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REVIEW ARTICLE

Crosstalk between Sensory Neurons and Local Immunity during Peripheral Inflammation

Muge Qile[1] and Shufang He[1] (✉)

[1] *Department of Anesthesiology and Perioperative Medicine, the Second Affiliated Hospital of Anhui Medical University; Key Laboratory of Anesthesiology and Perioperative Medicine of Anhui Higher Education Institutes, Anhui Medical University, Hefei 230032, China*

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ABSTRACT

Sensory neurons, also known as afferent neurons, perceive noxious stimuli from internal as well as external environments through nociceptive receptors and then transmit these signals to the central nervous system. Similarly, the innate immune system also recognizes external and internal danger signals from invading microbes or tissue injuries. The immune system and sensory neurons share mechanisms to respond to pathogen/damage-associated molecular patterns (PAMPs/DAMPs) through pattern recognition receptors. Recent studies have identified an inseparable bidirectional connection between sensory neurons and the immune system that is important for maintaining tissue homeostasis and regulating inflammatory states, as well as affecting the progression of inflammatory diseases. This review summarizes the recent findings on the crosstalk between sensory neurons and local immunity in peripheral tissues, including the skin, respiratory system, gastrointestinal tract, cornea, and joints. Understanding the mechanisms of this interaction can help in the development of therapeutic strategies to treat peripheral inflammatory diseases.

1 Introduction

Traditionally, the peripheral nervous system and the immune system have been considered two independent entities; however, evidence suggests the presence of a close complex relationship between them. When tissue damage or inflammatory infection occurs, danger signaling molecules, such as danger-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs), are released; these simultaneously activate peripheral sensory neurons and immune cells to establish a unified host defense system [1]. Under physiological or pathological conditions, peripheral sensory neurons and immune cells interact closely to form an important immune regulatory hub. Immune cells and nerve cells colocalize to different anatomical sites and interact with one another, acting as neuroimmune cell units (NICUs) [2]. They can also perceive environmental signals and respond to them, thus playing a crucial role

Address correspondence to sfhe@ahmu.edu.cn

in hematopoiesis, organ formation, inflammation, tissue repair, and thermogenesis [3].

Peripheral sensory neurons release various neuropeptides, including calcitonin gene-related peptide (CGRP), substance P (SP), and vasoactive intestinal peptide (VIP), that act on the innate and adaptive immune systems and vascular system to regulate the immune response or inflammatory processes. Conversely, immune cells can regulate the signaling and activity of sensory neurons by releasing cytokines and growth factors or by synthesizing and releasing neurotransmitters and neuromodulators, such as acetylcholine, dopamine, and catecholamines, that act on the corresponding receptors on sensory neurons. The interaction between sensory neurons and the immune system plays a significant role in the local immune response and inflammatory diseases of the skin, respiratory tract, gastrointestinal tract, cornea, and joints (Fig. 1). Understanding the mechanisms underlying the interaction between sensory neurons and local immune systems can aid in the identification of therapeutic targets for preventing and treating inflammatory and autoimmune diseases.

2 Crosstalk between sensory neurons and immune responses of the skin

As the largest barrier and protective organ in the body, skin comprises a dense neural network. This network majorly includes sensory nerve fibers from the dorsal root ganglion (DRG) and trigeminal ganglion that innervate the dermis

