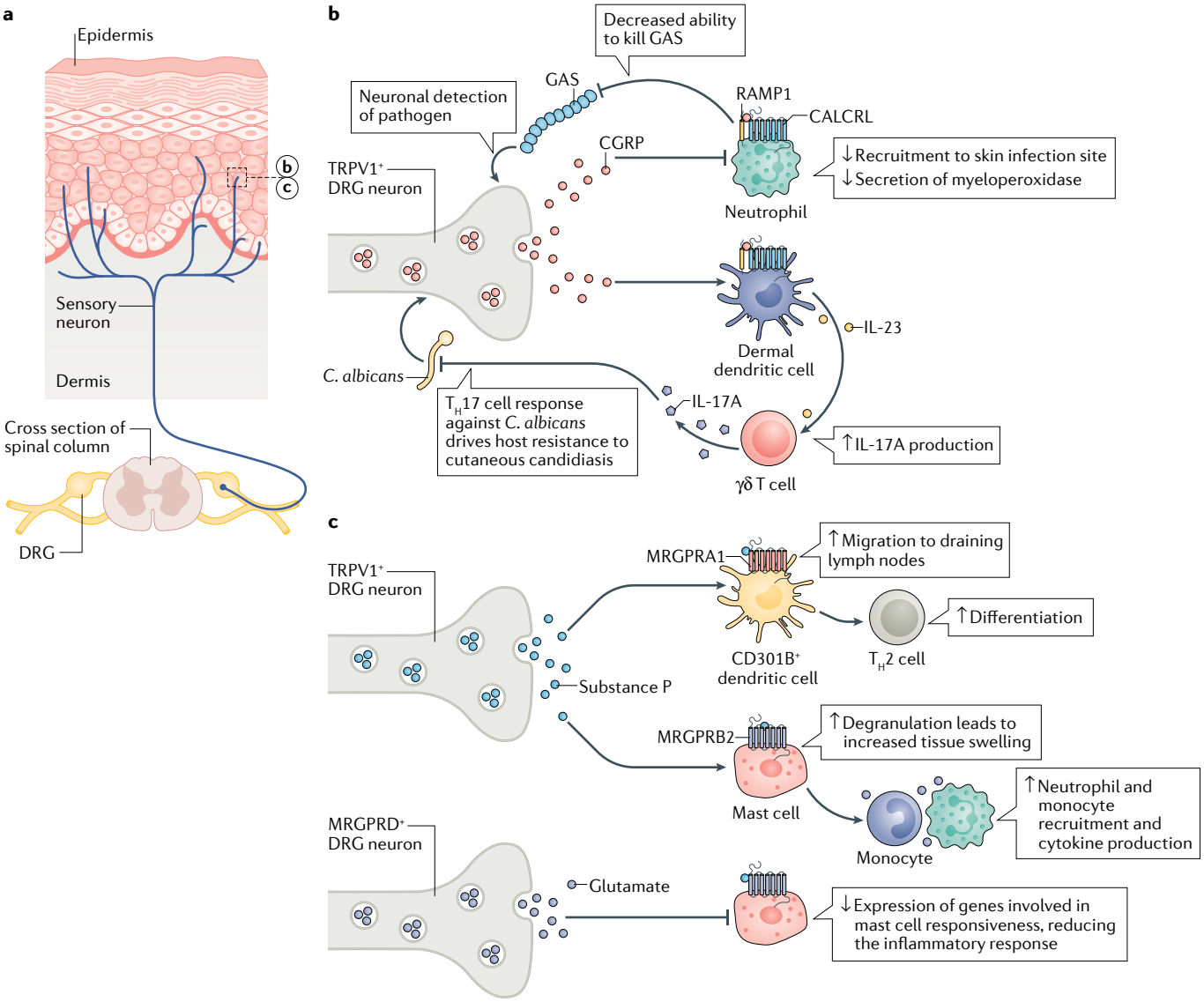

Fig. 1 | **Examples of sensory neuron–immune cell interactions in the skin. a** | Sensory neurons whose cell bodies reside in the dorsal root ganglia (DRG) densely innervate the skin, where they can secrete neuropeptides and neurotransmitters to modulate immune cell function. **b** | Transient receptor potential cation channel subfamily V member 1 (TRPV1)-expressing (TRPV1$^+$) DRG neurons can sense pathogens including the bacterium *Streptococcus pyogenes* (also known as Group A Streptococcus (GAS)) or the fungal pathogen *Candida albicans*. In turn, DRG neurons can signal to immune cells. In the case of GAS infection, DRG neurons release the neuropeptide calcitonin gene-related peptide (CGRP), which inhibits neutrophil recruitment and reduces bacterial killing (indicated by the inhibitory arrow) through the CGRP type 1 receptor (CALCRL)–receptor activity-modifying protein 1 (RAMP1) complex[6]. In *C. albicans* infection, release of CGRP by DRG neurons induces production of interleukin-23 (IL-23) by dermal dendritic cells, which drives IL-17A production by γδ T cells. This promotes defence against candidiasis, via a response involving IL-17-secreting T helper cells (T_H17 cells)[10]. **c** | DRG neurons also modulate cutaneous allergic and inflammatory immunity through their effects on dendritic cell and mast cell responses. Substance P that is secreted by TRPV1$^+$ DRG neurons interacts with CD301B-expressing (CD201B$^+$) dendritic cells via Mas-related G-protein-coupled receptor member A1 (MRGPRA1). This increases their migration to draining lymph nodes and induces T helper 2 cell (T_H2 cell) responses[19]. Substance P also acts directly on mast cells through MRGPRB2 to induce mast cell degranulation. This leads to increased tissue swelling, innate immune cell recruitment and increased levels of pro-inflammatory cytokines (including tumour necrosis factor (TNF), granulocyte–macrophage colony-stimulating factor (GM-CSF) and IL-8)[26]. Non-peptidergic MRGPRD-expressing (MRGPRD$^+$) DRG neurons release glutamate, which suppresses mast cell expression of MRGPRB2 and cutaneous inflammation, such as that involved in contact dermatitis[32].

Chemokines
A class of chemotactic cytokines that function as chemoattractants to induce the directional migration of other cells, notably leukocytes.

nociceptors drive dendritic cells to induce T_H17-type immunity in cutaneous infection — is also active in non-infectious inflammatory contexts, where it has a deleterious effect. In a mouse model of psoriasis-like disease induced by exposure to the TLR7 activating compound imiquimod, skin-innervating nociceptors communicate with dendritic cells to drive T_H17 cell-mediated inflammation. Ablation of Nav1.8$^+$ or TRPV1$^+$ nociceptors resulted in failure of dendritic cells to produce IL-23 and decreased IL-17 production by γδ T cells, decreasing inflammatory cell recruitment and reducing subsequent inflammation[18]. TRPV1$^+$ neurons also drive dermal dendritic cell migration to draining lymph nodes to prime subsequent T helper 2 cell (T_H2 cell) activation in

Neuropeptide
A short-chain peptide synthesized and released by neurons which functions to signal to neuronal substrates.

Axonal reflexes
Responses through which stimulation of one axon branch results in a nerve impulse that travels back at branching points to other axonal branches, resulting in stimulation of collateral branches.

T helper cells
A type of adaptive immune cell, also known as CD4-expressing (CD4$^+$) T cells, whose main function is the activation, recruitment and polarization of other immune cells.

Mast cell degranulation
An event that occurs in response to mast cell activation, in which preformed mediators from cytoplasmic granules are released into surrounding tissue.

response to the protease allergen papain in mice[19]. After subcutaneous papain injection, nociceptors released substance P, which acted on Mas-related G-protein-coupled receptor member A1 (MRGPRA1) expressed by dermal dendritic cells to induce their migration to draining lymph nodes, thus contributing to the allergic immune response[19] (FIG. 1c). Other studies have found that neuropeptides CGRP, VIP and pituitary adenylate cyclase-activating polypeptide (PACAP) can bias endothelial cells and Langerhans cells to differentially stimulate T_H1 cell, T_H2 cell or T_H17 cell responses[20–22].

