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Nociceptive Roles of TRPM2 Ion Channel in Pathologic Pain

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Abstract
Pain is a protective mechanism that enables us to avoid potentially harmful environments. However, when pathologically persisted and aggravated under severely injured or inflamed conditions, pain often reduces the quality of life and thus is considered as a disease to eliminate. Inflammatory and/or neuropathic mechanisms may exaggerate interactions between damaged tissues and neural pathways for pain mediation. Similar mechanisms also promote the communication among cellular participants in synapses at spinal or higher levels, which may amplify nociceptive firing and subsequent signal transmission, deteriorating the pain sensation. In this pathology, important cellular players are afferent sensory neurons, peripheral immune cells, and spinal glial cells. Arising from damage of injury, overloaded interstitial and intracellular reactive oxygen species (ROS) and intracellular Ca^{2+} are key messengers in the development and maintenance of pathologic pain. Thus, an ROS-sensitive and Ca^{2+}-permeable ion channel that is highly expressed in the participant cells might play a critical role in the pathogenesis. Transient receptor potential melastatin subtype 2 (TRPM2) is the unique molecule that satisfies all of the requirements: the sensitivity, permeability, and its expressing cells. Notable progress in delineating the role of TRPM2 in pain has been achieved during the past decade. In the present review, we summarize the important findings in the key cellular components that are involved in pathologic pain. This overview will help to understand TRPM2-mediated pain mechanisms and speculate therapeutic strategies by utilizing this updated information.

Keywords TRPM2 · Oxidative stress · Pain · Nociceptor · Immune cell

Introduction

Pain is an unpleasant feeling derived from physiological and psychological responses to harmful stimuli. Intense stimuli transiently cause pain, which is resolved upon removal of the stimuli. Acute pain sensation is a normal response necessary for survival to protect our body from damage. Injury and disease can often lead to chronically sustained inflammatory and neuropathic pain despite removal of the original stimulus. Aberrantly increased excitability and strengthened synapses in pain-mediating neural pathways cause such sustained pathologic pain. The alteration of the excitability and synaptic plasticity can be initiated by excessive firing of nociceptor afferents in many cases, where the afferent neurons interact with inflammatory components. Many inflammatory mediators secreted from immune cells that are recruited during the inflammatory process in injured periphery intensely activate and/or sensitize nociceptive ion channels that compose the basis of nociceptor excitability in direct or indirect manners [1, 2]. Cation influx and anion efflux through activated ion channels typically depolarize afferent nociceptors, and an accompanying increase in intracellular Ca^{2+} may intensify various nociceptive signals by elevating ion channel activity via Ca^{2+}-dependent enzymatic catalysis, increasing transmitter and neuropeptide release via vesicular modification, altering cellular metabolism via organellar overload, etc. Upon sustained nociceptor firing, a subset of neurons secretes neuropeptides, which may further promote immune activity and eventually intensify peripheral inflammation [3]. Similar interactions occur in the spinal nociceptor synapses, which is frequently

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called neuroinflammation. Increased neurotransmitters and mediators during heightened synaptic transmission stimulate neighboring spinal glia including microglia and astrocytes, which release cytokines and chemokines, and other various inflammatory mediators [4, 5]. Some of these mediators increase synaptic strength and others recruit glia and immune cells such as macrophages and neutrophils, which exacerbates neuroinflammation [4, 5].

Oxidative stress, which is mainly carried by reactive oxygen species (ROS), heightens during inflammation and is involved in the pathogenesis of inflammatory and neuropathic pain [6, 7]. ROS not only act as intercellular inflammatory messengers but also play as intracellular signals, which causes numerous biological modifications including oxidation of proteins and lipids [8, 9]. When modified by ROS, some of proteinous enzymes more generate their products that amplify neuronal excitability and some lipids begin to play as potent inflammatory mediators [8, 9]. Overloads of intracellular ROS, together with those of intracellular Ca^{2+} as mentioned above, are currently considered as a critical pathogenic step in inflammation and pathologic pain [10–13]. Therefore, inside the cellular components interactively developing the pathologic pain, one may need to focus on molecules that merge ROS and Ca^{2+} signaling, if any, in order to better understand the pathogenic mechanisms by validating its contributing level.