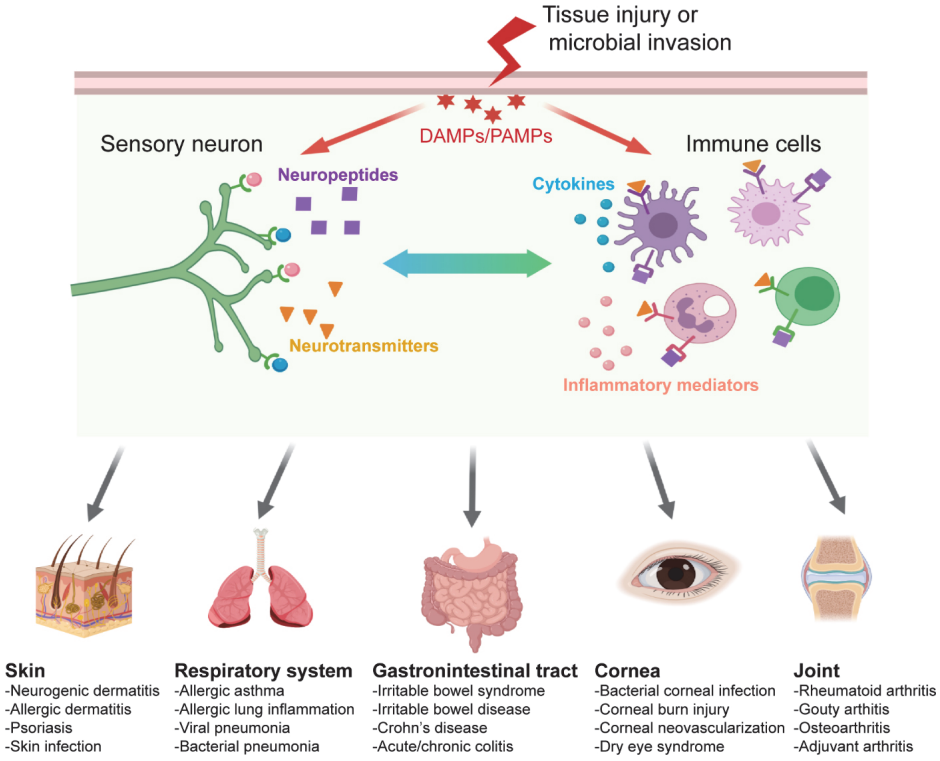

Figure 1 Schematic diagram for the crosstalk between sensory neuron and immune cells in peripheral inflammatory diseases. After tissue injury or microbial invasion, danger signal molecules, such as danger-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs), are released. These can simultaneously activate peripheral sensory neurons and immune cells. Sensory neurons release neuropeptides or neurotransmitters from their axon terminals, which then bind and activate their corresponding receptors expressed on local immune cells and lead to local immune modulation by the nervous system. Subsequently, immune cells release cytokines or inflammatory mediators, which in turn, bind to their receptors on sensory neurons, sensitizing or inhibiting neuronal activity. The imbalance or abnormal crosstalk between sensory neuron and local immune cells may contribute to inflammatory diseases in different peripheral tissues, including the skin, respiratory system, gastrointestinal tract, cornea, and joints.

and epidermis of the skin and help perceive pain, touch, and itching sensations. The skin also contains resident immune cells to cope with damage to the stability of the internal environment. Regulation of the neuroimmune interaction is essential in some skin inflammatory diseases, such as neurogenic dermatitis, allergic dermatitis, psoriasis, and skin infections.

As the first line of defense against pathogen invasion, the skin contains specialized immune cells, known as dermal dendritic cells (DDCs), and γδT cells that produce IL-17 (γδT17). DDCs primarily produce IL-23, which then induces γδT17 to secrete large amounts of IL-17 to promote skin inflammatory syndromes, such as psoriasis [4]. Sensory neurons that express TRPV1 and Nav1.8 are important for driving IL-23-induced psoriasis-like skin inflammation. These sensory neurons regulate the IL-23/IL-17 pathway and control skin immune response by interacting with DDCs [5]. The activation of TRPV1+ neurons is sufficient to elicit a local type-17 cutaneous inflammatory response that depends on the vesicle release of CGRP. This local neuron activation results in type 17 responses and augments host defense in the unstimulated skin through a nerve reflex arc [6].

Proteinase-activated receptor-2 (PAR-2), which is expressed on the primary afferent nerve fibers, plays a key role in the development of itchy skin disorders, such as atopic dermatitis. Studies have shown that in patients with atopic dermatitis, increased PAR-2 staining was observed in nerve fibers closely associated with mast cells in the affected skin [7]. When endogenous PAR-2 agonists were intracutaneously administered, it induced prolonged itching sensations. The itching sensation caused by mast cell degranulation could not be treated using local antihistamines in patients with atopic dermatitis [7]. PAR-2 is expressed by various inflammatory cells, including mast and T cells; this indicates a connection between the inflammatory and sensory phenomena of atopic dermatitis. Therefore, enhanced PAR-2 signaling represents an important link between inflammation and development of itching sensations in atopic dermatitis [7].

3 Crosstalk between sensory neurons and immune responses in the respiratory system

The respiratory system is directly exposed to the external environment, leaving it vulnerable to invasion by harmful substances. The interaction between dense network of nerves and large number of immune cells in the lungs is crucial for maintaining host defense.

Peripheral sensory afferent neurons that innervate the respiratory tract include vagal and spinal sensory neurons, the cell bodies of which are located in the vagal ganglia (VG) and DRG, respectively. These sensory neurons play a vital role in recognizing airway irritation, inflammation, and mechanical strain. The axon terminals of these neurons contain ion channels, such as TRPV1 and TRPA1, as well as G protein-coupled receptors, both of which form the foundation of immune response neural regulation. Type 2 innate lymphoid cells (ILC2s) maintain mucosal homeostasis and promote pathological inflammation in allergic asthma. Neurotransmitters such as SP, CGRP, and VIP can potentially regulate ILC2s and contribute to lung inflammation [8].