Skin inflammation also occurs following UV-induced damage. Sensory neurons were recently shown to interact with skin macrophages through the neuropeptide TAFA4 to promote tissue repair after such damage: neurons expressing the $G\alpha_i$-interacting protein (GINIP) produced TAFA4, which promotes IL-10 production by dermal macrophages, and this prevented fibrosis after UV exposure[23].

Mast cells, which are often juxtaposed to sensory neurons in barrier tissues[24,25], have important roles in skin inflammatory responses to both damage and allergens. Recently, mast cells were shown to specifically express the substance P receptor MRGPRB2 in mice and its orthologue MRGPRX2 in humans[26], suggesting a mechanism by which sensory neurons could drive mast cell degranulation via substance P release. This substance P–MRGPRB2 axis was shown to drive neurogenic inflammation in a mouse model of skin injury: activation of mast cells by substance P via MRGPRB2 drove cytokine production, tissue swelling and neutrophil and/or monocyte recruitment[27]. Similarly, in a mouse model of atopic dermatitis induced by house dust mite (HDM) exposure, HDM-activated nociceptors released substance P, which activated the MRGPRB2 receptor on contiguous mast cells, leading to their degranulation[28]. Substance P can also activate human mast cells to induce degranulation via MRGPRX2 (REF.[26]). Human mast cells present at different anatomical sites demonstrate variable expression and function of MRGPRX2, suggesting a plausible mechanism for differential effects of neuronal signalling at different sites[29].

Although these findings point to a key role for the MRGPRB2 receptor in mast cell-induced inflammation, substance P was previously thought to induce neurogenic inflammation mainly by binding to its canonical receptor NK-1R (also known as TACR1), which is expressed by endothelial cells[30]. NK-1R antagonists are currently in clinical trials for treatment of pain and inflammation[31]. However, whereas substance P injection-induced immune cell recruitment in the skin was significantly impaired in *Mrgprb2*$^{-/-}$ mice, it was unaffected in *Tacr1*$^{-/-}$ mice[27]. The role of each receptor in neurogenic inflammation is thus controversial, although it is possible the receptors may mediate different aspects of pain and inflammation.

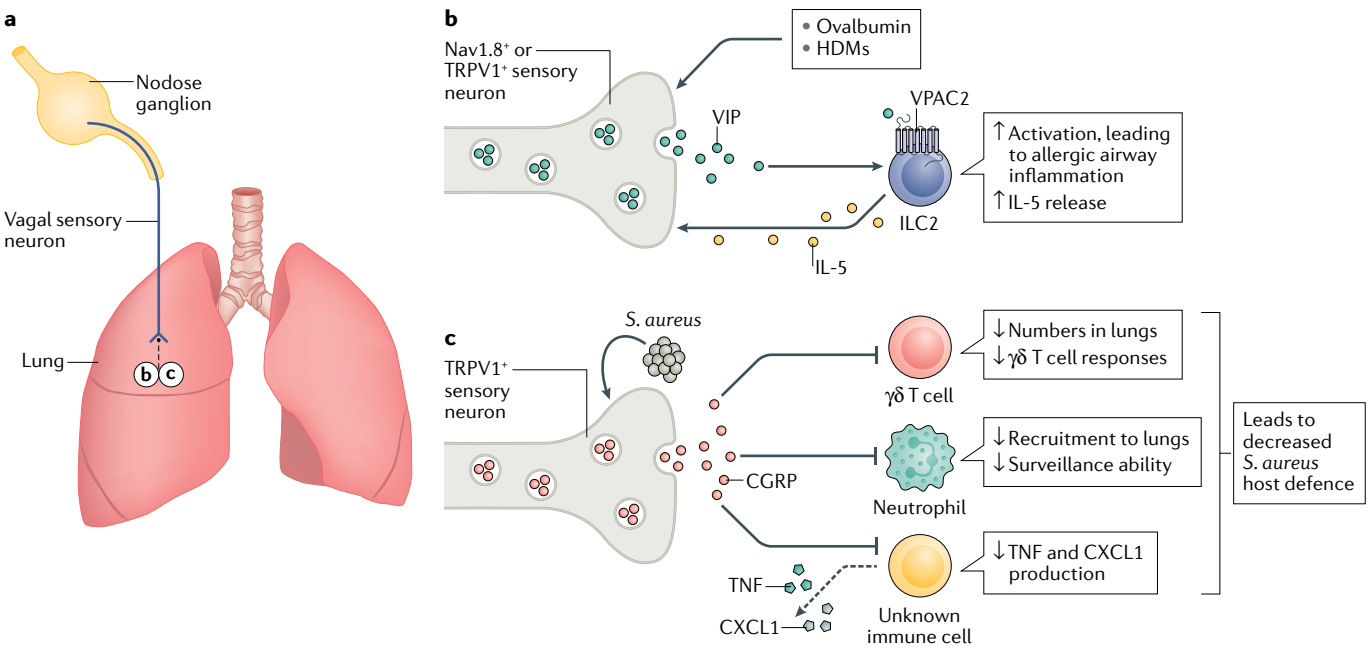

Fig. 2 | **Examples of sensory neuron–immune cell interactions in the respiratory tract. a** | Lung-innervating vagal sensory neurons, whose cell bodies reside in the nodose ganglia, interact with immune cells to mediate immune responses in allergic and infectious respiratory diseases. Selected studies of neuroimmune interactions in the respiratory tract are highlighted in **b** and **c**. **b** | In animal models of ovalbumin or house dust mite (HDM)-induced asthma, Nav1.8-expressing (Nav1.8$^+$) or transient receptor potential cation channel subfamily V member 1-expressing (TRPV1$^+$) vagal sensory neurons are directly or indirectly activated by these substances, leading to neuronal release of vasoactive intestinal peptide (VIP) which acts via the VIP receptor 2 (VPAC2) receptor on type 2 innate lymphoid cells (ILC2s) to drive immune responses and allergic airway inflammation[35]. The ILC2s secrete interleukin-5 (IL-5), which provides potent positive feedback to neurons. **c** | In *Staphylococcus aureus*-induced bacterial pneumonia, vagal TRPV1$^+$ neurons detect *S. aureus* and, in response, secrete the neuropeptide calcitonin gene-related peptide (CGRP) into the lungs, which reduces the recruitment of and lung surveillance by neutrophils, the numbers of γδ T cells present in the lungs and their responses, and the production of the cytokines tumour necrosis factor (TNF) and C–X–C chemokine ligand 1 (CXCL1) by as-yet unidentified immune cells (dashed arrow)[15]. Silencing of TRPV1$^+$ nociceptive neurons and CGRP signalling enhances host defence against *S. aureus* and leads to increased survival in mice.

Lymphoid tissues
A set of tissues that consist of primary lymphoid tissues (which include the bone marrow and thymus) in which lymphocyte production and development takes place, and secondary lymphoid tissues (which include the lymph nodes, spleen, Peyer's patches and mucosa-associated lymphoid tissue (MALT)) where naive mature lymphocytes come into contact with antigens to initiate adaptive immune responses.

In contrast to peptidergic sensory neurons that activate mast cells via substance P, MRGPRD-expressing (MRGPRD$^+$) non-peptidergic sensory neurons suppress mast cell activity (FIG. 1c). These non-peptidergic neurons release glutamate, which was shown to signal to mast cells during cutaneous immune responses[32]. Glutamate drives expression of multiple genes that reduce mast cell degranulation and responsiveness[32]. Ablation of MRGPRD$^+$ neurons made mice more resistant to dermonecrotic *S. aureus* infection, but led to exaggerated inflammatory responses in contact dermatitis[32]. Thus, distinct subsets of sensory neurons can have contrasting roles in immunomodulation.

