TRPV1 in Pain and Itch

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Abstract

Transient receptor potential vanilloid type 1 (TRPV1) is a nonselective cation channel that is intensively expressed in the peripheral nerve system and involved in a variety of physiological and pathophysiological processes in mammals. Its activity is of great significance in transmitting pain or itch signals from peripheral sensory neurons to the central nervous system. The alteration or hypersensitivity of TRPV1 channel is well evidenced under various pathological conditions. Moreover, accumulative studies have revealed that TRPV1-expressing (TRPV1$^+$) sensory neurons mediate the neuroimmune crosstalk by releasing neuropeptides to innervated tissues as well as immune cells. In the central projection, TRPV1$^+$ terminals synapse with the secondary neurons for the transmission of pain and itch signalling. The intense involvement of TRPV1 and TRPV1$^+$ neurons in pain and itch makes it a potential pharmaceutical target. Over decades, the basis of TRPV1 channel structure, the nature of its activity, and its modulation in pathological processes have been broadly studied and well documented. Herein, we highlight the role of TRPV1 and its associated neurons in sensing pain and itch. The fundamental understandings of TRPV1-involved nociception, pruriception, neurogenic inflammation, and cell-specific modulation will help bring out more effective strategies of TRPV1 modulation in treating pain- and itch-related diseases.

Keywords

TRPV1 · Itch · Pain · Sensory neurons

12.1 Introduction

The transient receptor potential (TRP) channels are a superfamily that is made up of 28 members in mice and 27 members in humans [1]. As non-selective cation-permeable channels, the TRP family is capable to respond to multiple external and internal stimuli, including changes in thermal, pH, chemical irritants, as well as mechanical and osmotic cues. Therefore, they are implied in numerous physiological and pathological conditions and have become an increasing focus in basic science, translational research, and drug development.

Generally, the TRP superfamily is divided into six subfamilies: canonical (TRPC), vanilloid (TRPV), ankyrin (TRPA), melastatin (TRPM), polycystin (TRPP), and mucolipin (TRPML).

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Among them, the TRPV subfamily, which includes four members TRPV1 to TRPV4, are broadly involved in nature responses like pain and itch across mammals. The TPRV1 channel is also known as vanilloid receptor 1 and was cloned and identified as the receptor for heat and capsaicin in 1997 by David Julius lab [2]. It consists of six transmembrane domains with a pore formed by transmembrane segments 5–6 (S5–S6) and the intervening pore loop, which is flanked by S1–S4 voltage-sensor-like domains [3]. Various stimuli such as noxious heat (>43 °C), capsaicin, and pH acting on TRPV1 can directly lead to the channel opening and the consequent cation entry [2, 4]. TRPV1 is highly expressed in the peripheral nerve system (PNS) particularly C-fiber [5]. Ever since its discovery, TRPV1 has attracted broad attention in multiple studies that focus on pain or itch [6–11]. In this chapter, we will start with the introduction of basic biology in neuroscience and then interpret how TRPV1 participates in pain and itch perception. Furthermore, based on its biology, we will discuss the potential of TRPV1 modulation as drug interventions in pathologic sensory conditions.

12.2   TRPV1 Biology in Pain and Itch

12.2.1   The Basics of Pain and Itch

In mammals, the skin, mucous membrane, and muscles are highly innervated by primary somatosensory fibers. Their cell bodies are located in trigeminal ganglia which innervate the head and neck and the dorsal root ganglia (DRG) which receive signals from the rest of the body. These afferent neurons are pseudo-unipolar neurons, which project long axons to the skin and deeper body structures, and transmit impulse signaling through the other axonal branches synapse with neurons in the brain stem nuclei or spinal cord dorsal horn. The information is then relayed by higher order neurons towards the cortex where various senses such as warmth, coldness, touch, pressure, pain, and itch are ultimately perceived. While pain is defined as "an

unpleasant sensory and emotional experience associated with actual or potential tissue damage" [12], the itch was introduced as "An unpleasant sensation that provokes the desire to scratch" [13]. Generally, sensory neurons that are specialized to sense pain and itch are referred to as nociceptors and pruriceptors, respectively. Due to the protective behaviors subsequentially aroused by pain and itch, hosts can be aware of or protected from environmental dangers.

Historically, sensory neurons have been classified according to the amount of myelination which dictates conduction velocity (fast or slow) and diameter (large or small). There are three main types of sensory neurons: large diameter (heavily and moderately myelinated Aβ fibers), medium diameter (thinly myelinated Aδ fibers), and small diameter (unmyelinated C fibers). While various mechanosensations such as touch and pressure are mainly elicited by Aδ and Aβ fibers, the vast majority of pain and itch is mediated by Aδ fibers and unmyelinated C fibers with free nerve endings.

12.2.2   TRPV1 and TRPV1^{+} Sensory Neurons

TRPV1 is the most well-characterized TRP channel and is the specific receptor of capsaicin (the spicy ingredient of chili peppers). However, a wide range of endogenous and exogenous stimuli such as noxious temperature (~43 °C), acidic or basic pH, vanilloid compounds, can also activate this ion channel [2, 4].

It is well established that TRPV1 activation and consequential cation ion flow are required for transduction of a number of pain or itch signaling. Meanwhile, nociceptors rely on molecular sensors like TRPV1 to detect noxious stimuli. It has been demonstrated in numerous studies that ~40–50% of sensory neurons express TRPV1 [14, 15]. More recently, emerging studies using unbiased single-cell RNA sequencing (scRNA seq) of murine DRG neurons updated the sensory neuron classification system according to their gene expression [16–19]. In 2015, Usoskin et al. identified that a subpopulation of Aδ fibers

expresses the gene of calcitonin-gene related peptide (CGRP, *Calca*) and nerve growth factor receptor (TrkA; *Ntrk1*). They classified this population as peptidergic (PEP) 2. Those C fibers that express the above two genes plus neuropeptides substance P (SP; *Tac1*), are classified into PEP1. Other C fibers that were previously classified as non-peptidergic (NP) neurons (P2rx3 expression and predicted IB4 binding), were classified into three subclusters NP1, NP2, and NP3. Interestingly, some NP neurons like NP2 also contain markers for peptidergic neurons (i.e., CGRP gene *Calca*) [18, 19]. Therefore, NP neurons still have the capability to release neuropeptides. It has been revealed by sc-RNA seq data that *Trpv1* is abundantly expressed in the PEP1, NP2, and NP3 [18, 19], suggesting the critical role played by these three subpopulations in transmitting noxious and pruriceptive stimuli (Figs. 12.1 and 12.2).

12.2.3 TRPV1 in Pain Sensation

12.2.3.1 Pain Classification

Pain can be simply divided into acute pain and chronic pain. Acute pain refers to the new onset of tissue damage or injuries, usually featured as self-limited healing and relief within hours or days. From this direction, acute pain provides warning signals and provokes avoidance from dangers. However, when the pain pathway is altered or pain sensation tends to last longer or recurs, chronic pain can be defined. In order to better identify chronic pain, given the first priority to pain etiology, the Task Force group of IASP (International Association for the Study of Pain) has defined chronic pain as "pain that lasts or recurs for longer than 3 months" in the year 2015 [20], regardless the specific pain phenotypes. Chronic pain is further classified as: (1) chronic primary pain; (2) chronic cancer-related pain; (3) chronic postsurgical or posttraumatic pain; (4) chronic neuropathic pain; (5) chronic secondary headache or orofacial pain; (6) chronic secondary visceral pain; and (7) chronic secondary musculoskeletal pain. More details regarding ICD-11 (the 11th version

of International Classification of Diseases) codes for chronic pain were also extensively defined in the year 2019, which benefits to identify patients with chronic pain [21, 22].

The clear-cut definition and ICD-11 codes for chronic pain are attributed to the up-to-date efforts of the majority body of clinical and basic science research. Chronic pain has several debilitating features in which hypersensitivity is the most dominant one. Hypersensitivity refers to the "tissue or nerve damage elicits hyperactivity to promote guarding of the injury area" [23]. As a result, innocuous stimuli such as light touch could be perceived as pain (allodynia), and painful stimuli will induce greater intensity (hyperalgesia). This phenomenon is driven by various sensitization pathways and corresponding mechanisms. The mechanism for sensing and transmitting pain sensation is complex and involves multiple factors, leading to difficulties in pain treatment [23]. As the predominated nociceptor in the peripheral sensory system, TRPV1$^+$ neurons possess numerous receptors for pain mediators such as adenosine triphosphate (ATP), serotonin, and bradykinin. Of the utmost importance, the TRPV1 channel is also a potent sensor for noxious stimuli and can be sensitized in a broad spectrum of chronic pain environments.