Neuropeptide U (NMU) is primarily released by cholinergic sensory neurons in the DRG [9]. Dendritic cells, monocytes, and other antigen-presenting cells also secrete NMU but to a lesser extent [10]. Resident ILC2s in the lungs preferentially express the NMU receptor (NMUR1) in a steady state or after IL-25 stimulation. NMU activates ILC2s *in vitro* and *in vivo*. Combining NMU with IL-25 significantly promotes allergic inflammation [11]. Additionally, under sepsis

conditions, the expression of NMU in the lungs as well as the selective expression of NMUR1 on ILC2s increases. NMU also activates ILC2s by binding to NMUR1, promoting γδ T cell expansion, and IL-17 secretion [12]. Therefore, the NMU–NMUR1 signaling pathway plays a significant role in promoting ILC2-mediated inflammatory response. This highlights the importance of the crosstalk between sensory neurons and respiratory immune responses [11].

Respiratory viruses can act directly or indirectly through receptors expressed on sensory neurons, such as TRP channels or acid-sensing ion channels. Respiratory syncytial virus and measles virus can infect both sensory neurons and bronchial epithelial cells, leading to the upregulated expression of TRPV1, TRPA1, and ASIC3 in both cell types as well as increased levels of inflammatory cytokines such as IL-8 and IL-16 [13]. In a model of lethal pneumonia induced by *Staphylococcus aureus*, TRPV1+ sensory neurons in the VG exert an immunosuppressive effect by releasing CGRP. Targeted elimination or depletion of TRPV1+ neurons increases survival, induces cytokine production, and promotes bacterial clearance in the lungs [14].

4 Crosstalk between sensory neurons and immune responses in the gastrointestinal tract

The gastrointestinal tract is supplied with a complex network of neurons and includes parts of the extrinsic as well as intrinsic nervous systems. The extrinsic nervous system includes the spinal and vagal afferent sensory neurons originating from DRG and nodose/jugular ganglion, respectively, whereas the intrinsic enteric nervous system (ENS) comprises the myenteric and submucosal plexuses that are present along the entire gastrointestinal tract. Peptidergic neurons act on the mucosal immune system by secreting neuropeptides CGRP and SP. Moreover, immune cells within the gastrointestinal tract express several neuropeptide receptors, such as the CGRP, SP, and NPY receptors, making them direct targets for neuronal action [15].

Bidirectional communication between the nervous and immune systems plays an essential role in various gastrointestinal diseases. For patients with irritable bowel syndrome (IBS), colonic mucosal biopsies revealed increased inflammatory mediators, such as histamine and serine proteases from mast cells. This effectively makes the ENS more sensitive to mechanical stimuli [16]. Cytokines such as IL-1β, TNF-α, and IL-6, which are usually high in patients with IBS, could be used to sensitize murine colonic afferents to mechanical stimuli by activating the afferent-expressing receptors, and the levels of these proinflammatory cytokines are correlated with pain symptoms [17]. Moreover, the pathophysiology of inflammatory bowel disease (IBD) involves interaction between the intestinal mucosal immune system and ENS and includes the secretion of various mediators, such as neuropeptides and serotonin. Specific receptors expressed by intestinal immune cells, such as macrophages, mast cells, and dendritic cells, play an important role in such communication [18].

TRPA1 is a temperature-sensitive receptor that activates and releases SP, subsequently leading to the degranulation of mucosal mast cells, promotion of neurogenic inflammation, and damage to gastric mucosal tissue [19]. SP is an essential neuropeptide produced in the intestine that acts on neurokinin receptors 1, 2, and 3 (NK-1, NK-2, and NK-3) and has the highest affinity for NK-1 [20]. In patients with IBD, SP expression and NK-1 receptor levels are increased. In contrast, SP levels are decreased in the intestinal mucosa of patients with Crohn's disease, suggesting that the effects of SP differ based on the disease stage or nature. For example, researchers speculate

that SP has a pro-inflammatory effect on acute colitis [19] but promotes intestinal epithelial cell proliferation and mucosal healing during chronic colitis [21].