One such molecule is transient receptor potential melastatin subtype 2 (TRPM2), a Ca^{2+}-permeable nonselective cation channel that is directly activated by cytosolic adenosine diphosphate ribose (ADPR) and indirectly by ROS such as hydrogen peroxide (H_2O_2) [14, 15]. In the peripheral somatosensory system, TRPM2 is expressed ubiquitously in afferent sensory neurons of dorsal root ganglia (DRG) and trigeminal ganglia (TG) [16]. In the spinal cord, TRPM2 is expressed in glial cells including microglia and astrocytes [17]. TRPM2 is also highly expressed in peripheral immune cells such as monocytes, macrophages, and neutrophils [18]. In the last decade, there has been notable progress in defining the role of ROS-sensitive and Ca^{2+}-permeable TRPM2 of those cells in pain exacerbation. In this review, we summarize recent findings in TRPM2-related molecular and cellular signaling, pain phenotypes, and unsolved issues regarding the function of TRPM2 in pathologic pain.

TRPM2 Monitors Oxidative Stress

TRPM2 was first cloned in the late 1990s, but its role in sensory neuronal excitation was first proposed over a decade later [19, 20]. Currently, TRPM2 has known to be activated by intracellular ADPR, oxidative stress, and moderate heat in various cell types [21–23].

Unlike other TRP channels, TRPM2 has a unique structure with an enzymatic domain (NudT9-H) in the C terminus. The NudT9-H region shares significant homology with nucleoside diphosphate linked moiety X-type motif 9 (NudT9, an ADPR pyrophosphatase) that hydrolyzes ADPR into adenosine monophosphate (AMP) and a ribose. As shown in Fig. 1, the cytosolic free ADPR could be generated by membrane-bound CD38, mitochondrial nicotinamide adenine dinucleotide nucleosidase (NADase), and the orchestrated action of poly(ADPR) polymerase (PARP)/poly(ADPR) glycohydrolase (PARG) in the nucleus [24–26]. In general, the specific ADPR binding to the NudT9-H region of TRPM2 causes cation currents through gating of TRPM2 pore with ADPR hydrolysis [23, 27, 28].

The ADPR is also involved in the gating of TRPM2 by oxidative stress because the activities of these ADPR-producing enzymes are highly regulated by oxidative stress [29–31]. For example, mutational disruption of the ADPR binding cleft in the TRPM2 NUDT9-H domain impairs ADPR binding and H_2O_2-induced cellular Ca^{2+} influx [32]. An ADPR-independent mechanism for H_2O_2-induced TRPM2 activation was once reported using a splice variant of TRPM2 with a C terminus deletion that retains its responsiveness to oxidative stress, but this result was not replicated [33, 34]. Moreover, pharmacological inhibition of PARP effectively suppresses H_2O_2-induced TRPM2 activation [35]. Similarly, genetic deletion in *PARP-1* in DT40 cells causes loss of H_2O_2-induced TRPM2 activation [36]. Collectively, these results indicate that TRPM2 responds to oxidative stress that may occur in various subcellular and extracellular regions via enhanced activity of ADPR-producing enzymes located in the plasma membrane, mitochondria, and nucleus.

In addition, TRPM2 is sensitive to warm temperatures and the exposures of warmth and ADPR are mutually synergistic for TRPM2 activation [21, 37]. This thermal sensitivity of TRPM2 has been shown to be important in insulin secretion, hypothalamic temperature regulation, and somatosensation of non-noxious warmth [21, 38, 39].

Expression and Function of TRPM2 in Pain-Mediating Neurons

Somatosensory pathways in the nervous system relay signals caused by environmental changes to the brain, leading to perceptions of touch and pain. Afferent neurons of dorsal root ganglia (DRG) and trigeminal ganglia (TG) play the primary roles of detecting changes and transducing them into electrical signals. The peripheral endings of DRG and TG neurons innervate the body and face, where they detect the environmental changes such as temperatures, mechanical stress, and exposure to external or internal chemicals including irritants, inflammatory mediators, and ROS. Primary afferent sensory