A second layer of sensory neuron regulation of cutaneous immunity may occur in peripheral lymph nodes, which have been recently shown to be innervated by DRG neurons that are predominantly peptidergic but are distinct from skin-innervating neurons in mice[33]. Inflammatory stimuli, including LPS injection, resulted in increased sensory fibre volume, paralleling the increased lymph node volume seen in inflammation. Optogenetic activation of these sensory nerves resulted in transcriptional changes in lymph node stromal cells, as well as in immune cells including neutrophils and natural killer cells[33]. The functional role of this neuroimmune circuit, however, remains to be delineated.

Sensory regulation of immune responses in mucosal barriers. Sensory neurons can regulate innate lymphoid cells (ILCs), which are critical for orchestrating barrier immunity at mucosal surfaces. In the lungs, activation of the nociceptive ion channel TRPA1 regulates airway responses in ovalbumin-induced airway inflammation and hyper-reactivity in mice[34]. Ablating or silencing vagal Nav1.8$^+$ or TRPV1$^+$ sensory neurons substantially decreased airway inflammation in mouse models of asthma induced by ovalbumin or HDMs[35,36] (FIG. 2). This was due, at least in part, to the loss of a positive feedback loop in which nociceptors release the neuropeptide VIP, which signals via its receptor VIP receptor 2 (VPAC2) to activate type 2 ILCs (ILC2s). The activated ILC2s secrete the cytokine IL-5, which can activate sensory neurons[35]. It would be interesting to determine whether the substance P–mast cell axis also plays a role in these airway inflammation models, given its role in HDM-induced allergy models in the skin[28].

Sensory neurons can also regulate gut mucosal barrier immunity via interactions with epithelial cells. In a mouse model of *Salmonella typhimurium* enteric infection, TRPV1$^+$ nociceptor neurons protected against infection by modulating the density of the Peyer's Patch microfold cells, epithelial cells that serve as entry points for invasive bacteria, and by maintaining luminal and mucosal levels of segmented filamentous bacteria, which provide resistance to *Salmonella* infection[37].

Summary. Sensory neurons can directly detect inflammatory mediators and microbial components. Upon activation, these neurons signal to the CNS to mediate pain and concurrently release neuropeptides or non-peptidergic mediators from their peripheral terminals that can potently modulate immune cell types in acute and chronic inflammation. Because the somatosensory system is highly diverse (with 14 or more distinct subsets of neurons identified via single-cell transcriptomic analyses in adult mice[38]), further work is required to determine how different neuronal subsets interface with immune cells. Some sensory neuron–immune cell interactions promote immune responses[16,18,27], whereas others lead to their suppression[6,32]. The biological rationale for each of these neuroimmune axes is not yet completely clear, and future work is necessary to determine the context-dependent role of sensory neurons in immunity. It would also be interesting to determine whether pharmacological agonists or antagonists of sensory neurons and their signalling pathways (such as the CGRP antagonists used to treat migraine) can modulate immunity in infection, allergic or autoimmune diseases. Targeting these signalling axes could have unintended side effects or, conversely, could offer novel approaches to treat immune diseases.

Sympathetic regulation of immunity

A second crucial pathway for neuroimmune communication involves the direct effects of sympathetic nervous system activity on immune cells (FIG. 3). The cell bodies of sympathetic preganglionic neurons are found along the length of the spinal cord, with their axons terminating on the cell bodies of postganglionic sympathetic neurons in the sympathetic paravertebral or prevertebral ganglions. The axons of postganglionic neurons exit the ganglia and project to effector tissues. Notably, the cells of the adrenal medulla are innervated directly by preganglionic sympathetic neurons and essentially function as postganglionic neurons, secreting their neuroeffectors into the bloodstream rather than directly in the target tissues.

Noradrenaline as a modulator of immune cell function. Most sympathetic postganglionic neurons use noradrenaline as their primary neurotransmitter, and sympathetic neuron–immune cell regulation often occurs via noradrenaline signalling, although sympathetic nerves can also synthesize and secrete other neurotransmitters such as neuropeptide Y[39,40]. Dynamic alterations of sympathetic nerve activity and noradrenaline levels have been demonstrated in lymphoid tissues in response to systemic stressors including endotoxemia and bacterial infection[41–43].

Many immune cells, including macrophages, dendritic cells, T lymphocytes, B lymphocytes, natural killer cells and ILCs, express adrenergic receptors, allowing them to respond to noradrenaline signalling[44–47]. Most signalling occurs via the β2-adrenergic receptor (β2AR)[48], which exerts most of its effects on immune cells by inducing downstream cAMP–protein kinase A (PKA) signal transduction. In vitro and in vivo studies have demonstrated that noradrenaline signalling inhibits production of pro-inflammatory cytokines (such as TNFα, IL-1, IL-6 and IL-12) and upregulates production of anti-inflammatory cytokines (including IL-10) from innate immune cells[49–51]. Data also indicate the expression of other adrenergic receptors on some immune cells, with the functional significance of these