In the gastrointestinal tract, TRP channels regulate the secretion of CGRP. The activation of TRPV1+ neurons induces the release of CGRP, this helps reduce mucosal damage. Nonetheless, the role of TRPV1 in intestinal inflammation remains controversial [22]. CGRP antagonists can aggravate colitis; however, it may play a protective role in IBD as intravenous CGRP injection can alleviate colitis inflammation [22]. Another study revealed that in TRPM8-deficient mice, insufficient CGRP is released from the sensory neuron axon terminals into the microenvironment, which leads to dendritic cell dysfunction; in contrast, inflammation is reversed when treated with CGRP [23].

VIP is another important neuropeptide that is primarily derived from the myenteric and submucosal plexuses of neurons in the gut. The receptors of VIP, VPAC1 and VPAC2, are expressed in immune cells such as dendritic cells and macrophages. VIP plays an important role in the neural regulation of intestinal immune responses by inhibiting the activation of NF-κB; reducing the expression of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-12p40; and enhancing the expression of the anti-inflammatory cytokine IL-10 in macrophages [24]. VIP activates VPAC1, which then induces the expression of CD80, CD86, and CD40 as well as IL-10, the anti-inflammatory cytokine, in response to lipopolysaccharide (LPS) stimulation [25].

Mast cells are primarily located in the mucosal and submucosal layers of the gastrointestinal tract. They are anatomically connected with sensory neuron axon terminals, creating a tight link for bidirectional communication. Mast cells respond to neuropeptides released from the axon terminals by releasing inflammatory mediators, including histamine and 5-hydroxytryptamine, in contrast, neurons expressing histamine and 5-hydroxytryptamine receptors can provide feedback to maintain the homeostasis of the mucosal barrier [26]. Histamine released by mast cells activates the TRPV1, TRPV4, TRPA1, and Nav1.8 channels, thereby increasing neuronal firing rates and causing abnormal pain perception. Similarly, serotonin increases the excitability of afferent neurons and the sensitivity of TRPV1 and TRPV4 channels, contributing to pain sensation [27]. ILCs are co-localized with neurons in the gastrointestinal tract and expresses neuropeptide receptors, including NMU, VIP, and CGRP receptors. NMUR1 is selectively expressed on ILC2s, whereas the VIP receptor, Vipr2, is expressed on both ILC2s and ILC3s [28, 29].

5 Crosstalk between sensory neurons and immune responses in the cornea

The cornea is considered an immune-privileged site because of its anatomical features, cellular barriers, ocular-induced immune tolerance, and immune-suppressive microenvironment, among other mechanisms [30]. The cornea does not have blood and lymphatic vessels and is directly exposed to the external environment. This makes bidirectional communication between sensory neurons and resident immune cells in the cornea important to maintain ocular homeostasis and resist external stimuli.

Various resident immune cell populations, including dendritic cells, macrophages, mast cells, and ILCs, are present in the corneal epithelium and stroma [31]. In case of corneal injury, neutrophils migrate to the injured site and release growth factors, including vascular endothelial growth factor, to promote corneal nerve growth. The corneal nerve supply primarily comprises sensory neurons from the trigeminal nerve [32], including multimodal nociceptors, pain receptors,

and cold-sensitive neurons [33]. These neurons can increase blink frequency and tear secretion to initiate a protective reflex in response to external stimuli [34]. Additionally, corneal nerves secrete neurotrophic factors and neuropeptides. Neuroimmune modulation mediated by the nervous system can regulate inflammation and promote wound healing during bacterial corneal infections [35].

Several studies have highlighted the important role of sensory neurons in the regulation of corneal inflammation and wound healing. *Pseudomonas aeruginosa* infections can activate corneal sensory neurons, leading to the recruitment of macrophages and upregulation of CGRP [36]. CGRP, in turn, induces the transition of macrophages from a pro-inflammatory (M1) to an anti-inflammatory (M2) phenotype; this reduces inflammation and decreases corneal pathological damage [36, 37].

Similarly, in corneal inflammation induced by epithelial abrasion, TRPV1+ sensory neurons can inhibit the recruitment of neutrophils and γδT cells and modify macrophage function to suppress inflammation and support corneal wound healing [38]. However, SP plays a dual role in corneal neuroimmune regulation as it can promote or inhibit inflammation depending on the circumstance. It has been shown that in cases with corneal alkali burns, the levels of SP and its receptor NK1R rapidly increase in the cornea, thus leading to ocular diseases, such as corneal neovascularization and dry eye syndrome [39].