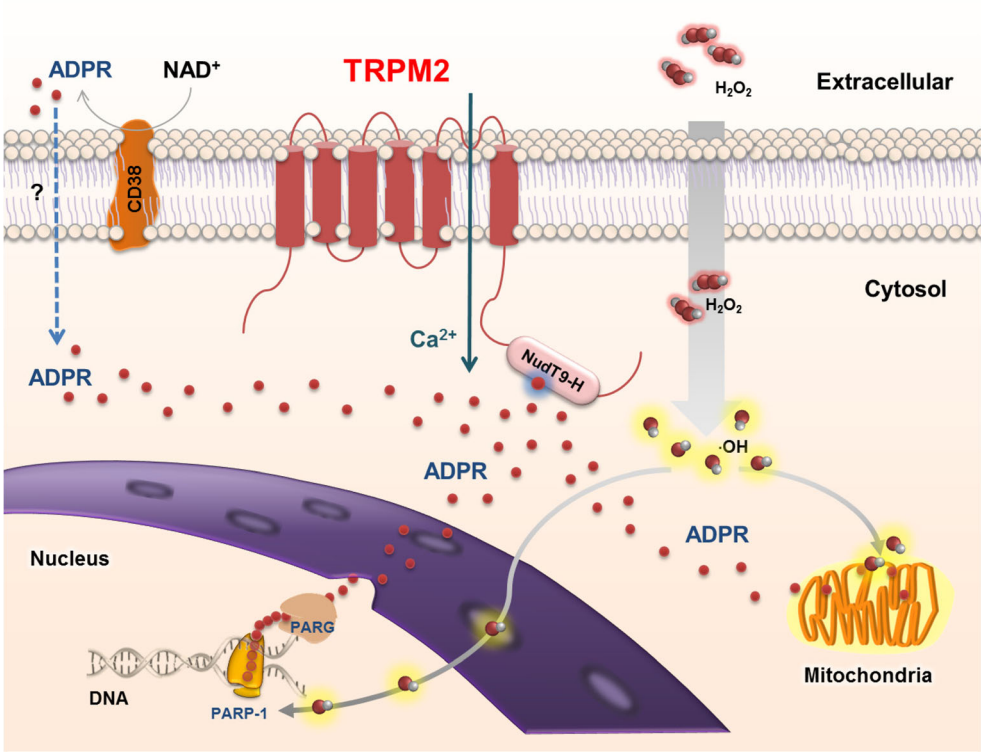

Fig. 1 Ca^{2+}-permeable TRPM2 ion channel located in the plasma membrane is activated by ADPR, which is produced by enzymes sensitive to oxidative stress

neurons are anatomically divided into four subpopulations: C- and Aσ-nociceptors, Aβ touch fibers, and proprioceptors [40]. The most abundant subpopulation is C-fibers that have relatively small-sized cell bodies (10 to 30 μm in diameter) and unmyelinated axons, and these C-fibers are mainly responsible for pain perception by transducing potentially harmful ranges of temperatures, stretches, and presences of painful substances into electrical depolarization [40–42]. Some C-fibers contain neuropeptides such as substance P and calcitonin gene related-peptide (CGRP), and are known as peptidergic C-fibers [3, 40]. Upon sustained stimulation, peptidergic C-fibers secrete neuropeptides to their peripheral innervating tissues and spinal synapses, exacerbating tissue inflammation by stimulating infiltrated immune cells and elevating vascular permeability, and strengthen synaptic transmission. These outcomes contribute to development of chronic and pathologic pain.

In primary afferent neurons, TRP ion channels serve essential roles as molecular transducers that convert environmental changes into neuronal depolarization via gated cationic flux. Vandewauw and colleagues determined expression levels of TRP channels in murine DRG and TG by quantitative analysis of mRNAs transcribed from all 28 TRP genes and showed that 17 TRPs were expressed [16]. TRPM2 appears to be ubiquitously expressed throughout subpopulations of DRGs and TGs according to their results from TGs and separate 27 DRGs that were anatomically defined by segments of the spinal cord [16]. Consistent with this observation, 90% of mouse DRG neurons express TRPM2 according to in situ hybridization [39]. Another recent immunohistochemical analysis detected intense immunoreactivity of TRPM2 in both neurofilament 200 (NF200)-positive medium to large-sized A-fiber neurons and in isolectin B4 (IB4)-bound small-sized C-fiber neurons of rodent lumbar and sacral DRG sections [43]. Moreover, TRPM2 protein was also detected in both peptidergic and non-peptidergic C-fiber neurons [43]. Such patterns of TRPM2 expression in the primary afferent ganglia imply that the neurons might not only utilize TRPM2 generally as an effector to cope with oxidative stress, but also ascribe a subpopulation-specific role to TRPM2, for example pain initiation upon harmful oxidative attacks potentially originating from inflammations or injuries.