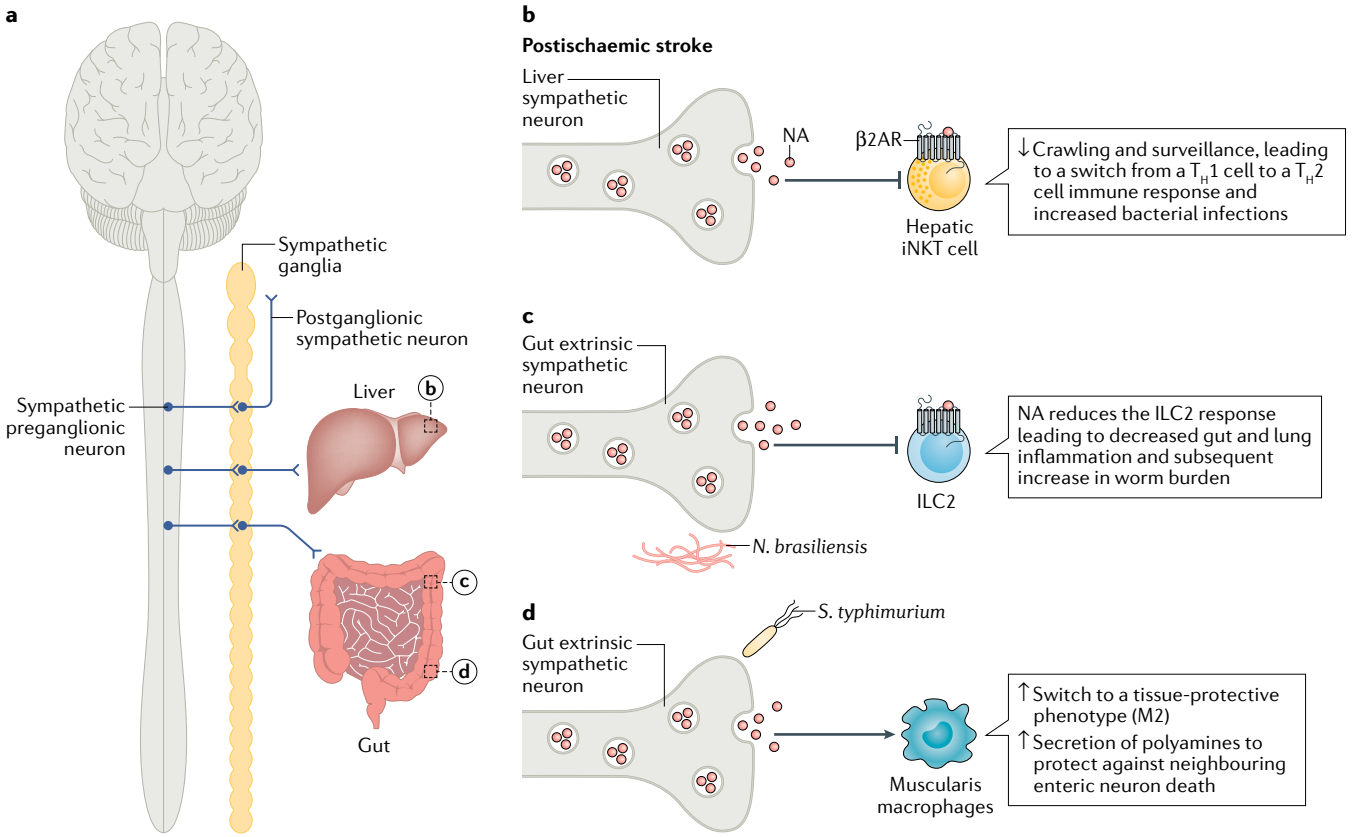

Fig. 3 | **Examples of sympathetic neuron–immune cell interactions.** **a** | Sympathetic preganglionic neurons originate from the thoracolumbar spinal cord and travel to a ganglion (paravertebral ganglia or prevertebral ganglia) to synapse on postganglionic neurons, which then innervate target organs and tissues. The sympathetic nervous system can directly signal to immune cells via noradrenaline (NA), which mediates neuroimmune communication in several inflammatory contexts. Selected roles of sympathetic neurons in regulating the immune response are illustrated in **b**–**d**. **b** | In postischaemic stroke in mice, sympathetic neurons innervating the liver increase their release of NA, which acts on hepatic invariant natural killer T cells (iNKT cells) via the β2-adrenergic receptor (β2AR)[67]. This results in decreased surveillance and crawling of hepatic iNKT cells, in comparison with iNKT cell activity in absence of cerebral ischaemia, with subsequent increases in bacterial infection rates and a switch from T helper 1 cell (T_H1 cell) to T_H2 cell-driven immune responses. **c** | During gut infection with the parasitic helminth *Nippostrongylus brasiliensis*, gut-innervating sympathetic neurons secrete NA, which modulates the responses of type 2 innate lymphoid cells (ILC2s) by binding to β2AR (REF.[46]). The reduced ILC2 response reduces inflammation, resulting in increased worm burden; in contrast, β2AR knockout mice had increased ILC2s, increased inflammation and reduced worm burden. **d** | Gut luminal infection with *Salmonella typhimurium* results in activation of gut-innervating sympathetic neurons and NA signalling to muscularis macrophages via β2AR (REF.[56]). These muscularis macrophages switch to a M2-like phenotype, secreting protective polyamines to prevent the death of neighbouring enteric neurons.

still under investigation[52,53]. The traditional model of sympathetic–immune cell crosstalk suggests that sympathetic nerves are activated and release noradrenaline at sites of inflammation. Noradrenaline then acts on immune cells via β2AR to suppress cell-mediated immune responses, restoring immune system homeostasis and driving the resolution of inflammation. This feedback circuit is crucial in various disease contexts, including multiple types of infections and autoimmune diseases. However, sympathetic neurons can have both activating and inhibitory effects on immunity. One hypothesis is therefore that β2AR signalling activates numerous alternative non-canonical pathways to induce context-dependent stimulatory or inhibitory effects on immune cells[54].

Sympathetic neuron crosstalk with innate immune cells. The dominant anti-inflammatory effect of the sympathetic nervous system polarizes macrophages towards a tissue-protective (or 'M2-like') phenotype. In a mouse model of chemical peritonitis induced by the fungal polysaccharide zymosan A, chemical sympathectomy via 6-hydroxydopamine (6-OHDA) administration increased inflammation, characterized by increased macrophage and granulocyte numbers and diminished resolution[55]. The resolving effect of sympathetic nerves may involve repulsive guidance molecule A (RGMA). RGMA was initially identified as a neural chemorepulsive molecule, but has more recently been appreciated to have roles in attenuating inflammation by inhibiting leukocyte trafficking. RGMA administration rescued the hyperinflammation caused by chemical sympathectomy and RGMA expression in peritoneal neurofilaments was decreased by 6-OHDA treatment[55]. In another mouse model, enteric infection with a non-invasive strain of *S. typhimurium* resulted in rapid activation of gut-innervating extrinsic sympathetic neurons and noradrenaline signalling to β2AR on

Resolution
An active and highly regulated phase of the immune response which acts to counter-regulate inflammation and restore tissue homeostasis.

muscularis macrophages in the myenteric plexus of the gut, driving them towards tissue-protective phenotypes[56] (FIG. 3d). A recent study showed that this sympathetic-driven macrophage phenotype is critical for the protection of intrinsic enteric neurons following infection with *S. typhimurium* and other enteric pathogen infections[57]. Following infection with attenuated *S. typhimurium*, there was specific loss of excitatory enteric neurons, and depletion of muscularis macrophages leads to enhanced neuronal loss following infection whereas β2AR signalling in macrophages and local sympathetic neuron activation limits neuronal loss[57].

Sympathetic neurons also regulate innate immune cells in tumours. Chemical ablation of sympathetic neurons in tumour-bearing mice increased the number of immature myeloid-derived suppressor cells, which decreased the antitumour immune response and increased tumour growth. This sympathetic signalling promoting myeloid cell maturation was through an α-adrenergic receptor[58].

Another recent study showed that ILC2s express β2AR and are in close proximity to adrenergic neurons in the mouse intestine[46]. In a model of gastrointestinal parasitic infection with the helminth *Nippostrongylus brasiliensis*, β2AR-deficient animals (*Adrb2*$^{-/-}$ mice) demonstrated reduced worm burden when compared with wild-type mice as well as increased ILC2 responses and increased type 2 inflammation in the intestine and the lung. Treatment with a β2AR agonist impaired ILC2 responses in wild-type mice and dampened inflammation, resulting in higher worm burden[46] (FIG. 3c). One limitation of these findings is that global β2AR knockout and/or agonist treatment would affect other immune cell populations as well as gastrointestinal motility and bronchoconstriction, all of which could contribute to parasite clearance; however, it is noted that conditional knockout of β2AR in CD127-expressing cells, including ILC2s, also reduced worm burden.

Sympathetic neuron crosstalk with T cells and B cells. There is extensive direct sympathetic innervation of primary and secondary lymphoid tissues, and sympathetic fibres have been shown to be in close apposition to immune cells in these tissues (reviewed in REFS[44,59,60]). Sympathetic nerve signalling has been implicated in suppressing lymphocyte trafficking in these tissues in several studies. In mouse models, treatment with selective β2AR agonists inhibited egress of lymphocytes from lymph nodes, through an enhancement of retention-promoting signals, and thus rapidly produced lymphopenia (an effect that could be abrogated via 6-OHDA treatment)[61]. Adrenergic receptor agonist treatment also decreased inflammation and reduced lymphocyte numbers in affected tissues in mouse models of experimental autoimmune encephalomyelitis and ovalbumin-induced skin hypersensitivity[61]. In a mouse model of HSV-1 infection, treatment with a β2AR agonist reduced recruitment of virus-specific T cells to the infection site and reduced cytotoxic T cell activity[62]. Recent work in mouse models confirmed that these effects mimic the endogenous actions of sympathetic neurons: chemogenetic activation of sympathetic neurons recapitulated noradrenaline-mediated impairment of T cell locomotion in lymphoid tissues, an effect that was independent of adrenergic receptors on haematopoietic cells and was secondary to vasoconstriction of the lymphoid vasculature[62]. In rhesus macaques with simian immunodeficiency virus (SIV) infection, spatial analysis showed that there was increased viral replication adjacent to catecholaminergic varicosities in lymph nodes[63]. These data suggest that local catecholaminergic signals could impair lymphocyte responses to virus, potentially via effects on lymphocyte trafficking. The sympathetic regulation of lymphoid trafficking may serve a physiological role by driving circadian oscillations in leukocyte recruitment[64].