6 Crosstalk between sensory neurons and immune responses in the joint

Neuroimmune crosstalk plays an important role in the pathogenesis of common inflammatory joint diseases, including rheumatoid arthritis (RA), gouty arthritis (GA), osteoarthritis (OA), and aseptic loosening of implants (AL). Capsaicin-sensitive sensory nerves are densely distributed in the joint capsule and synovium. These sensory nerves release SP and CGRP to dilate blood vessels and recruit immune cells or somatostatin to inhibit inflammation [40]. Further, these nerves mediate mechanical hypersensitivity during the late stages of chronic antibody-induced arthritis [40].

Sensory neuron–derived neuropeptides, such as SP, have a significant pro-inflammatory effect in models of adjuvant arthritis. Notably, intra-articular administration of an SP receptor antagonist reduces cartilage loss and pain sensitivity [41]. The peripheral release of CGRP results in vasodilation at the joint, which contributes to pain and neurogenic inflammation. In the joint, CGRP acts on its receptor that is expressed on resident synovium cells, inflammatory cells, and sensory neurons and attenuates angiogenesis, inflammation, and peripheral sensitization in chronic arthritis [42]. Moreover, secreted frizzled-related protein 2 (sFRP2) released by DRG neurons promotes M1 macrophage polarization and migration by regulating Wnt/β-catenin and NF-κB signaling pathways, thus promoting inflammation in GA [43].

Immune cells produce cytokines that play complex roles in the pathogenesis of arthritis. During the inflammatory process of arthritis, sensory neurons expressing cytokine receptors, such as IL-1R, IL-6R, IL-17R, and TNF-R, can bind to their respective cytokines and transmit information to DRG or central nervous system (CNS); this induces the release of CGRP, SP, and other neuropeptides [44]. In an antigen-induced arthritis model, IL-1β and its receptor may be associated with arthritis-induced thermal hyperalgesia. Furthermore, IL-1β upregulates TRPV1 expression in DRG neurons, whereas IL-1 antagonists downregulate TRPV1 expression during arthritis and relieve thermal hyperalgesia [45].

7 Therapeutic strategies targeting the neuroimmune crosstalk in inflammatory diseases

Abnormal and prolonged peripheral inflammatory responses may lead to tissue damage, organ failure, and chronic pain. Traditional therapies targeting inflammation have limited efficacy and can have various side effects. Therefore, novel therapeutic strategies that focus on the crosstalk between the nervous and immune systems have attracted increasing attention.

One promising strategy is to inhibit the TRP channels expressed on sensory nerves using small molecular inhibitors or induce the desensitization/depletion of the sensory nerves. Clinically, the topical application of capsaicin has been used as a treatment for patients with arthritis and inflammatory skin diseases [46]. Notably, although the inhibition of TRP channels expressed on sensory nerves may offer a promising therapeutic strategy for inflammatory diseases, TRPV1+ neurons may exert tissue protective effects in certain situations. For example, ablation of gut-innervating TRPV1+ neurons may enhance susceptibility to intestinal damage and inflammation [47].

Blocking neuropeptide signaling components, such as SP and CGRP, through the use of their respective receptor antagonists can alleviate inflammatory diseases. Antagonism of NK1R-mediated SP signaling reduces corneal inflammation, decreases neovascularization, and ameliorates dry eye disease [48]. Recently, a clinically approved NK-1R antagonist, aprepitant, attenuated local inflammation in an *in vivo* mouse model of post-traumatic staphylococcal osteomyelitis [49]. Additionally, CGRP antagonists or CGRP neutralizing antibodies have been used to alleviate neurogenic inflammation and arthritis pain in preclinical studies [42, 50].

Another promising strategy is the use of electrical stimulation to manipulate the neuroimmune axis. By targeting the communication pathway between the nervous and immune systems, vagus nerve stimulation (VNS) can effectively suppress inflammation and alleviate pain under various conditions, including RA, IBD, and sepsis [51, 52]. This approach involves the use of electrical signals delivered to the vagus nerve, which runs from the brainstem to the abdominal cavity, to modulate immune cell and cytokine activity. Clinical trials have demonstrated the safety and efficacy of this approach, although more studies are warranted to determine the optimal parameters and long-term effects of the use of VNS in the treatment of inflammatory diseases.