12.2.3.2 TRPV1 Serves as the Sensor for Pain Sensation

In general, direct activation of the TRPV1 channel by capsaicin and noxious heat (above 43 °C) can induce a burning sensation in the applied region. Capsaicin is known as the pain mediator long before its receptor was identified in 1997 [2]. By binding to the residue of Y511 located at the transmembrane spanning segment 4 (S4), capsaicin induces the opening of the TRPV1 channel and introduces calcium influx, the first sign for pain sensation singling in the peripheral. Similarly, noxious heat enables TRPV1 channel opening and triggers intracellular calcium increase. The intracellular calcium enhancement due to the receptor potential of TRPV1 activation could further trigger the voltage-gated ion channels to generate action potentials and result in the peripheral transmission of burning pain sensation. The

Fig. 12.1 Maximum likelihood estimated expression of selected genes in mouse dorsal root ganglia neuron subpopulations. Nociceptors are considered to primarily be in PEP1 and PEP2 populations, while pruriceptor populations are considered to be NP1, NP2, and NP3. (Full database is available in Usoskin et al. [18])
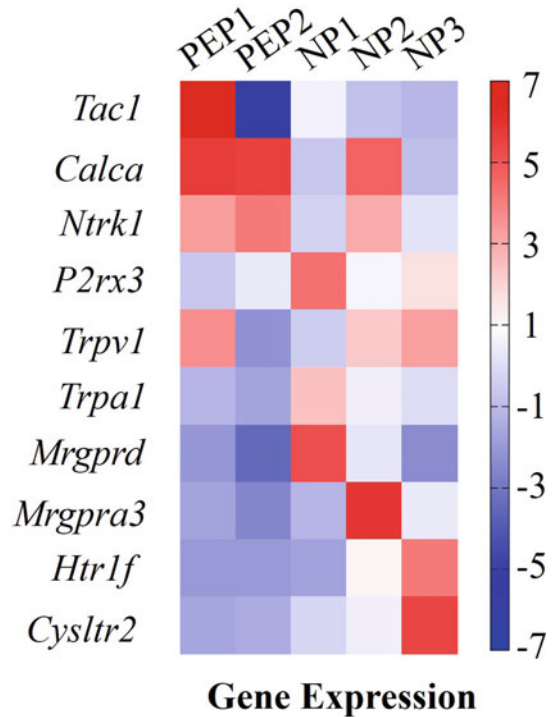
property of sensing heat and capsaicin to produce pain sensation makes TRPV1 the sensor for these two fundamental noxious as well as thermal and chemical stimuli in the sensory nervous system.

Acidosis is common in the context of inflammation, tissue damage, and ischemia, in which protons are the important pain mediators. Proton (also described as hydrogen ion, acid, or low pH in different research papers) can directly activate the TRPV1 channel when the pH value hits lower than 6 at room temperature, by binding the E648 site of the extracellular loop and triggering cation entry for pain transmission [24]. Interestingly, in
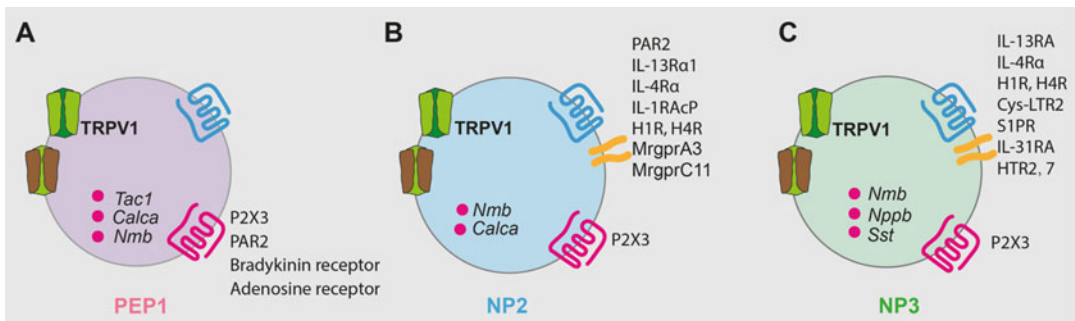

Fig. 12.2 Pain- and itch-sensing receptors are broadly expressed in TRPV1$^+$ subpopulations. (**a**) Peptidergic TRPV1$^+$ neurons express the majority body of pain-sensing receptors and release the corresponding neuropeptides such as SP (coded by gene *Tac1*), CGRP (coded by *Calca*), and NMB (coded by *Nmb*). (**b**, **c**) Itch-sensing neurons are mainly expressed in NP2 and NP3 TRPV1$^+$ subpopulations. Neuropeptides releasing from these two subpopulations including NMB, CGRP, and SST (coded by gene *Sst*), Nppb (coded by gene *Nppb*). Of note, MrgprA3 and Nppb are the two well-accepted makers for itch populations

addition to protons, TRPV1 can also detect basic deviations from homeostatic pH. Alkaline pH such as ammonia can also induce irritant and pain sensation, which is common in the environment of artificial fertilizers and industrial pollutants. Via exposure to the external NH_4Cl solutions to get the diffusion-free NH_3 (ammonia), cultured DRG neurons and TRPV1-coexpressing human embryonic kidney 293 (HEK293) cells showed robust calcium responses [4]. In TRPV1-expressing HEK293 cells, the cell activity induced by intracellular pH of 9.5 was nearly abolished when TRPV1-antagonist was introduced. These results indicated the responsible role of TRPV1 in sensing alkaline chemicals and intracellular basic pH. Distinct from the proton binding site of E648, the base-sensing residue is detected at the site of H378 located in TRPV1 N-terminals [4]. Although TRPA1 (transient receptor potential ankyrin 1) can also respond to ammonia and intracellular base, so far, TRPV1 is the only identified ion channel that senses both acid and alkaline pH [4].

Some toxin peptides like venoms (which contains three types of inhibitor cysteine knot peptides) from spiders, snakes, cone snails, or scorpions, functioning as vanillotoxins, can also directly activate TRPV1 and induce inflammatory pain [25]. One such classical peptide toxin named as double-knot toxin (DkTx) from the Earth Tiger tarantula, can specifically bind to the residues within the S5-P-S6 pore region, and exhibit antibody-like bivalency to produce pain sensation in a virtually irreversible manner [26].

While sensing the noxious stimuli, TRPV1 activity is also magnified via sensitization in the context of inflammatory pain. Studies have revealed that TRPV1 responses to pain-producing chemicals and thermal stimuli, subsequently triggers heat-evoked pain or hypersensitivity in injured tissues [27]. Genetic TRPV1 knockout mice lack the thermal hypersensitivity in the context of inflammation, indicating that TRPV1 serves as the pain sensor upon activation by internal and external stimuli [11].

12.2.3.3 TRPV1+ Sensory Neuron in Pain Sensation

Besides the direct activation by heat and chemical irritants, TRPV1 protein actually labels the nociceptive PEP1 population based on the classification of sensory neuron types by the unbiased large-scale scRNA-seq [18]. Among the aforementioned types of pain classified by IASP, TRPV1 plays an extremely important role in inflammatory pain. Injuries or damaged tissues can release the classical "inflammatory soup", which comprises the major pain-inducing chemicals such as ATP, bradykinin, prostaglandins, 5-HT (5-hydro-xytryptamine, also known as serotonin), and endothelin-1. From experimental data and the unbiased sequencing analysis, TRPV1+ neurons possess the dominant nociceptive populations sensing the above pain mediators. That is, TRPV1+ PEP1 neurons express purinergic receptor P2rX3, bradykinin B2 receptor, protease-activated receptor 2 (PAR2), and adenosine 2 receptor and so on for sensing pain mediators (Summarized in Fig. 12.2a) [1, 18]. In the field of acute pain, postoperative pain is the most common one that requires acute anti-pain treatment otherwise would potentiate chronic pain. Postoperative pain also attributes to inflammation in wounds. TRPV1 is necessary for heat (but not mechanical) hyperalgesia after incision, which has been evidenced by genetic knockout and pharmacologic antagonism in tested mice [28]. Genetic ablation of TRPV1-lineage neurons results in the overall deficit to either thermal hyperalgesia or neurogenic inflammation, although this is partially due to other thermal TRPs co-expressed in the TRPV1-lineage population [9]. Also, ablation of TRPV1+ neurons and fibers by the potent agonist resiniferatoxin (RTX) treatment has been shown to impair thermal nociception without affecting mechanical nociception in adult rats. Furthermore, during the projection from DRG to the dorsal horn, the loss of TRPV1+ neurons significantly eliminates the expression of presynaptic mu opioid receptors in DRG, and also potentiates the analgesic effect

of opioid, indicating the inhibition effect of the intact mechano-nociception afferents [29].