Sympathetic signalling also directly decreases T lymphocyte and B lymphocyte responses outside its effects on cell trafficking. In a mouse sciatic denervation model, the loss of sympathetic innervation of local lymph nodes led to a cellular expansion within these nodes as a result of increased interferon-γ (IFNγ) production in CD8$^+$ T cells[65]. Similarly, in a mouse model of severe influenza pneumonia, sympathetic abrogation via 6-OHDA treatment increased anti-influenza CD8$^+$ T cell responses[66]. The sympathetic depression of lymphocyte activity may be one mechanism by which diverse pathological states lead to immunosuppression. For example, ischaemic stroke in mice induces profound immunosuppressive changes in hepatic invariant natural killer T cells (iNKT cells), with this effect now demonstrated to be largely mediated by noradrenaline signalling[67] (FIG. 3b). Chemical depletion of sympathetic neurons with 6-OHDA or the administration of propranolol (a β-adrenergic receptor blocker) reversed the iNKT cell phenotype induced by stroke[67]. Moreover, mice treated with 6-OHDA or propranolol demonstrated significantly reduced spontaneous bacterial infections at 24 h post stroke in comparison with untreated animals[67]. In mouse models of spinal cord injuries, injury at the upper thoracic level (which affects sympathetic preganglionic neurons, including those projecting to the spleen) was associated with increased noradrenaline levels in the spleen, splenic atrophy[68] and deficient antigen-specific antibody responses that could be overcome by pharmacological blockade of β2ARs (REF.[69]). This contrasted with lower spinal cord injuries that do not remove sympathetic preganglionic neurons from brainstem control. Intriguing work suggests that the effects of upper thoracic injuries may arise as a result of the development of new autonomic circuitry below the injury level, leading to aberrant and exaggerated reflex sympathetic activation[70]. These data implicate sympathetic signalling in post-traumatic immune suppression.

Not all sympathetic signalling suppresses immune cell activity. A sensory neuron–sympathetic neuron circuit has been implicated in gating T cell entry into the CNS. In a mouse model of experimental autoimmune encephalomyelitis, activation of the sensory neurons by leg muscle activity led to sympathetic chain activation, which in turn stimulated expression of CCL20 by endothelial cells and allowed accumulation of pathogenic CD4-expressing (CD4$^+$) T cells in the lumbar spinal cord[71]. Work in mice that lacked dopamine β-hydroxylase (*dbh*$^{-/-}$ mice), and thus cannot produce noradrenaline and adrenaline,

Type 2 inflammation
An inflammatory pathway characterized by activation of T helper 2 cells (T_H2 cells), type 2 innate lymphoid cells (ILC2s), secretion of particular cytokines including interleukin-4 (IL-4), IL-5 and IL-13, IgE production and downstream activation of other immune cells such as mast cells or basophils.

Lymphocyte trafficking
The process by which lymphocytes adhere to and migrate across vascular endothelium to a tissue or site of inflammation.

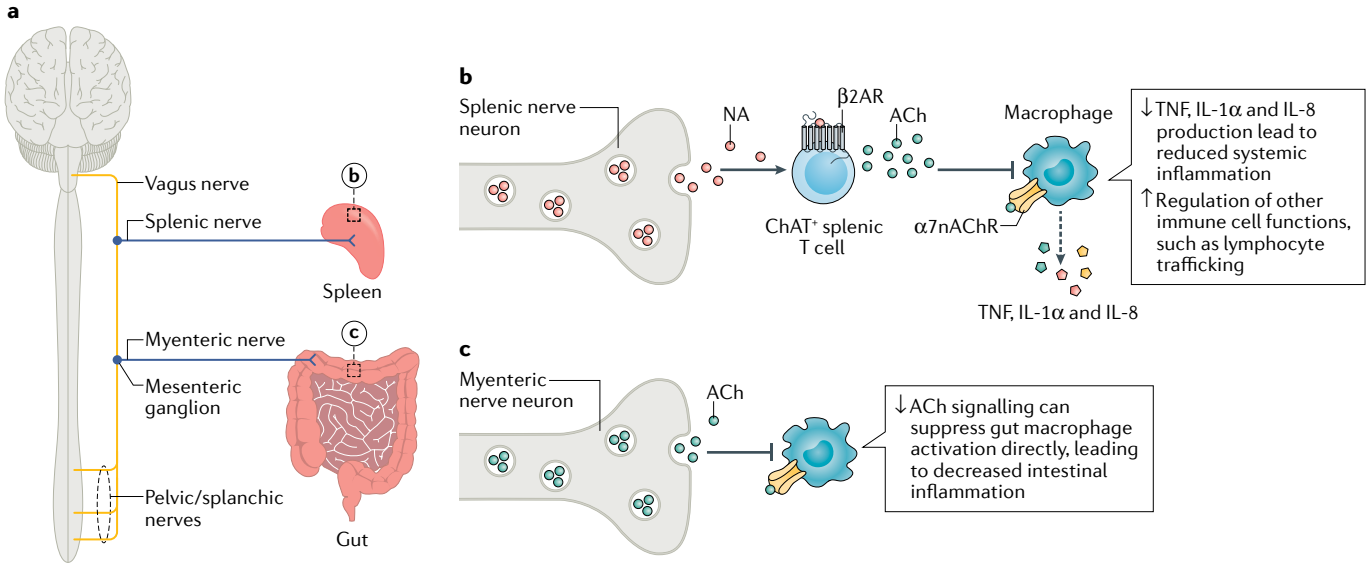

Fig. 4 | **Examples of parasympathetic regulation of immune cells. a** | The vagus nerve provides parasympathetic innervation to most visceral organs of the body. Activation of the afferent arm of the vagus nerve via cytokines results in anti-inflammatory signalling by parasympathetic efferent neurons. Two such pathways are highlighted in **b** and **c**. **b** | In response to endotoxic shock induced by systemic lipopolysaccharide (LPS) administration, the efferent arm of the vagus nerve stimulates activation of the catecholaminergic splenic nerve, which results in release of noradrenaline (NA) in the spleen. NA acts on choline acetyl transferase-expressing ($ChAT^+$) T cells via the β2-adrenergic receptor (β2AR)[76,84–86,88]. $ChAT^+$ T cells, in turn, release acetylcholine (ACh), which acts via α7-nicotinic acetylcholine receptor (α7nAChR) on macrophages to suppress production of inflammatory cytokines (including tumour necrosis factor (TNF), interleukin-1α (IL-1α) and IL-8; reduced production indicated by dashed arrow) and subsequent systemic inflammation. **c** | The efferent vagus nerve also activates cholinergic myenteric nerve signalling to suppress intestinal inflammation in a rodent model of gut inflammation in response to surgery and postoperative ileus[106]. Cholinergic myenteric neurons release ACh, which acts directly on gut-resident macrophages via α7nAChR, resulting in decreased macrophage activation and inflammation.

demonstrated impaired T cell responses and T_H1 cell cytokine production when infected with *Listeria monocytogenes* or *M. tuberculosis*, supporting a role for noradrenaline in stimulation of T_H1 cell-driven immunity[72]. In complementary work, chemical sympathectomy increased the innate immune response but decreased the adaptive response to *L. monocytogenes* infection[73]. Similarly, chemical sympathectomy diminished T_H1 cell-mediated delayed hypersensitivity in a mouse model of epicutaneous trinitrophenyl sensitization[74].