8 Conclusions and future perspectives

In summary, sensory neurons and immune cells engage in bidirectional communication to maintain homeostasis and barrier tissue integrity in response to environmental stimuli. Upon sensing signals, the sensory neurons release neuropeptides and neurotransmitters that bind to local immune cells and lead to immune modulation by the nervous system. In contrast, immune cells release cytokines and inflammatory mediators that act on sensory neurons to enhance or inhibit their activities. The interactions between sensory neurons and local immune systems have been implicated in inflammatory diseases of various peripheral tissues, such as skin, respiratory system, gastrointestinal tract, cornea, and joints. Although similar immune cell populations, cytokines, inflammatory mediators, neuropeptides, and neurotransmitters are involved in sensory neuron–immune cell interactions in different tissues, the specific mechanism involved in each tissue depends on their local environment. More research is warranted to understand the specific

mechanisms involved in each tissue, determine the complex interplay between sensory neurons and immune cells, and identify novel therapeutic targets for inflammatory diseases.

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Author Contribution

S.F.H. and M.G.Q.L. participated in the conception and design of the review. M.G.Q.L. prepared the first draft of the manuscript. S.F.H. revised the manuscript. All authors approved the final version of the manuscript.

Declaration of conflicting interests

The authors declare no conflict of interest.

Data Availability Statement

None

Ethics approval

None

Consent to participate

None

References

[1] Chiu I M, Hehn C A v, Woolf C J . Neurogenic inflammation and the peripheral nervous system in host defense and immunopathology. *Nat Neurosci*, 2012, 15(**8**): 1063–1067.

[2] Veiga-Fernandes H, Pachnis V. Neuroimmune regulation during intestinal development and homeostasis. *Nat Immunol*, 2017, 18(**2**): 116–122.

[3] Godinho-Silva C, Cardoso F, Veiga-Fernandes H. Neuro-Immune Cell Units: A New Paradigm in Physiology. *Annu Rev Immunol*, 2019, 37: 19–46.

[4] Cai Y, Shen X, Ding C, et al. Pivotal role of dermal IL-17-producing gammadelta T cells in skin inflammation. *Immunity*, 2011, 35(**4**): 596–610.

[5] Riol-Blanco L, Ordovas-Montanes J, Perro M, et al. Nociceptive sensory neurons drive interleukin-23-mediated psoriasiform skin inflammation. *Nature*, 201*4,* 510(**7503**): 157–161.

[6] Cohen J A, Edwards T N, Liu A W, et al. Cutaneous TRPV1(+) Neurons Trigger Protective Innate Type 17 Anticipatory Immunity. *Cell*, 2019, 178(**4**): 919–932 e914.

[7] Steinhoff M, Neisius U, Ikoma A, et al. Proteinase-Activated Receptor-2 Mediates Itch: A Novel Pathway for Pruritus in Human Skin. *J Neurosci*, 2003, 23(**15**): 6176–6180.

[8] Chen W, Shu Q, Fan J. Neural Regulation of Interactions Between Group 2 Innate Lymphoid Cells and Pulmonary Immune Cells. *Front Immunol*, 2020, 11: 576929.

[9] Moriyama M, Furue H, Katafuchi T, et al. Presynaptic modulation by neuromedin U of sensory synaptic transmission in rat spinal dorsal horn neurones. *J Ph*ysiol, 2004, 559(**Pt 3**): 707–713.

[10] Hedrick J A, Morse K, Shan L, et al. Identification of a Human Gastrointestinal Tract and Immune System Receptor for the Peptide Neuromedin U. *Mol Pharmacol*, 2000*,* 58(**4**): 870–875.

[11] Wallrapp A, Riesenfeld S J, Burkett P R, et al. The neuropeptide NMU amplifies ILC2-driven allergic lung inflammation. *Nature*, 2017, 549(**7672**): 351–356.

[12] Chen W, Lai D, Li Y, et al. Neuronal-Activated ILC2s Promote IL-17A Production in Lung gammadelta T Cells During Sepsis. *Front Immunol*, 2021, 12: 670676.

[13] Omar S, Clarke R, Abdullah H, et al. Respiratory virus infection up-regulates TRPV1, TRPA1 and ASICS3 receptors on airway cells. *PLoS One*, 2017, 12(**2**): e0171681.

[14] Baral P, Umans B D, Wei Y, et al. Nociceptor sensory neurons suppress neutrophil and γδ T cell responses in bacterial lung infections and lethal pneumonia. *nature medicine*, 2018, 24(**4**): 417–426.

[15] Khalil M, Zhang Z, Engel M A. Neuro-Immune Networks in Gastrointestinal Disorders. *Visc Med*, 2019, 35(**1**): 52–60.

[16] Barbara G, Wang B, Stanghellini V, et al. Mast cell-dependent excitation of visceral-nociceptive sensory neurons in irritable bowel syndrome. *Gastroenterology*, 2007, 132(**1**): 26–37.