Most of the pain mediator receptors are not only located in the TRPV1^{+} neurons but also employ TRPV1 as the downstream ion channel for nociception sensitization. Activation of the bradykinin B2 receptor by bradykinin during tissue inflammation mainly elicits pain sensation by sensitizing TRPV1 via phospholipase C (PLC) and cyclooxygenase-1 activation [30]. Meanwhile, TRPV1 is also required for a number of G-protein coupled receptors (GPCRs), such as the 5-HT2 receptor and PAR2 receptor when sensing pain mediators [23]. Notably, TRPV1 may have some alterations upon chemical stimulation to augment the pain sensation. For example, during pain sensitization, multiple intracellular signals like protein kinase A (PKA) and protein kinase C (PKC) pathways can phosphorylate the TRPV1 channel and produce pain sensitization, which provides a unique strategy to modulate TRPV1 activity for analgesia [31].

12.2.3.4 TRPV1-TRPA1 Complex in Pain Sensation

TRPV1^{+} neurons co-express several TRP channels that are also nociception sensors. TRPA1 is the sole member of TRPA subfamily and serves a broad spectrum of biophysiological functions in different species. TRPA1 is largely co-expressed with TRPV1 in sensory neurons, where they act closely in modulating pain [11, 32]. TRPA1 senses exogenous irritant chemicals such as pungent products isothiocyanates (AITC) [33, 34] as well as endogenous metabolites such as reactive carbonyl species like 4-hydroxynonenal (4-HNE) and 4-oxoonenal (4-ONE) [35, 36]. Hence TRPA1 is viewed as the "gate-keeper" for inflammation within sensory nervous system [37]. The role of TRPA1 involved in pain sensation has been well-documented [38, 39]. The most intriguing inhibition effect of TRPV1 on TRPA1 has been observed in pain conditions [40]. Until recently, the finding of Tmen100 protein as the modulator for TRPA1-mediated hyperalgesia in a TRPV1-dependent manner [41], has shed light on a new strategy for pain treatment. In general, Tmem100

is a 134-amino-acid transmembrane protein highly conserved in vertebrates [42]. In the tested rodent DRGs, Tmem100 is exclusively expressed in the peptidergic population. Importantly, Tmem100 has the capacity to release the inhibition of TRPA1 by TRPV1, resulting in inflammatory-mediated hyperalgesia. Mutation of Tmem100 with Q-Q-Q in the charged K-R-R sequence in the C terminal enhances the binding with TRPV1, which causes disconnection or low affinity with TRPA1. The consequence of this structure change contributes to the relief of TRPA1-mediated hyperalgesia [41]. Therefore, the regulation effect of TRPV1-TRPA1 correlation is also considered as a new target in neurogenic inflammation [43].

12.2.4 TRPV1 in Itch Sensation

12.2.4.1 Itch Is a Distinct Neural Process from Pain

Although it has been long considered that an itch is a mild form of pain, recent innovations in neuroscience and neuroimmunology have identified how itch pathways are distinct from pain.

In 2007, Sun and Chen discovered the first itch-specific pathway in the nervous system defined by gastrin-releasing peptide (GRP) and its receptor (GRPR), indicating that itch is a trackable and distinct sensory process from pain [44]. Later in 2009, Liu et al. identified that murine mas-related G-protein-coupled receptor (Mrgpr) A3 is the receptor of chloroquine (CQ), an anti-malaria drug that can induce serve itch sensation [45]. Mrgpr family are GPCRs and comprise ~8 genes and pseudogenes in humans and 27 in murine, most of which are expressed by primary sensory neurons [46]. CQ can cause robust itch in both humans and mice [45]. Interestingly, deletion of a cluster of Mrgpr genes significantly reduced mice scratching behavior induced by CQ but not histamine. They also identified that human MRGPRX1 has a similar primary sequence to MrgprA3 and can be specifically activated by CQ [45]. In the year 2013, the same group further found that

MrgprA3-expressing neurons were the itch selective population. To demonstrate this, they adopted a unique approach by inserting the TRPV1 cation channel only in MrgprA3$^+$ sensory neurons in TRPV1-deficient mice. Following capsaicin intradermal injection, they observed itch-induced scratching behavior rather than pain-related behaviors in those animals [47]. Other Mrgpr family expressing in neurons mediates itch sensation include MrgprC11 and MrgprD, which can be activated by bovine adrenal medulla peptide 8–22 [45] and β-alanine [48], respectively. Collectively, the discoveries of specific Mrgprs on sensory neurons and their itch function provide landmark advances in itch biology and neurology.

12.2.4.2 TRPV1$^+$ Sensory Neuron in Itch Sensation

The scRNA-seq studies classified MrgprA3 (overlapped with MrgprC11)-expressing neurons into NP2 itch subpopulation (Figs. 12.1 and 12.2b). In addition to the NP2 subpopulation, NP3 is the other itch sensory neuron with significant TRPV1 expression (Figs. 12.1 and 12.2c). However, during the sensory nervous system development, TRPV1-lineage neurons in mice differentiate into DRG neuron subsets with diverse TRP markers that include TRPV1, TRPA1, and TRPM8. Therefore, in addition to TRPV1$^+$ neurons, the animal tool of TRPV1-linage deficiency may also have impaired TRPA1-, TRPM8-, and even Mrg-expressing neurons [9]. However, administration of RTX, a potent agonist of TRPV1, provides an effective study approach to ablate only TRPV1$^+$ neurons in the fully developed sensory nervous system [49].

NP3 is characterized by high enrichment of gene *Nppb* for brain natriuretic peptide (BNP), a neurotransmitter that activates itch in the spinal cord, along with genes that code the pruritogen receptors: interleukin (IL)-31RA (*Il-31ra*) and CysLTR2 (*Cysltr2*) (Fig. 12.2c). Stimuli that act on sensory neurons and directly induce itch are defined as pruritogens. IL-31 is a type 2 immune cytokine and is predominantly released by T helper (Th) 2 cells in the context of atopic dermatitis (AD), a common itchy and inflammatory skin disease. IL-31 is the first cytokine that has been identified as a pruritogen. In 2014, Cevikbas et al. identified that IL31RA is expressed by both human and mouse DRG neurons [50]. Either intradermal or intrathecal injection of IL-31 was sufficient to evoke robust itch behavior in naive wild-type (WT) mice. Notably, those IL-31-responsive sensory neurons also largely co-express with TRPV1. Later, the connection between IL-31 and Nppb$^+$ neurons was further confirmed by the findings in which IL-31 is sufficient to upregulate *Nppb* in both skin and DRG [51]. More recently, we identified that the potent pruritogen leukotriene (LT) C4 and its receptor CysLTR2 neural pathway is the key mechanism in AD-associated itch flares [52]. However, although CysLTR2 siRNA knockdown in trigeminal ganglia was sufficient to alleviate acute itch flares in this context, it remains undefined whether this phenotype is specifically dependent on TRPV1$^+$ neurons. Notwithstanding this, the Hoon group directly demonstrated that Nppb$^+$ neurons are sensors of mast cell-derived LTC4 and TRPV1-linage neurons are required for *N*-methyl LTC4 (N-met LTC4)-induced itch. Moreover, they also revealed that itch elicited by serotonin and sphingosine-1 phosphate (S1p) is dependent on the Nppb$^+$ subpopulation and these itch pathways further rely on the canonical GRPR-spinal cord circuit. Taken together, these results highlight that the Nppb-labeled sensory neurons are specifically responsible for IL-31-, LTC4-, serotonin-, and S1p-evoked itch. However, whether the cellular sources of these pruritogens play different roles towards itch neuron populations is still an interesting question for further research.

Histamine is a classical pruritogen that can be released from mast cells and basophils. So far, four distinct GPCRs (H1R, H2R, H3R, and H4R) for histamine have been found. Three of these receptors are expressed by neurons. However, only H1R and H4R are expressed by pruriceptive DRG and mediate histaminergic itch [53, 54]. Both NP2 and NP3 are found to have histamine receptor RNA expressed in sc-RNA

seq studies (Fig. 12.2). Consistent with this, TRPV1-DTA animals exhibited a remarkable reduction of scratch responses to histamine intradermal injection [55].