The sympathetic nervous system has also been implicated in the beneficial immune effect of the reward system. Chemogenetic activation of the ventral tegmental area enhanced adaptive and innate immunity in response to *Escherichia coli* exposure in mice. This included enhanced antibacterial and phagocytic activity of innate immune cells and reduced bacterial load, and a heightened T cell response upon re-exposure to heat-killed pathogen. These effects were abrogated by chemical ablation of sympathetic neurons[75].

Given their pleiotropic effects on immune responses, further work is required to delineate the immune drivers of the differential roles of sympathetic nervous system signalling. One area of further investigation is the immunomodulatory role of sympathetic neuroeffectors other than noradrenaline, such as neuropeptide Y.

Parasympathetic regulation of immunity

Often juxtaposed to or opposing the sympathetic response is the parasympathetic branch of the autonomic nervous system, which can also induce distinct immune responses. The major efferent arm of the parasympathetic nervous system innervates the body's internal organs via fibres that originate in the dorsal motor nucleus and nucleus ambiguous in the brainstem and project to visceral organs in the thorax and abdomen via the vagus nerve. Vagal preganglionic fibres release acetylcholine (ACh) to activate postganglionic neurons near or within the innervated organs. Postganglionic fibres also predominantly release ACh, which acts on ACh receptors on target tissues. The vagus nerve also contains sensory afferent fibres, which can be activated by cytokines, inflammatory products and molecular ligands from pathogens, as described above. The subsequent activation of vagal parasympathetic efferent neurons and the release of ACh can potently regulate the immune response in both systemic and local inflammation (FIG. 4).

Vagus nerve in suppression and resolution of inflammation. Electrical stimulation of the vagal nerve (vagal nerve stimulation (VNS)) during lethal endotoxin administration in rats can suppress inflammatory cytokine release and subsequent shock via the release of ACh[76], a phenomenon dubbed the 'cholinergic anti-inflammatory reflex'. This pathway limits systemic inflammation in multiple pathological states, including mouse models of *E. coli*-induced lung injury[77], pancreatitis[78], inflammatory bowel disease[79], kidney ischaemia–reperfusion injury[80] and cisplatin-induced kidney injury[81], and rat models of haemorrhagic shock[82] and myocardial ischaemia–reperfusion[83].

It was initially demonstrated that the vagal anti-inflammatory effect (FIG. 4b) is mediated via the α7-nicotinic acetylcholine receptor (α7nAChR) on macrophages and other immune cells[84], suggesting that inflammatory stimuli or VNS results in vagal efferent activation and peripheral Ach release. However, further work has suggested that the functional circuitry of the anti-inflammatory reflex does not involve only the vagus nerve. The spleen is the dominant source of systemic inflammatory cytokines in these models[85,86] and splenectomy abrogated the beneficial effect of VNS[85]. However, cholinergic innervation of the spleen is sparse[87]. It is now known that the anti-inflammatory effect of vagal stimulation is dependent on activation of postganglionic catecholaminergic neurons carried in the splenic nerve[86] and that the splenic nerve signals via β2AR to choline acetyltransferase (ChAT)-expressing T cells[88]. These T cells synthesize and release ACh, which then acts via α7nAChR on macrophages to suppress inflammatory cytokine response. This vagal to splenic nerve pathway has also been implicated in the regulation of other aspects of immune cell function, including lymphocyte trafficking[89,90].

Based on these findings, it was posited that the cholinergic anti-inflammatory pathway involves direct synapses between vagal efferents and catecholaminergic splenic neurons in the coeliac or superior mesenteric ganglia. However, the proposed circuitry remains contentious, as evidence for these direct connections has not been reported by all groups[91–94]. An alternate hypothesis is that the anti-inflammatory effect of VNS is due to vagal afferent stimulation with sympathetic splanchnic nerves serving as the efferent arm[95]. Resection of splanchnic nerves results in enhanced inflammation in response to LPS in rodents[96,97] and selective stimulation of vagal afferents alone is able to recapitulate intact VNS suppression of systemic inflammation in certain models[80,98,99]. However, selective vagal efferent stimulation remains able to drive system anti-inflammatory activity, and the dependence on splenic ChAT$^+$ T cells seems unique to a vagal efferent pathway[99,100]. A likely reconciliation of these disparate data sets is that there are at least two discrete pathways, with a vagal afferent or centrally mediated mechanism with predominantly sympathetic output contributing to anti-inflammatory autonomic signalling in certain contexts[99,101]. Much of the work described above is potentially limited by confounding effects of surgical approaches, and further interrogation of the molecular circuitry of these pathways via genetic approaches is needed.

There is evidence that splenic nerve signalling to ChAT$^+$ T cells is involved in the signal transduction that modulates immune function in multiple additional pathways. Splenic nerve denervation in mice showed that splenic nerve activity augments T cell-dependent plasma cell formation[102]. This effect was dependent on ChAT$^+$ T cells signalling to B cells via the α9-nicotinic receptor. Intriguingly, this immunostimulatory pathway did not seem to be part of a vagal reflex arc but, instead, to be a result of activation of the central nucleus of the amygdala and paraventricular nucleus[102].

ChAT$^+$ T cells are also found outside the spleen. For example, ChAT$^+$ T cells are recruited to the large intestine and reduce bacterial burden during enteric *Citrobacter rodentium* infection in mice[103]. Circulating ChAT$^+$ T cells also modulate blood pressure through signalling to endothelial cells[104]. Furthermore, during chronic infection by lymphocytic choriomeningitis virus (LCMV) in mice, ChAT$^+$ T cells mediate vasodilation and migration of antiviral T cells into infected tissues[105]. Thus, these cells are well positioned to represent a nexus of neuroimmune crosstalk in tissues other than the spleen.

The vagus nerve can suppress intestinal inflammation independent of splenic nerve signalling (FIG. 4c). VNS remains effective in improving intestinal inflammation in splenic denervated and T cell-deficient mice, but not in α7nAChR-deficient mice[106]. Close contact between cholinergic myenteric neurons and intestinal resident macrophages and the modulation of macrophage activation and cytokine production by α7nAChR activation have been demonstrated, suggesting that vagal signalling suppresses intestinal inflammation via cholinergic myenteric nerve signalling to intestinal macrophages[106]. Signalling by the parasympathetic nervous system is also implicated in the production of lipid and protein mediators of inflammation resolution. In a mouse model of bacterial peritonitis, vagotomy decreased concentrations of PCTR1 (protein conjugates in tissue regeneration 1), which promotes resolution, and elevated levels of inflammation-initiating eicosanoids and was associated with a delay in resolution of the infection[107]. This effect was posited to be partially mediated by ACh-mediated upregulation of PCTR synthesis in type 3 ILCs (ILC3s). In another model of peritonitis, the vagus nerve regulated expression of netrin 1, which reduced neutrophil numbers, reduced pro-inflammatory mediators and stimulated production of resolvins[108].

Given this ability to modulate inflammation, VNS is being trialled as a strategy to address several inflammatory conditions in humans including rheumatoid arthritis[109] and Crohn disease[110,111]. As clinical experience and demonstrated safety of VNS in the treatment of drug-resistant epilepsy and depression exist, there is considerable interest in exploring its efficacy in these other inflammatory conditions[112].

Enteric neuron regulation of immunity

The gastrointestinal tract is the largest mucosal interface in the body and is innervated by both extrinsic and intrinsic neurons. Extrinsic neurons from the somatosensory system and the autonomic nervous system synapse directly onto myenteric ganglia and the smooth muscle and mucosa of the gastrointestinal tract. The gastrointestinal tract's intrinsic network of neurons, dubbed the ENS, innervates its breadth and depth and can function autonomously. Enteric neurons have recently been found to interact with and powerfully regulate immune cell function in the gut.