[17] Hughes P A, Harrington A M, Castro J, et al. Sensory neuro-immune interactions differ between irritable bowel syndrome subtypes. *Gut*, 2013, 62(**10**): 1456–1465.

[18] Korzenik J R, Podolsky D K. Evolving knowledge and therapy of inflammatory bowel disease. *Nat Rev Drug Discov*, 2006, 5(**3**): 197–209.

[19] Engel M A, Leffler A, Niedermirtl F, et al. TRPA1 and substance P mediate colitis in mice. *Gastroenterology*, 2011, 141(**4**): 1346–1358.

[20] Margolis K G, Gershon M D. Neuropeptides and inflammatory bowel disease. *Curr Opin Gastroenterol*, 2009, 25(**6**): 503–511.

[21] Koon H W, Zhao D, Na X, et al. Metalloproteinases and transforming growth factor-alpha mediate substance P-induced mitogen-activated protein kinase activation and proliferation in human colonocytes. *J Biol Chem*, 2004, 279(**44**): 45519–45527.

[22] Populin L, Stebbing M J, Furness J B. Neuronal regulation of the gut immune system and neuromodulation for treating inflammatory bowel disease. *FASEB Bioadv*, 2021, 3(**11**): 953–966.

[23] de Jong P R, Takahashi N, Peiris M, et al. TRPM8 on mucosal sensory nerves regulates colitogenic responses by innate immune cells via CGRP. *Mucosal Immunol*, 2015, 8(**3**): 491–504.

[24] Di Giovangiulio M, Verheijden S, Bosmans G, et al. The Neuromodulation of the Intestinal Immune System and Its Relevance in Inflammatory Bowel Disease. *Front Immunol*, 2015 6: 590.

[25] Delgado M, Gonzalez-Rey E, Ganea D. The Neuropeptide Vasoactive Intestinal Peptide Generates Tolerogenic Dendritic Cells. *J Immunol*, 2005, 175(**11**): 7311–7324.

[26] Stakenborg N, Viola M F, Boeckxstaens G E. Intestinal neuro-immune interactions: focus on macrophages, mast cells and innate lymphoid cells. *Curr Opin Neurobiol*, 2020, 62: 68–75.

[27] Salzer I, Gantumur E, Yousuf A, et al. Control of sensory neuron excitability by serotonin involves 5HT2C receptors and Ca(2+)-activated chloride channels. *Neuropharmacology*, 2016, 110(**Pt A**): 277–286.

[28] Seillet C, Luong K, Tellier J, et al. The neuropeptide VIP confers anticipatory mucosal immunity by regulating ILC3 activity. *Nat Immunol*, 2020, 21(**2**): 168–177.

[29] Klose C S N, Mahlakoiv T, Moeller J B, et al. The neuropeptide neuromedin U stimulates innate lymphoid cells and type 2 inflammation. *Nature*, 2017, 549(**7671**): 282–286.

[30] Hori J, Vega J L, Masli S. Review of ocular immune privilege in the year 2010: modifying the immune privilege of the eye. *Ocul Immunol Inflamm*, 2010, 18(**5**): 325–333.

[31] Liu J, Li Z . Resident Innate Immune Cells in the Cornea. *Frontiers in Immunology*, 2021, 12:620284.

[32] Al-Aqaba M A, Dhillon V K, Mohammed I, et al. Corneal nerves in health and disease. *Prog Retin Eye Res*, 2019, 73: 100762.

[33] Belmonte C, Aracil A, Acosta M C, et al. Nerves and sensations from the eye surface. *Ocul Surf*, 2004, 2(**4**): 248–253.

[34] Parra A, Madrid R, Echevarria D, et al. Ocular surface wetness is regulated by TRPM8-dependent cold thermoreceptors of the cornea. *Nat Med*, 2010, 16(**12**): 1396–1399.

[35] Lasagni Vitar R M, Rama P, Ferrari G. The two-faced effects of nerves and neuropeptides in corneal diseases. *Prog Retin Eye Res*, 2022, 86: 100974.

[36] Yuan K, Zheng J, Shen X, et al. Sensory nerves promote corneal inflammation resolution via CGRP mediated transformation of macrophages to the M2 phenotype through the PI3K/AKT signaling pathway. *Int Immunopharmacol*, 2022, 102: 108426.

[37] Fukui S, Iwamoto N, Takatani A, et al. M1 and M2 Monocytes in Rheumatoid Arthritis: A Contribution of Imbalance of M1/M2 Monocytes to Osteoclastogenesis. *Frontiers in Immunology*, 2018, 8: 1958

[38] Liu J, Huang S, Yu R, et al. TRPV1(+) sensory nerves modulate corneal inflammation after epithelial abrasion via RAMP1 and SSTR5 signaling. *Mucosal Immunol*, 2022, 15(**5**): 867–881.