IL-4 and IL-13 are the other two canonical types 2 effector cytokines. They have been shown to directly activate sensory neurons and promote itch in the context of AD-like disease [56, 57]. Compared with the receptors for IL-31 (*Il31ra* and *Osmrβ*), the gene of IL-4 and IL-13 shared receptor subunit (*Il4ra*) is broadly expressed across NP1, NP2, and NP3 itch sensory neurons [18, 57]. More importantly, the humanized anti-IL-4Rα mAb (dupilumab) has demonstrated outstanding anti-itch effects in patients with AD or other chronic pruritic diseases such as chronic pruritus of unknown origin [58–64]. Taken together, these advances highlight how cytokines dramatically promote itch. However, whether these cytokine itch pathways will be inhibited by targeting TRPV1^{+} neurons is unclear. Further studies may unveil the role and mechanisms of specific sensory subpopulations in cytokine-induced itch.

12.2.4.3 Role of TRPV1 Ion Channel for Itch Signaling

In addition to investigating the function of TRPV1^{+} sensory neurons in itch signaling, numerous basic studies have explored the molecular mechanisms of itch sensation.

It is well established that histaminergic itch is TRPV1-dependent. TRPV1-deficient mice exhibited less histamine-induced scratch compared with WT controls, whereas α-5HT- or endothelin 1-elicited itch was unaffected. The TRPV1 channel opening is critically required for histamine to activate sensory neurons via H1R [2, 65]. TRPV1 opening consequently causes increases in intracellular calcium (Ca^{2+}) concentrations that prepare for neuronal action potentials. This process likely involves phospholipase (PL) A_2 or lipoxygenases (LO) as a PLA2 inhibitor or a LO inhibitor is sufficient to block the histamine-induced Ca^{2+} influx in sensory neurons [66]. In addition, other analyses indicated that phospholipase (PL) Cbeta3 has overlapped

expression with H1R in a subpopulation of C fibers and PLCbeta3 specifically mediates histamine-induced calcium responses through the H1R in cultured sensory neurons. The PLCbeta3-deficient murine strain showed significant defects in histamine-induced scratching behavior [67]. Notwithstanding this, the precise molecular mechanisms underlying histamine receptor-TRPV1 pathways will be an exciting area for further investigation. For the newly discovered H4R, recent studies suggest that TRPV1 and PLC are also required for H4R-mediated itch signaling in vitro [68].

In addition to histaminergic itch, multiple non-histaminergic itch mechanisms that involve TRPV1 include IL-31, IL-4/IL-13, LTB4, and LTC4. To explore which TRP channels are involved in IL-31-mediated itch, Cevikbas et al. employed TRPV1- and TRPA1-deficient mouse strain, respectively, and found that either TRPV1 or TRPA1 deletion can significantly decrease IL-31-evoked itch [50]. Using calcium imaging in vitro, they confirmed that the percentage of IL-31-responsive neurons was significantly reduced in TRPV1-or TRPA1-deficient DRG. Taken together, these results indicate that IL-31 employs both TRPV1 and TRPA1 to fully mediate itch. To investigate the downstream of TRP channels in the IL-31 itch pathway, in the same study, authors first observed that IL-31-stimulated murine DRG neurons induced ERK1/2 phosphorylation in vitro. Then they demonstrated that administration of U0126 which can completely prevent ERK1/2 phosphorylation was sufficient to reduce scratching bouts in WT mice that received IL-31 intradermal injections. Thus, ERK1/2 might provide a future direction to study the TRP downstream phosphorylation in the IL-31-induced itch pathway.

Although it appears that cultured DRG neurons from either *Trpa1*^{−/−} or *Trpv1*^{−/−} mice exhibited fewer responses to both IL-4 and IL-13, whether TRPV1 or TRPA1 is required for IL-4 and IL-13 enhanced scratching behavior remains undefined. However, Oetjen et al. demonstrated that IL-4/IL-13 needs Janus kinase (JAK) to transmit their signals into neurons [57]. The

JAK family has four members: JAK1, JAK2, JAK3, and TYK2 [69]. The conditional deletion of JAK1 in sensory neurons led to a marked reduction in scratching behavior in the setting of AD-like disease. Moreover, in humans, JAK inhibitors are shown to significantly reduce itch severity in patients suffering from chronic pruritus [70]. Therefore, whether there is any connection between TRPV1 and JAKs would be interesting for future investigation.

LTs are a family of eicosanoid inflammatory mediators and are produced in leukocytes, particularly mast cells and basophils [71, 72]. LTs are generated by the oxidation of arachidonic acid and the essential fatty acid eicosapentaenoic acid via the 5-LO pathway. LTs are divided into two classes: the chemoattractant LTB4 and the cysteinyl LTs (CysLTs: LTC4, LTD4, and LTE4) [73]. It has been shown that intradermal injections of LTB4 resulted in scratching behavior in mice [74, 75]. Similar to IL-31-induced itch, either TRPV1 or TRPA1 antagonists are sufficient to inhibit itch behavior proved by LTB4 [75]. For CysLTs, while the LTC4-CysLTR2 itch pathway has been confirmed by multiple research groups [52, 76, 77], the role of LTD4 and LTE4 as pruritogens remains controversial. Interestingly, although LTC4-activated sensory neurons showed large coexpression with TRPV1 and TRPA1, either TRPV1 or TRPA1 knockout could not reduce the percentage of LTC4-responsive DRG neurons. Only TRPV1 and TRPA1 compound deletion is capable to ameliorate the neuronal responsiveness towards LTC4. In line with these in vitro results, mice lacking either TRPV1 or TRPA1 exhibited unaltered scratching behavior following *N*-met LTC4 injection compared with their littermate controls. However, TRPV1 and TRPA1 double knockout attenuated LTC4-induced scratching responses. Taken together, we can conclude that CysLTR2 is equally reliant on either TRPV1 or TRPA1 to fully mediate LTC4-elicited itch. In other words, both canonical TRPV1 and TRPA1 signaling must be impaired to limit LTC4-mediated itch.

12.3 TRPV1 Activity Modulation in Pain and Itch

12.3.1 TRPV1 Upregulation in the Context of Pain

In many pathological conditions of chronic pain, the functional upregulation of TRPV1 is likely induced by inflammatory mediators such as nerve growth factors released from adjacent non-neural cells. The elevation of TRPV1 protein, but not mRNA levels, indicates the cytoplasm assembly upon activation, rather than transcription-independent overexpression [78]. Interestingly, the increased TRPV1 protein then is transported to the peripheral membrane of a cell body, but not the central C-fiber terminals for synapse transmission. The TRPV1 upregulation is implied in tissue inflammation and thermal hypersensitivity. Further studies revealed that p38 MAPK activation is required for TRPV1 overexpression [78], indicating MAPK pathways in induction and maintenance of peripheral sensitization and persistent chronic pain [79].

Under pathological situations, TRPV1 has been detected in previous TRPV1-absent sensory neurons. To a large extent, hyperalgesia could be ascribed to this mechanism. Take TRPM8-dependent cold allodynia as an example, we have demonstrated that pleasant cool temperature that only causes cool sensation to the skin surprisingly induces cold allodynia to the cornea [80]. The significance of this phenomenon is that such cold allodynia becomes more severe in multiple pathological conditions such as dry eyes. We further identified that TRPV1 is highly expressed in TRPM8$^+$ neuron-innervated cornea rather than other tissues. The expression of TRPV1 in TRPM8$^+$ neurons was further elevated under dry eye conditions. Via electrophysiological approaches, we found that TRVP1 enables TRPM8$^+$ cold-sensing neurons to depolarize and fire action potentials more easily. In line with in vitro results, TRPV1 deficiency and pharmacological antagonist significantly alleviated corneal

cold allodynia. Meanwhile, TRPV1 upregulation is sufficient to cause cold allodynia as genetical overexpression of TRPV1 in TRPM8-expressing sensory neurons led to cold allodynia in both cornea and skin even without any pathological changes [80]. Taken together, it is reasonable that the upregulated TRPV1 ion channel initiates neural hypersensitivity in the TRPV1$^+$ neuron population and results in phenomena of hyperalgesia.

12.3.2 TRPV1 Upregulation in the Context of Chronic Itch

TRPV1 upregulation has also been seen in itchy conditions. In a pure chronic itch model, dry skin conditioning was performed by the acetone–ether–water procedure for sequential days to induce robust itch behavior, known as dry skin model. In the mouse model, we evidenced that the TRPV1$^+$ fiber largely expanded their territory in the skin compared with the control treatment. This is confirmed by histochemistry staining of placental alkaline phosphatase in the genetic TRPV1-reporter mouse line [81]. In this study, the upregulation of TRPV1 was confirmed on both gene and protein levels and the upregulated TRPV1 was sufficient to provoke enhanced calcium responses to the low dose of capsaicin, indicating its intact function. Importantly, in this dry skin model, a low dose of capsaicin injection strikingly induced robust scratching behavior rather than pain behavior, suggesting that TRPV1 might have broader functions in some specific pathologic conditions.