Neurons of the ENS reside in ganglionated networks within the intestinal tube, with cell bodies organized within two layers: the myenteric plexus and the submucosal plexus. ENS cells include intrinsic primary afferent

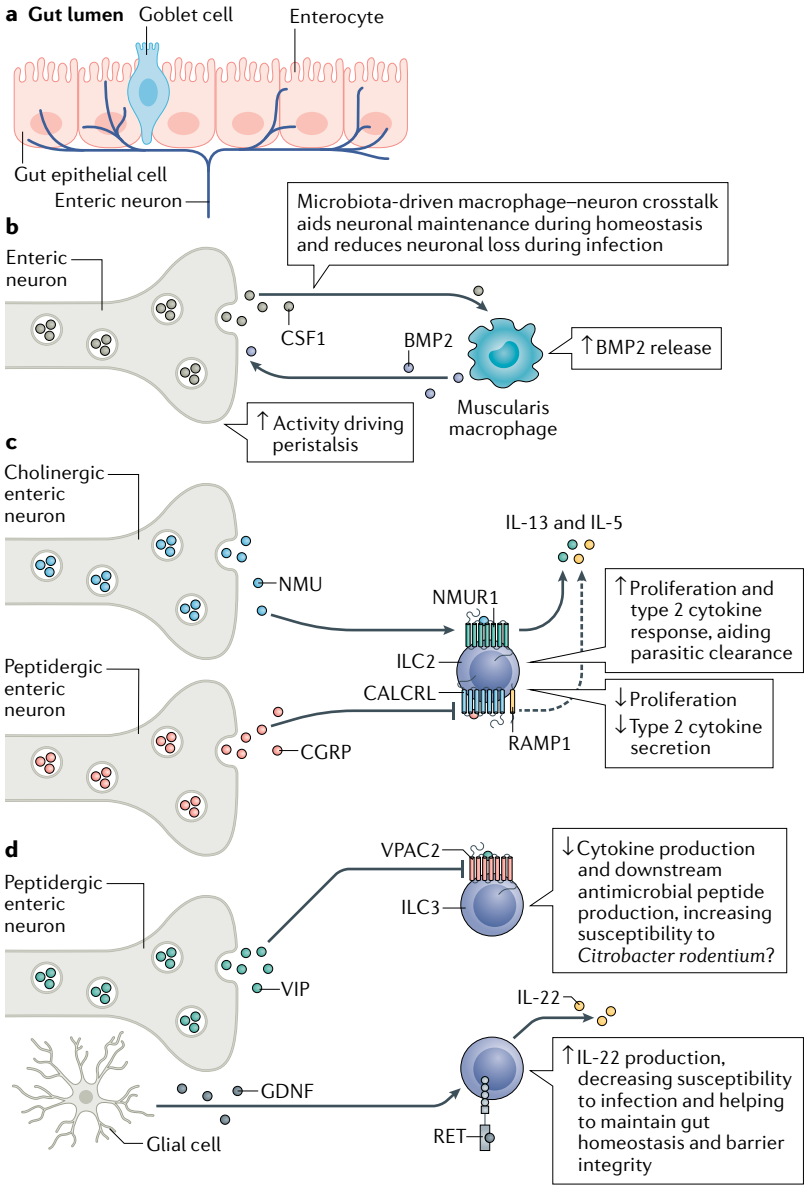

Fig. 5 | **Examples of enteric neuron–immune cell interactions. a** | Intrinsic enteric neurons of the gastrointestinal tract crosstalk extensively with immune cells and specialized cells in the gut, including goblet cells. Selected mechanisms of enteric nervous system (ENS)–immune cell crosstalk are illustrated in **b**–**d**. **b** | Enteric neurons secrete macrophage colony-stimulating factor 1 (CSF1) that stimulates muscularis macrophages to secrete bone morphogenetic protein 2 (BMP2)[113]. BMP2 then acts on enteric neurons to stimulate peristalsis. This neuron–macrophage signalling loop is dependent on the microbiota. **c** | Cholinergic enteric neurons and enteric sensory neurons regulate gut type 2 innate lymphoid cells (ILC2s) via neuromedin U (NMU) and calcitonin gene-related peptide (CGRP), respectively. NMU binds to the NMU receptor 1 (NMUR1) and increases ILC2 proliferation and production of type 2 cytokines (including interleukin-13 (IL-13) and IL-5), improving parasite clearance during *Nippostrongylus* infection[115,116]. By contrast, CGRP binds to the CGRP type 1 receptor (CALCRL)–receptor activity-modifying protein 1 (RAMP1) complex and decreases ILC2 proliferation and cytokine production[117–119]. **d** | The ENS also regulates type 3 innate lymphoid cells (ILC3s). Enteric neurons secrete vasoactive intestinal peptide (VIP) which acts on ILC3s via VIP receptor 2 (VPAC2). It has been reported that this results in decreased cytokine production and antimicrobial peptide secretion, increasing susceptibility to *Citrobacter* infection[120]. However, other studies suggest the opposite effect[121]. Glial cell-derived neurotrophic factor (GDNF) released from enteric glial cells increases IL-22 production by ILC3s via the RET receptor, resulting in decreased infection susceptibility and increased barrier integrity[122].

neurons (which detect chemical and mechanical stimuli), intrinsic motor neurons (which mediate motor, vasodilatory and secretomotor functions), connecting interneurons and enteric glial cells. Acting in concert, these neurons can detect luminal cues and mediate reflex motor and secretory function. They also maintain bidirectional communication with extrinsic sensory, parasympathetic and sympathetic neurons, allowing for integrated control of gastrointestinal function. Similar to the extrinsic neurons discussed above, neurons of the ENS can also crosstalk with gastrointestinal tract immune cells (FIG. 5).

Enteric neuron crosstalk with innate immune cells. Tissue-resident macrophages are one of the most numerous immune cells in the intestinal mucosa and muscularis and are found proximate to enteric neurons[113,114]. In mouse models, muscularis macrophages secrete bone morphogenetic protein 2 (BMP2), which acts on enteric neurons to stimulate peristalsis; in turn, enteric neurons secrete macrophage colony-stimulating factor 1 (CSF1) (FIG. 5b). Antibiotic treatment decreased both CSF1 expression in the colonic muscularis and muscularis macrophage numbers, with luminal microbiota transfer rescuing CSF1 expression, suggesting that the gut microbiota drives this enteric neuron–macrophage crosstalk[113]. Gut macrophage populations have been linked to maintenance of enteric neurons during homeostasis[114] and to limiting enteric neuronal damage during intestinal infection[57], as part of a circuit that involves signalling from extrinsic sympathetic neurons.

Enteric neurons also interact with other immune cells. Recent work has shown that NMU is released from cholinergic enteric neurons and regulates ILC2s (FIG. 5c). ILC2s express high levels of the NMU receptor NMUR1, and NMU acts on ILC2s to increase proliferation and the type 2 cytokine response. Challenge with the helminthic parasite *N. brasiliensis* increased levels of NMU, and mice with global or ILC2-specific loss of NMUR1 were less able to clear infection[115,116]. By contrast, CGRP, which is expressed by enteric neurons along with somatosensory neurons and immune cells, can suppress ILC2 proliferation and type 2 inflammatory cytokine production[117–119] (FIG. 5c). Thus, there are contrasting roles for distinct neuronal signals.

Enteric neurons also modulate the activity of ILC3s. ILC3s in intestinal lymphoid tissue clusters and colonic lymphoid patches are in close proximity to lamina propria neurons expressing VIP[120] and ILC3s express VPAC2 (REFS[120,121]). Feeding activates enteric neurons, which leads to VIP secretion. VIP inhibits the production of cytokines (including IL-22) from ILC3s and, consequently, decreases antimicrobial peptide secretion in mice (FIG. 5d), allowing for increased segmented filamentous bacteria levels to occur following feeding. Chemogenetic activation of VIPergic neurons also increased mouse susceptibility to *C. rodentium* infection[120]. By contrast, another study found that VIP injection led to increased production of IL-22 by ILC3s and that VPAC2 deficiency in mice led to impaired IL-22 production[121] (FIG. 5d). These discrepancies could be due to methodological differences: the first study utilized chemogenetics to

Antimicrobial peptide
A class of protein secreted by cells of the innate immune system that has broad and potent microbicidal properties and includes peptides with antibacterial, antifungal and antiviral properties.

activate or silence all VIP-producing neurons, whereas the second utilized VIP injections. It is also possible that VPAC2 is finely tuned by the concentration of VIP present and its kinetics of activation.