[39] Liu L, Dana R, Yin J. Sensory neurons directly promote angiogenesis in response to inflammation via substance P signaling. *The FASEB Journal*, 2020, 34(**5**): 6229–6243.

[40] Borbely E, Botz B, Bolcskei K, et al. Capsaicin-sensitive sensory nerves exert complex regulatory functions in the serum-transfer mouse model of autoimmune arthritis. *Brain Behav Immun*, 2015, 45: 50–59.

[41] Uematsu T, Sakai A, Ito H, et al. Intra-articular administration of tachykinin NK(1) receptor antagonists reduces hyperalgesia and cartilage destruction in the inflammatory joint in rats with adjuvant-induced arthritis. *Eur J Pharmacol*, 2011, 668(**1**–**2**): 163–168.

[42] Walsh DA, Mapp PI,Kelly S. Calcitonin gene-related peptide in the joint: contributions to pain and inflammation. *Br J Clin Pharmacol*, 2015, 80(**5**): 965–978.

[43] Mei J, Zhou F, Qiao H, et al. Nerve modulation therapy in gouty arthritis: targeting increased sFRP2 expression in dorsal root ganglion regulates macrophage polarization and alleviates endothelial damage. *Theranostics*, 2019, 9(**13**): 3707–3722.

[44] Gao D, Gao X, Yang F, et al. Neuroimmune Crosstalk in Rheumatoid Arthritis. *International Journal of Molecular Sciences*, 2022, 23(**15**) : 8158.

[45] Ebbinghaus M, Uhlig B, Richter F, et al. The role of interleukin-1beta in arthritic pain: main involvement in thermal, but not mechanical, hyperalgesia in rat antigen-induced arthritis. *Arthritis Rheum*, 2012, 64(**12**): 3897–3907.

[46] Silverman HA, Chen A, Kravatz NL, et al. Involvement of Neural Transient Receptor Potential Channels in Peripheral Inflammation. *Front Immunol*, 2020, 11: 590261.

[47] Zhang W, Lyu M, Bessman NJ, et al. Gut-innervating nociceptors regulate the intestinal microbiota to promote tissue protection. *Cell,* 2022, 185(**22**): 4170–4189 e20.

[48] Yu M, Lee SM, Lee H, et al. Neurokinin-1 Receptor Antagonism Ameliorates Dry Eye Disease by Inhibiting Antigen-Presenting Cell Maturation and T Helper 17 Cell Activation. *Am J Pathol*, 2020, 190(**1**): 125–133.

[49] Johnson MB, Suptela SR, Sipprell SE, et al. Substance P Exacerbates the Inflammatory and Pro-osteoclastogenic Responses of Murine Osteoclasts and Osteoblasts to Staphylococcus aureus. *Inflammation*, 2023, 46(**1**): 256–269.

[50] Benschop RJ, Collins EC, Darling RJ, et al. Development of a novel antibody to calcitonin gene-related peptide for the treatment of osteoarthritis-related pain. *Osteoarthritis Cartilage*, 2014, 22(**4**): 578–585.

[51] Bonaz B, Sinniger V, Pellissier S. Anti-inflammatory properties of the vagus nerve: potential therapeutic implications of vagus nerve stimulation. *J Physiol*, 2016, 594(**20**): 5781–5790.

[52] Bonaz B, Sinniger V, Pellissier S. Therapeutic Potential of Vagus Nerve Stimulation for Inflammatory Bowel Diseases. *Front Neurosci*, 2021, 15: 650971.

Shufang He received her Ph.D. degree from the Anhui Medical University, China (2012). She was a visiting scholar in Stanford University (2017–2020). She is now a professor in Department of Anesthesiology and Perioperative Medicine, the Second Affiliated Hospital of Anhui Medical University, Anhui. She has published many high-quality papers on journals including *The Journal of Clinical Investigation, Basic Research in Cardiology,* and *British Journal of Anesthesia*. Her current research interests are focused on neuron-heart interaction mechanisms. E-mail: sfhe@ahmu.edu.cn.

Muge Qile received her Bachelor's degree from Baotou Medical College (2021). She is now studying for her Master's degree in Anhui Medical University, majoring in anesthesiology. Her research interests are focus on neuron-heart interaction mechanisms. E-mail: qilemuge330@163.com.