12.3.3 TRPV1 Structure Modulation

TRPV1 channel possesses highly modulable pockets for cation of calcium, magnesium, and sodium ion. A three-dimensional study revealed that TRPV1 has an ion permeation pathway via S5 and S6 and an intervening pore loop region (S5-P-S6) [3], which serves as dominant modulation sites. Based on the high allosteric coupling between upper and lower gates during activation, inflammatory agents are capable to modulate

TRPV1 and such modulation is found to contribute to acute and persistent pain [23]. TRPV1 has two activated structures that have been detected by pharmacological probes (a peptide toxin, DkTx, and a small vanilloid agonist, RTX). Such diversity highlights the modulable property of TRPV1 and implies its potentials in regulating neuron activities [82]. In 2007, the high-resolution structure of the TRPV1 domain was described as cytosolic ankyrin repeat domain (ARD). This advanced finding helps better understand protein interactions folding in TRPV1 and indicates that the calcium-dependent regulation may involve competitive interactions between ATP and calmodulin at the TRPV1-ARD-binding site [83].

12.3.4 TRPV1 Phosphorylation

12.3.4.1 PKC Pathway

As the dominant downstream TRP channels for GPCRs-mediated pain and itch, the TRPV1 channel can be modulated by three major pathways. The process of TRPV1 phosphorylation is the most important pathway for the transmission of pain and itch signaling. The PKC-dependent pathway is the most common way for TRPV1 sensitization. Generally, TRPV1 phosphorylation mediated by PKC involves the Gαq/11-PLC-phosphatidylinositol (4,5) bisphosphate (PIP2)-diacylglycerol (DAG)-PKC intracellular pathway [84]. This pathway is crucial for various GPCRs such as bradykinin B2 receptor, 5-HT receptors, purinergic receptors, protease-activated receptors, and Mrgprs. Many chemokines can also directly sensitize TRPV1 and contribute to hyperalgesia during inflammation. Pro-inflammatory chemokines such as CCL3 can activate CCR1 (co-expressing with TRPV1 in more than 85% of small-diameter neurons) and induce calcium influx and PKC activation, hence are responsible for sensitization in a receptor crosstalk manner [85].

PIP2 is one of the first noticeable intracellular molecules for phosphorylation in sensory neurons. PLC is capable to hydrolyze PIP2 to produce DAG and isositol triphosphate (IP3). IP3 further promotes the release of calcium ions

in cells and acts synergistically with DAG in the process of activating PKC. PKC activation phosphorylates the TRPV1 channel, hence triggers the sensitization effect from the upstream signaling. In fact, TRPV1 interaction with PIP2 and calmodulin is the classical pathway for the activity modulation within neurons. Cation permeability induced by TRPV1 agonists is dynamic and could be intensively modulated in a PKC-dependent pathway. The permeability of cation led by TRPV1 opening is time- and agonist concentration-dependent for large cations and calcium entry. This phenomenon has been evidenced in native or recombinant TRPV1 channels in rats and attributes to the cation selectivity led by different agonists that phosphorylate site Ser800 or Ser502 in a PKC-dependent manner. This property may further change the TRPV1 activity in pain sensation, as well as in neurotransmitter release or agonist-related cytotoxicity [86]. The putative binding sites for TRPV1 activity have been indicated to be Lys571 and Arg575 in the linker between the S4 and S5 of one TRPV1 subunit and Lys694, and the predicted PIP2–TRPV1 interaction region has relied on Leu777-Ser820 [87].

However, controversial results have revealed the negative regulatory role of PIP2 on the TRPV1 channel [88]. Researchers reconstituted purified TRPV1 into artificial liposomes and tested the precise effect of various phosphoinositides by introducing them into the TRPV1-expression system, respectively. Through this way, they found that membrane lipids including PIP2, PI4P, and phosphatidylinositol, can actually inhibit TRPV1-mediated sensitivity [88]. They also claimed that TRPV1 is fully functional without phosphoinositides. The ongoing exploration found that phospholipids, specifically phosphoinositides are important for heat-induced channel open status [89]. With regard to the controversial results for PIP2 involvement in TRPV1 sensitization, as the TPRV1 channel possesses multiple binding sites for activity modulation, further evidence could be applied to confirm the role of phosphoinositide in TRPV1 modulation based on the binding site regulation [90].

12.3.4.2 PKA Pathway

The sensitization and phosphorylation of TRPV1 via Gαs-activation are relied on Gαs- adenylyl cyclase (AC)-cAMP-PKA pathway. Briefly, activation of Gαs by pain and itch mediators could activate AC to generate cAMP, leading to the activation of PKA. PKA activation further sensitizes TRPV1 channels and sequentially triggers the hyperactivity of cation entry. Hence, any disturbance of this pathway will impair the overall sensitivity of TRPV1 phosphorylation. The GPCR-related Gαs-activation is very important for pain and itch mediator transmission. While Gαs-coupled receptors (such as 5-HT4 and 5-HT7) have positive regulation effects on the cAMP-dependent modulation of TRPV1, the Gαi/o-coupled receptors (e.g. μ-opioid receptor, cannabinoid receptors 1 and 2) play a negative regulation role [84].

Prostaglandin E2 is a classical TRPV1-mediated noxious stimulus that could act on Gαs. In this pathway, the downstream desensitization of TRPV1 can be achieved by altering Ser116 and Thr370 at the PKA binding site. On the contrary, pretreatment with forskolin to activate AC is ineffective to reduce TRPV1 desensitization. These results indicate the involvement of PKA-dependent reduction of desensitization of capsaicin-activated currents [91]. Nevertheless, other binding sites for PKA-dependent phosphorylation at the site of Thr144 or Ser502 have also been discovered [87].

Either opioids or cannabis is effective to reduce nociception provoked by noxious stimuli. Interestingly, both of their receptors, particularly at the postsynaptic membrane, are largely co-expressed with TRPV1 in peripheral sensory neurons. They both negatively regulate TRPV1 activity by acting on Gαi/o-coupled receptors. μ-opioid receptor (MOR)-mediated activation of Gαi/o-coupled receptors is sufficient to reduce AC activity and cAMP levels, leading to the decreased neural activity and thus anti-pain effects [92]. However, opioid withdrawal can significantly increase the cAMP level and increase the PKA activity. It has been demonstrated in transfected HEK293 cells and dissociated DRG

neurons that capsaicin-induced TRPV1 activity plays a vital role in hyperalgesia resulted from opioid withdrawal [93]. Cannabis has two receptors like cannabinoid receptor subtype 1 and 2, both of which are Gαi/o-coupled receptors and are expressed in many types of neurons including TRPV1 positive ones. Cannabis has been prescribed to treat many refractory pain disorders including headache, arthritis, and post-operation pain, indicating the importance of cannabinoid receptors activation in pain relief [94]. Endogenous cannabinoids are bioactive lipids known as endocannabinoids and are derived from dietary omega-3 and omega-6 poly-unsaturated fatty acids [95]. The endocannabinoid-TRPV1 axis represents an intrinsic prologetic pathway. Recently, a study identified epoNADA (epoxidation of N-arachidonic acid-dopamine) and epoNA5HT (epoxidation of *N*-arachidonic acid-serotonin), which are formed by CYP peroxygenases under inflammatory conditions, are bifunctional rheostat modulators of the endocannabinoid-TRPV1 axis. They demonstrated that epoNADA and epoNA5HT are more potent than their precursors (NADA and NA5HT respectively) in modulating TRPV1 activity. Their capability as strong antagonists is shown by suppressing intracellular calcium response and membrane currents provoked by capsaicin in sensory neurons. In addition, epoNA5HT is also a complete cannabinoid receptor subtype 1 agonist. These molecules can further effectively reduce pro-inflammatory biomarkers such as IL-6, IL-1β, and TNF-α. Collectively, these results indicate that cannabinoids are potential candidates in the development of anti-pain and anti-inflammation therapeutics [96].