Non-neuronal ENS cells also contribute to the regulation of gut ILC3 function. Glial cell-derived neurotrophic factor (GDNF) can directly modulate IL-22 production by gut ILC3 cells, with glial cell-specific ablation of the myeloid differentiation primary response protein MYD88 resulting in decreased downstream GDNFs and leading to impaired production of IL-22 by ILC3s, and thus susceptibility to gut infection[122]. GDNF signalling is mediated via the GDNF receptor RET, expressed by ILC3s (REF.[122]) (FIG. 5d). As RET is also expressed on other immune cells, its activation may provide a broader mechanism for ENS–immune cell crosstalk. Enteric glia also drive muscularis macrophage activation through connexin 43-dependent CSF1 release in a mouse model of colitis; specific targeting of this mechanism of glial intercellular communication demonstrated that it contributes to development of visceral hypersensitivity post colitis without affecting severity of acute inflammation[123]. In contrast, depletion of enteric glial cells in mouse models results in fulminant bowel inflammation, supporting a role of glial cells in maintaining gut homeostasis and barrier integrity[124,125].

Enteric neuron–immune–gut microbiome interactions. Enteric neurons may also modulate adaptive immune responses. Intriguing work suggests that modulation of enteric sensory neurons by intestinal symbionts may drive distinct immunological responses. In cell culture, enteric neurons could modulate the differentiation of intestinal regulatory T cells (T_{reg} cells), reducing their expression of FOXP3 but increasing the fraction of cells expressing of RORγ[126]. This effect was mediated mainly via neuronal production of IL-6. However, loss of CGRP and VIP reduced ENS production of IL-6 and downstream T_{reg} cell frequencies. In vivo, introduction of the commensal RORγ-expressing T_{reg} cell inducer *C. ramosum* to germ-free mice led to a reduction in total ENS density followed by a reduction in neuronal IL-6 expression[126], suggesting one mechanism by which gut microbial organisms could tune colonic T_{reg} cell pools.

Enteric neurons can also regulate gastrointestinal immunity via interactions with gut epithelial cells. IL-18 is a key host protective factor against certain invasive enteric infections, with immune or epithelial IL-18 thought to be critical for mucosal barrier maintenance[127]. However, intestinal enteric neurons also produce IL-18, and deletion of IL-18 from neurons increased bacterial infiltration and invasion in *S. typhimirium* infection in mice. Enteric neuronal IL-18 production was critical for goblet cell antimicrobial protein production, suggesting that enteric neuronal signalling is key to homeostatic mucosal barrier maintenance and that other sources of IL-18 may be redundant[128]. Goblet cell microbial sensing is also responsive to ACh acting on muscarinic ACh receptor 4, suggesting another mechanism by which enteric neurons could modulate gut epithelial immunity[129].

Current studies have thus delineated a few enteric neuron–immune cell circuits; however, given the complexity of the ENS, the gut microbiome and the gastrointestinal immune system, it is likely that our understanding of the role of enteric neuronal communication with immune cells remains in its infancy. The anatomic co-localization of immune cells and gut-innervating neurons is suggestive of additional roles, as are changes seen in various disease states. For example, mast cells in the intestine are located close to enteric neurons[130,131] and increased mast cell infiltration and mediator release near intestinal nerves is seen in patients with irritable bowel syndrome[132]. Although mast cells have been shown to contribute to visceral pain, how they are regulated by neurons in the gut is less well understood. Thus, further research into the role of ENS communication with diverse innate and adaptive immune cells at homeostasis and during inflammation is needed.

Conclusions

In this Review we have highlighted the compelling body of evidence that demonstrates the pivotal role of the PNS in regulating our body's defence mechanisms and coordinating immune responses. Sensory neurons detect invading pathogens and immune cell activation and, in response, relay signals to the CNS and act locally to regulate immune cell function. Efferent autonomic neurons, acting in reflex circuits that are integrated with sensory afferent inputs and overlaid by the CNS, also provide integral control of immune function at both the local and systemic level. This serves to induce and amplify local immune responses, but also to resolve inflammation and restore homeostasis. These mechanisms are crucial for appropriate protective immunity against multiple pathogens, with hijacking of immunoinhibitory neural pathways exploited by certain pathogens to facilitate invasion. In the context of autoimmune disorders, stimulation of activating neural pathways or silencing of inhibitory pathways can lead to inappropriate and excess inflammation. The same PNS arms can clearly exert differential and even opposing effects on immune cells depending on different disease, tissue and timing contexts. Understanding the distinct drivers that govern the temporal and spatial regulation of neuronal response is therefore of crucial importance. One mechanism that is likely to underlie this heterogeneous response is the presence of distinct subsets of neurons within the various PNS arms. With novel genetic tools, we can start to uncover this functional diversity and identify neuronal subpopulations. Given the sophistication of the neuron–immune dialogue, it is also likely that additional neuronal mediators can regulate immune cells; identification of these effectors is an area of further investigation.

Although current work has largely focused on neuronal roles in specific infectious and autoimmune or allergic illnesses, it is increasingly clear that neuroimmune crosstalk is a critical mediator of tissue immunity and is likely to play a role in additional disease processes in which immune responses are dysregulated, such as cancer[58,133]. Neuroimmune communication may

additionally have implications for interventions ranging from vaccines to transplantation and therapeutic modalities that alter peripheral neuron communication deserve further investigation.

Most exciting are the possibilities of translating our understanding of neuroimmune communication to new therapies, especially given the possibility of repurposing the neuron-specific pharmacologic agents that have already been developed. Neural circuits that control inflammation and immunity offer novel targets for the treatment of a wide array of diseases. Currently, many chronic inflammatory diseases are treated with systemic immunomodulatory therapy; addressing the neural component could offer a more targeted, localized approach or, in combination with immunomodulatory treatment, a more effective therapy. Similarly, inhibiting immunosuppressive neural signalling could offer benefit in various infectious diseases, particularly in the case of invasive or resistant pathogens, whereas augmenting the neural communication that drives resolution could offer therapeutic benefit in infections where pathological inflammation drives morbidity. Translating these mechanistic insights into therapeutics will require a comprehensive understanding of how neural signals integrate with specific immune cells across the spectrum of physiological and pathological states.

Published online 7 January 2022

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Acknowledgements
I.M.C.'s laboratory received funding from the National Institutes of Health (NIH) (R01DK127257, R01AI130019), Chan-Zuckerberg Initiative, Food Allergy Science Initiative, Kenneth Rainin Foundation, GSK Pharmaceuticals, Abbvie Pharmaceuticals and Burroughs Wellcome Fund. S.U. received support from the NIH under T32 AI007061.

Author contributions
S.U. researched the data for the article. S.U., K.B. and I.M.C. made substantial contributions to the discussion of content, wrote the article and reviewed/edited the article before submission.

Competing interests
S.U. is a current employee of Vertex Pharmaceuticals and may own company stock. K.B. is a current employee of Genoskin Inc. I.M.C. serves on scientific advisory boards for GSK Pharmaceuticals and Limm Therapeutics. His laboratory receives research support from Abbvie Pharmaceuticals, GSK Pharmaceuticals and Moderna Inc.

Peer review information
Nature Reviews Neuroscience thanks N. Gaudenzio, D. Kaplan, K. Tracey and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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