12.3.4.3 CaMKII-Dependent Phosphorylation

CaMKII, refers to Ca^{2+}-calmodulin-dependent kinase II, is essential for synaptic plasticity in peripheral TRPV1^{+} fibers. CaMKII phosphorylates TRPV1, thereby regulates vanilloid agonist binding to the receptor. Studies have shown that the dephosphorylation of TRPV1 by the protein phosphatase 2B, also known as calcineurin, leads to a desensitization

of the receptor [97]. Moreover, point mutations in TRPV1 at two putative consensus sites (Ser502 and Thr704) that are required for CaMKII binding lead to the failure of capsaicin-stimulate currents and cause a concomitant reduction in TRPV1 phosphorylation. In a word, CaMKII and calcineurin could control the balance between activation and desensitization in nociceptors by regulating TRPV1 binding [98]. A further study also revealed an interesting phenomenon named potentiation related to CaMKII. It is shown that activation of CaMKII and extracellular signal-regulated kinase (ERK)1/2 contribute to a time-dependent potentiation of Ca^{2+} responses elicited by repeated application of capsaicin during a 40-min interval. However, pretreatment with deltamethrin to block calcineurin and tachyphylaxis can enhance the potentiation effect. Therefore, potentiation may be an important peripheral auto sensitization mechanism that needs further investigation [99].

12.3.5 Other Modulators

12.3.5.1 Protons

Acidosis is the feature of many pathological microenvironments, hence acid-sensing ion channels represent the ion channel families that detect noxious chemical stimuli. It has been validated that the proton-sensing channels named ASIC1a and ASIC3, are preferentially expressed in TRPV1^{+} sensory neurons and function as nociceptive sensors [100]. In addition to binding its specific acid channels, protons could act as TRPV1 agonists by acting on the S6 domain or modulators by combining the S5 domain. Thermal hypersensitivity mainly attributes to TRPV1 sensitization by acidosis in pathological conditions [31]. By lowering pH value, TRPV1 capability responsive to heat and capsaicin is potentiated in a dose-dependent manner. When the extracellular pH decreases to 6.4, spontaneous openings of the TRPV1 channel are observed even at body temperature. The TRPV1 binding site of E600, but not E648, is responsible for this type of regulation and serves as a regulator in the acid environment rather than heat- or

capsaicin-evoked responses [24]. The potent effect of protons to lower the nociceptive threshold for temperature directly drives cation entry via TRPV1 opening at body temperature and contributes to the mechanisms of thermal pain (or hypersensitivity) in the context of tissue injury. This phenomenon can explain the clinical observation in which thermal hypersensitivity is usually exhibited in the context of infection, inflammation, and ischemia situations.

12.3.5.2   Pirt

Pirt is a membrane protein that is expressed in all peripheral neural tissues. It can bind both PIP2 and TRPV1 and is a positive regulator for TRPV1 [101]. Studies have shown that Pirt-deficient mice showed impaired responsiveness to noxious heat and capsaicin and responsible currents were significantly attenuated. Gain-of-function approaches indicated that TRPV1-mediated currents are enhanced by Pirt co-expression in a heterologous expression system. To achieve the modulation mechanism, the C terminus of Pirt directly binds to TRPV1 and PIP2 to strengthen TRPV1 activity [101].

Pirt regulation for TRPV1-dependent neuropathic pain has been observed in a chronic constriction injury model, which is a neuropathic pain model widely utilized in murine. In this context, pain behavior and TRPV1 over-expression were attenuated by knocking out Pirt gene [102]. In a visceral pain model that mimics uterine contraction-induced pain, Pirt expression and capsaicin-mediated activity were enhanced, leading to distinct pain behavior featured as writhing responses. However, this pain behavior was significantly attenuated in Pirt deficient-mice, indicating that Pirt might be involved in visceral pain that is mediated by TRPV1 [103].

In addition to pain, Pirt is also involved in itch modulation. Pirt deficit attenuates cellular and behavioral responses to various pruritogens such as histamine and CQ in animals. It has been shown that both TRPV1-dependent and TRPV1-independent itch likely need Pirt, suggesting its broad function in itch transmission [104].

12.3.5.3   GABA-Autocrine Feedback

Interestingly, TRPV1 activation can also trigger GABA release from peripheral nerve endings. GABA release serves as an autocrine feedback mechanism exclusively limiting TRPV1 sensitization in the setting of pathological inflammation. This feedback effect did not affect the TRPV1 response to capsaicin under physiological status. Also, this effect is independent of canonical G protein signaling but relies on the close juxtaposition of the GABAB1 receptor subunit and TRPV1 [105]. These modulation effects are essential for signaling transmission, helping expand neuroimmune interactions, and demonstrating self-protection by autocrine feedback mechanisms.

12.3.6   Pain-to-Itch Switch

In order to distinguish pain and itch phenotype in experimental mice, researchers have identified that upon intradermal injection of aversive chemicals into the cheek, pruritogens induce mice scratching behavior using hind paws, while pain signaling induces wiping behavior with forepaws [106]. Via behavior studies, substances like histamine, 5-HT, and agonists of protease-activated receptors PAR-2 and PAR-4, have been identified as itch-inducers. In contrast, capsaicin, AITC, and bradykinin that usually elicit dose-related forelimb wiping contribute to pain behavior [107]. However, under pathological conditions like allergic contact dermatitis in which bovine adrenal medulla 8–22 (a peptide that elicits histamine-independent itch via MrgprC11)-related scratching is enhanced, bradykinin that is supposed to cause pain behavior evokes both scratching behavior and wiping behavior, indicating a phenotype named as pain-to-itch switch [108]. This phenomenon has been confirmed in a dry skin mouse model, in which the increased innervation of TRPV1$^+$ fibers in dry skin was demonstrated [81]. Although the precise mechanisms remain undetermined, this phenomenon implies TRPV1 may contribute to neural function plasticity in pathological conditions.

A research group has carried out studies to test human sensation evoked by capsaicin and histamine spicules in volunteer subjects [109, 110]. They observed that while single spicule of capsaicin, histamine, or cowhage induced dose-dependent pruritic sensations that were usually accompanied by pricking/stinging and burning, a wider and deeper application by capsaicin intradermal injection only induced pain with hyperalgesia but not itch or alloknesis [109, 110]. Although why capsaicin could induce different sensations by different application methods (punctate v.s injection) remains unknown, it provides clues to further study the phenomenon of pain-to-itch switch.

12.4 TRPV1$^+$ Neurons as the Center of Neuroimmune Interactions

While pain and itch allow the host to sense and expel environmental stimuli, the immune system provides a following protective mechanism by fighting pathogens. Emerging evidences have revealed that immunity and nociception have crosstalk particularly in the skin and mucous barriers. On one hand, cytokines derived from immune cells or even environmental materials alone could act on sensory neurons. On the other hand, sensory neurons particularly nociceptors in turn release neuropeptides and cause immunity remodeling. In the sections above, we talk about mechanisms of pain and itch that are mediated by inflammatory mediators. In this section, we will focus on how the peripheral sensory nervous system regulates immune responses via neuropeptide releasing (Fig. 12.3).

Neuropeptides are signaling peptides that are mainly made by and released from neurons. Neuropeptides can affect both neurons and non-neuronal cells and are considered to be key mediators in the communication between neurons (in particular sensory neurons) and effector cells. A number of candidate neurotransmitters/neuropeptides released from peripheral sensory neurons towards the spinal cord include GRP, glutamate, SP, BNP, and neuromedin B (NMB), etc. [44, 55, 111–115]. Meanwhile, activated

nociceptors are capable of releasing neuropeptides to act on non-neural cells. These processes are particularly significant in pathologic conditions such as infectious immunity and allergic reactions.

12.4.1 Mast Cells: A Classic Neuroimmune Paradigm

The axon reflex represents a classic neuroimmune paradigm. The activation of nociceptors not only leads to the transmission of action potentials toward the central nervous system but also causes neuropeptide releasing along its fibers back to skin endings. These released peptides mainly include CGRP and SP. Both CGRP and SP have been shown to act on the vasculature and mast cells to induce vasodilatation, edema, degranulation, and consequent immune cell recruitment [116]. Vasodilatation caused by CGRP is mediated by receptors at precapillary arterioles, whereas SP induces plasma extravasation from venoles. Unlike neurokinin-1 receptor (NK1R) which is the receptor for SP in the spinal cord, recent studies have shown that MrgprB2 in mice (MRGPRX2 in humans) is the key receptor that induces SP-driven activation of mast cells [117, 118]. Therefore, mast cells appear to be the key cellular mechanism that bridges immunity and somatosensation. On the one hand, they release inflammatory mediators to promote pain and itch upon stimuli. On the other hand, they accept neuropeptide signaling from sensory nerves to further exemplify the noxious responses. Thus, the reaction of axon reflex is also called "neurogenic inflammation."

More interestingly, a recent study uncovered that common environmental allergens that have cysteine protease activity, e.g., house dust mites, can directly activate TRPV1$^+$ neurons to release SP. Further, SP acts on MrgprB2 on mast cells to promote type 2 inflammation in the skin. These findings elucidate how environmental stimuli directly activate nociceptors and regulate inflammation via the sensory system [119].
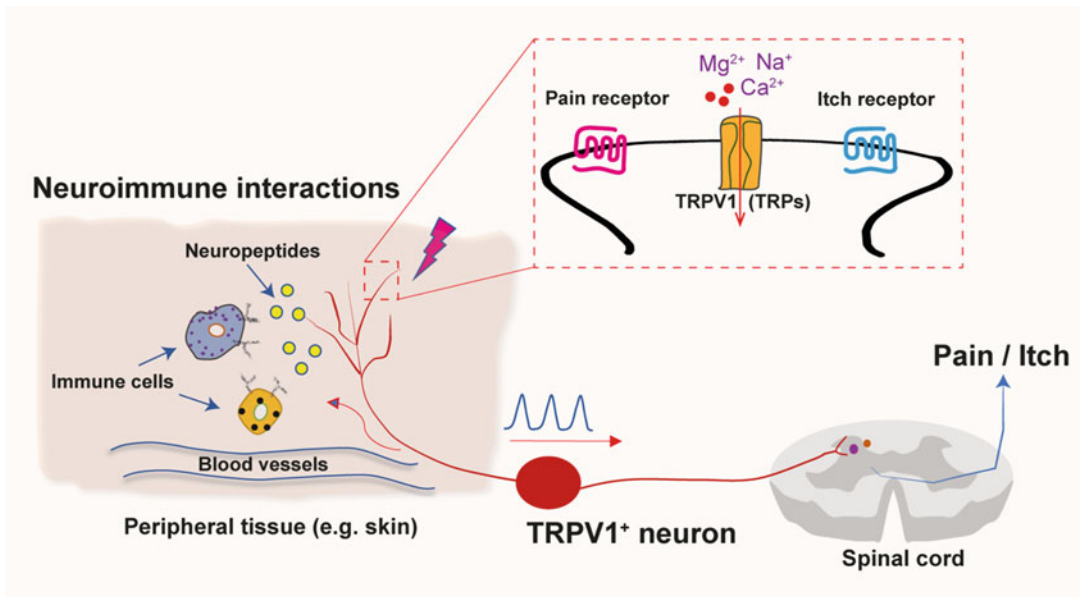
Fig. 12.3 Neuroimmune interactions mediated by TRPV1^{+} neurons in the context of pain and itch. TRPV1^{+} fibers in the peripheral tissues directly sense pain and itch mediators, evoking action potential to transmit the nociceptive signaling to feed into the central circuitry. On the other hand, TRPV1^{+} peripheral axons release abundant neuropeptides to provoke neuroimmune interactions

12.4.2 Beyond Mast Cells: Other Immune Cells Regulated by Nociceptors

In addition to mast cells, more innate immune cells have been found capable to respond to neuropeptides. Neutrophils are an innate immune cell population that is well known for rapidly responding to infections, helping resolve infections, and healing the damaged tissue. A number of bacteria infections provoke host pain sensation, but the precise mechanisms are not fully understood. In 2013, Chiu et al. firstly found that bacterial infections cause pain by directly activating nociceptors [120]. Later in 2018, the Chiu group identified that TRPV1^{+} nociceptors suppressed protective immunity against lethal *Staphylococcus aureus* pneumonia through suppression of the recruitment and surveillance of neutrophils and alteration of lung γδ T cell numbers [121]. Further, in the same year, the same research team reported that on the basis of nociceptor activation stimulated by *Streptococcus pyogenes*-released streptolysin S to produce pain, nociceptors, in turn, secrete neuropeptide CGRP to inhibit the recruitment of neutrophils and the killing of bacteria [122]. In the above studies, they employed the approach of RTX administration and TRPV1-DTR strain to demonstrate the role of TRPV1^{+} nociceptors in the context of bacterial infections. Taken together, it appears that nociceptors and their related neuropeptide CGRP are likely negative factors to defense bacterial pathogens across barriers from the skin to the lung.

Group 2 innate lymphoid cells (ILC2) belong to the family of innate lymphocytes and are a prominent source of type 2 cytokines [123]. ILC2s are found constitutively at the skin and mucosal barriers and in the spleen, fat-associated lymphoid clusters, and lymph nodes. The significant role of ILC2 plays in type 2 immunity like AD, metabolic homeostasis, and chronic pathologies like fibrosis has been demonstrated in both patients and animal models [124]. So far, the identified neuropeptides that can

regulate ILC2s include vasoactive intestinal peptide (VIP), neuromedin U (NMU), and NMB [125–129]. However, the most relevant neuropeptide released from nociceptors is VIP. VIP was first shown to stimulate gut ILC2s to release IL-5 through the VPAC2 receptor and cause eosinophil accumulation [130]. Another study conducted by Talbot et al. identified that IL-5 directly activates nociceptors to induce the secretion of VIP. Then VIP further activates resident ILC2s and effector CD4$^+$ T cells via VPAC2. This positive feedback loop formed by cytokine, nociceptors, and immune cells significantly amplifies the pathological allergic conditions, which suggests targeting the nervous system as a treatment option in allergies. NMU and NMB have been, respectively, found to promote lung ILC2 and helminth-induced ILC2 responses [127–129]. However, while the main cellular source of NMU is cholinergic neurons, the major source of NMB in the setting of helminth infection remains unclear. Notwithstanding this, these studies highlight how significant the nervous system is in innate immunity regulation and imply that nervous systems might also play a role in the link between innate immunity and adaptive immune responses.

Dendritic cells (DCs) are important antigen-presenting cells and are resident in multiple barriers. They are responsible to process and present antigens or allergens to adaptive immune cells like T cells and promote their differentiation. *Candida albicans* is the most common pathogen that causes cutaneous candidiasis. In a murine model of cutaneous candidiasis, Kashem et al. discovered that IL-23-derived from CD301$^+$ dermal DCs could augment γδ T cells to release IL-17A and inhibit cutaneous *Candida albicans* infection. Interestingly, CGRP released from TRPV1$^+$ neurons that are directly activated by *Candida albicans* is sufficient to promote IL-23 releasing from dermal DCs [131]. The role of the other neuropeptide SP released from TRPV1$^+$ neurons play in DCs and antigen-presenting processes were reported recently. In the study published by Perner et al. [132], authors identified that environmental allergens like papain and Alternaria extract were sufficient to provoke scratching behavior in mice and this phenotype was dependent on TRPV1$^+$ sensory neurons. Intriguingly, using TRPV1-DTR mouse strain, they surprisingly found that allergen-induced CD301b$^+$ DC migration required the TRPV1$^+$ neuron subset as well as SP. Collectively, these studies highlight the significance of TRPV1$^+$ sensory neurons in antigen-presenting process for both infectious and allergic immune responses.

Studies to explore somatosensory neurons in adaptive immune cells are not as many as in innate immune responses. In 2019, Cohen et al. employed a novel optogenetic approach to activate TRPV1$^+$ neurons. They generated mice (TRPV1-Ai32) in which TRPV1$^+$ neurons in the skin could express the light-gated cation channel channelrhodopsin-2 and be activated by cutaneous light stimulation [133]. Strikingly, this optogenetic stimulation is capable of initiating skin inflammation which is predominated by Th17 (type 3) immune responses. The biological effect of such skin immunity was further shown to enhance host local defense to *Candida albicans* and *Staphylococcus aureus*. More importantly, this defense effect can be propagated to adjacent, unstimulated skin areas through a nerve reflex arc. Thus, although the concept of "neurogenic inflammation" was established a century ago, this study demonstrated that activation of sensory neurons alone is sufficient to results in inflammation and might be a future target to augment local immune responses in fighting pathogens.

12.5 Therapeutic Strategy and Perspectives

12.5.1 Agonist

The basic concept for analgesic effects of capsaicin refers to the selective excitation and subsequent desensitization of TRPV1$^+$ fibers (pain and itch sensing fibers). This is widely used in relieving pain and itch related to many sensory disorders. This acute desensitization occurs rapidly within 20 s upon activation and is dependent on the calcium influx, which represents a feedback mechanism protecting

nociceptors from toxic calcium overload [87]. This effect of "activation triggers sequential desensitization" has been repeatedly verified in capsaicin topical application to alleviate pain and itch. In pain clinic, 8% capsaicin topical patch has been used in the painful disorders, such as diabetic neuropathy, chemotherapy-induced peripheral neuropathy, and peripheral neuropathy associated with hypereosinophilic syndrome [134–138]. Furthermore, direct capsaicin injection into the joint has been used to relieve osteoarthritis-related pain [139]. Unlike "activation triggers sequential desensitization," tachyphylaxis is another type of desensitization and refers to the reduced responses due to repeated activation. Further studies are needed to verify its anti-itch or anti-pain effects in clinical practice.

Although topical capsaicin has been approved by Food and Drug Administration (FDA) for neuropathic pain treatment, its advantages are significant as it not only desensitizes the TRPV1 channel-related pain sensation, but also disrupts TRPV1$^+$ peripheral terminals to abolish the potential nociception transmission via other co-expressed channels or receptors. However, one major concern is the disruption of physiological functions mediated by neuropeptides released TRPV1$^+$ peripheral nerves. Disrupting or desensitizing the TRPV1$^+$ fibers in a period of time will inevitably lead to the absence of neuropeptide releasing in various noxious conditions such as axon reflex. Furthermore, long-term use of the capsaicin patch might null the somatosensation of the treated skin, which might attenuate the response upon harmful stimulation, such as noxious heat. Finally, activation of TRPV1 in skin lesions causes painful sensation before desensitization occurs, which is not acceptable to some fatigue patients or children.

12.5.2 Antagonist

TRPV1 antagonists are expected to treat pain and itch sensation by inhibiting receptor potential and preventing convey of nociceptive signaling from peripheral sites to the central nervous system. A series of novel drugs have been tested in clinical

trials. GlaxoSmithKline SB-705498 is a small molecular and a potent, selective, orally bioavailable antagonist for TRPV1 [140]. The anti-pain effect of SB-705498 has been tested in a cohort of 19 healthy volunteers who had pain symptom that was evoked by noxious heat, capsaicin or ultraviolet radiation B (UVB) irradiation [141]. The results appear positive as SB-705498 was revealed safe and well-tolerated and exhibited pharmacodynamic activities in alleviating pain and hyperalgesia.

However, some tested antagonists were found to potentiate hyperthermia or hypothermia. Given hyperthermia/hypothermia as the most common side effects, the pharmaceutical value of TRPV1 agonists was questioned. Thermoregulatory effects of TRPV1 antagonists in humans have been intensively studied. Controversial views are emerging as the tested compounds in vitro may have different binding potency in vivo and thus, the safety and efficacy of new TRPV1 antagonists should be reexamined. Accordingly, clinical trials revealed that polymodal TRPV1 antagonists (ABT-102, AZD1386, and V116517) cause an increase of body temperature, which was not shown in patients treated with mode-selective blocker NEO6860 [142]. In a Phase I clinical trial in which AMG517 is examined, subjects exhibited marked dose-dependent hyperthermia that might be related to the vasoconstriction and increasing thermogenesis [143]. Another potent and selective TRPV1 channel antagonist, JNJ-38893777, was tested in a single-center, double-blind, placebo-controlled, sequential group, single-ascending-dose phase 1 study. Results turned out promising as increases in body temperature or changes in Fridericia-corrected QT interval (QTcF) were not observed [144].

While systemic application of TRPV1 antagonist may face unexpected thermogenesis problems, topical administration could be a safer strategy. To treat itch-related skin problem, TRPV1-inhibitor 4-t-butylcyclohexanol based skin care cream has been tested to treat perioral dermatitis [145]. Perioral dermatitis is a skin problem and characterized by impaired skin barrier function that results in redness, dryness, burning, and pruritus. After TRPV1-inhibitor

treatment, skin barrier function was surprisingly restored, featured as the decreased transepidermal water loss values and increased stratum corneum hydration [145]. These results support that topical application of TRPV1 antagonists is better tolerated.

More profound TRPV1 antagonists in pain- and itch-associated phenotypes have been tested in laboratory animals. For example, pharmacological blockade of TRPV1 using AMG9810 (a potent and selective TRPV1 antagonist [146, 147]) significantly decreased calcium responses in sensitized neurons, suggesting pharmacological effects in hyperalgesia conditions. Indeed, in an allergic conjunctivitis mouse model, antagonizing TRPV1 by AMG9810 could effectively disrupt histamine-dependent itch behavior [148], indicating the topical application of AMG9810 might be effective in dealing with ocular discomforts.

The most common concern about the overall antagonization of the TRPV1 channel is that the normal physiological function is likely disrupted. Thus, more studies are still needed to explore how to reserve TRPV1 physiological function when targeting pathologic pain and itch [149].

12.5.3 TRPV1 Activity-Dependent Silencing by QX-314

In addition to molecular antagonists, cell-specific design and synthesis may open a new avenue to save the protective role of pain and itch. The newly proof-of-concept to silence a specific activated nociceptive population has become available when QX-314 was introduced into the field. QX-314 is a charged, membrane-impermeant lidocaine derivative and can only penetrate into the neurons via a hydrophilic pore in the cell membrane. After entering cells, QX-314 sequentially blocks sodium channels to inhibit the overall neural activity and thus functions as local anesthetics. This specific characteristic enables the selective effect in which nociceptors are silenced via an activity-dependent manner. In 2007, Binshtok, Woolf, and colleagues generated a novel strategy to inhibit

pain sensation [150]. They simultaneously applied QX-314 and capsaicin into rat hind paws or sciatic nerve and found that pain sensitivity was suppressed and the effect lasted for greater than 2 h without motor or tactile function impact [150]. This strategy opens a door to inhibit pain-responsible firing that is mediated by a broad range of factors. Since the opening of TRPV1 or/and TRPA1 channels is widely exhibited upon stimulation of pain mediators, which provides the critical condition of QX-314 entry. Besides for inflammatory mediators, pain induced by bacterial infections can also be blocked by QX-314. Three classes of PFTs-alpha-hemolysin (Hla), phenol-soluble modulins (PSMs), and the leukocidin HlgAB associated with methicillin-resistant *Staphylococcus aureus* (MRSA) have been identified to induce pain during the infection. Strikingly, QX-314 application revealed immediate and long-lasting blockade of pain sensation in a murine model infected by MRSA. Moreover, this approach is even more effective than analgesic reagents like lidocaine or ibuprofen [151].

Similarly, the effect of QX-314 was also confirmed in itch-related study. By applying QX-314 and histamine or chloroquine together, itch behavior was significantly inhibited [152]. Importantly, blocking itch-transmitting fibers did not reduce pain-associated behavior. Overall, this strategy not only helps identify the distinct populations for pain and itch mediators, but also provides a clinical anti-pruritic therapeutic approach for both histaminergic and non-histaminergic pruritus [152]. A specific case is the distinguishment of ocular pain and itch sensation. Although ocular discomforts can present as pain or itch, whether these signals are transmitted by the same or different sensory neurons remains not clear. Via tracing approaches, we found that pain and itch sensing sensory fibers have different anatomic territories. To be specific, while ocular itch is mediated by a subset of conjunctival-selective sensory fibers marked by MrgprA3, pain-sensing fibers were only observed in corneal innervations. By selectively silencing MrgprA3-expressing conjunctiva sensory fibers by using QX-314 and CQ (the

agonist of MrgprA3), we observed that the itching behavior was markedly reduced in both pruritogen-stimulated and allergic-related conditions [153]. Taken together, these results indicate that TRPV1 activity-dependent silencing by QX-314 may have great significance in research and development for anti-pruritic medications.

12.6 Summary

The broad integration of physiological and pathophysiological of TRPV1 has been well studied and documented in pain- and itch-related fields. Over time, advanced research progresses emerge and indicate TRPV1 as a potential pharmaceutical target for treating pathologic pain and itch. The resolution of TRPV1 structure in the steady-state and the observation and mechanisms of dynamic change in TRPV1 upon stimulation makes it possible to modulate TRPV1 in a variety of conditions [3, 82]. Of note, although adjustment of expression level and the channel activity have revealed prosperity in pain and itch relieving, TRPV1 antagonists in clinical trials have encountered difficulties due to their adverse effects such as hyperthermia or hypothermia [142, 143]. Notwithstanding this, how to modulate TRPV1 activity in specific tissues and avoid affecting its basic physiological function remains an active research field to achieve the anti-pain and anti-itch effects. Excitingly, the novel concept of TRPV1 activity-dependent silencing by QX-314 has provided a promising approach to block the selective pain sensation. Over time, the consistent studies of TRPV1 in pain and itch will lead a new era to solve debilitating sensory disorders.

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