Evidence has been also increasing in terms of molecular function of TRPM2 ion channel since the early 2010s. In whole-cell patch-clamp experiments with cultured DRG neurons, the presence of H_2O_2 induced inward electrical currents that were reversibly abolished by the TRPM2 inhibitors, 2-aminoethoxydiphenylborate (2-APB) and *N*-(*p*-amylcinnamoyl)anthranilic acid (ACA) [44–46]. These H_2O_2-induced and putatively TRPM2-mediated whole-cell currents were also attenuated by NADPH oxidase inhibitors such as apocynin and *N*-acetylcysteine, indicating that TRPM2 gating in response to H_2O_2 is due to the known indirect signaling axis of H_2O_2–ADPR–TRPM2 as mentioned above [47]. It is possible that the function of other somatosensory TRP channels including vanilloid subtype 1 (TRPV1) and ankyrin subtype 1(TRPA1) is also sensitive to the exposure of such oxidative stress despite employing independent

signaling mechanisms [8, 9]. For example, the TRPV1-specific inhibitor capsazepine additionally attenuated H_2O_2-induced currents in DRG neurons [47, 48]. A different important aspect of TRPM2 contribution to H_2O_2 signaling was tested using rodent trigeminal neurons. In cultured TG neurons, exposure to H_2O_2 significantly increased the mRNA and protein levels of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) and a chemokine (CXCL2) that play a crucial role in inflammatory pain [49–51]. Interestingly, the elevation of cytokine and chemokine levels was prevented by treatment with TRPM2 inhibitor 2-APB or by RNA interference against TRPM2 expression [49]. Therefore, TRPM2 appears to participate not only in the mechanisms underlying increased neuronal excitability but also in the increased pro-inflammatory capacity of the sensory neuron when exposed to oxidative stress.

Protein kinase C (PKC) is a serine/threonine kinase that not only mediates Ca^{2+}-associated signal transduction but also regulates the reduction oxidation (redox) balance of various species of proteins by responding to oxidative stress [52]. ROS produced under oxidative states is known to directly regulate the catalytic activity and localization of PKC through redox modifications of PKC cysteine residues [52, 53]. In DRG neuronal experiments, H_2O_2-evoked electrical currents were potentiated when incubated with the nonspecific PKC activator phorbol 12-myristate 13-acetate (PMA) [46]. The potentiated currents were attenuated by treatment withTRPM2 inhibitors 2-APB and ACA, or with the PKC inhibitor bisindolylmaleimide I, indicating that TRPM2 is one of the molecular effectors modulatable by PKC activity under oxidative conditions [46, 47].

Glutathione (GSH) is an abundant antioxidant in cells and prevents cellular damage caused by ROS including free radicals, peroxides, and heavy metals [54]. In whole-cell patch-clamp recording of cultured rodent DRG neurons, intracellular application of GSH completely prevented the putatively TRPM2-mediated electrical response to H_2O_2 exposure, indicating that intracellular redox state is critical to the converting process of H_2O_2 signaling to TRPM2 activation [44]. The same study examined the effect of blocking GSH biosynthesis. Incubation for 24 h with buthionine sulfoximine (BSO), which selectively inhibits γ-glutamylcysteine synthetase, the sole enzyme producing the GSH-precursor, γ-glutamylcysteine, did not significantly affect basal intracellular Ca^{2+} levels or basal membrane currents, indicating that TRPM2 activity is not dynamically modulated by residual GSH under normal conditions. However, this GSH inhibition boosted the H_2O_2 response by TRPM2, and GSH supplementation reversed this effect. Thus, despite not finely controlling the channel activity itself, GSH balance is important somewhere in the TRPM2 signaling axis. Interestingly, the increased level of lipid peroxidation and decreased level of GSH peroxidase in cultured DRG neurons upon BSO treatment, which may be caused by BSO-induced GSH depletion, were normalized by 2-APB treatment. Because the role for TRPM2 in such a protective effect remains obscure in DRG neurons and 2-APB is known to modulate activities of other different proteins including sensory neuronal TRPV channels, the notion seems to await further mechanistic approaches.

Collectively, TRPM2 is expressed in primary somatosensory neurons including C-fiber nociceptors. Oxidative stress produced by disease or injury may depolarize nociceptor neurons and elevate intracellular Ca^{2+} via enzymatic generation of ADPR and its direct gating of TRPM2, which might be controlled by endogenous protection mechanisms. Resultant neuronal activation possibly initiates pain perception and promotes pro-inflammatory processes including secretion of inflammatory mediators from the neuron itself.

Expression and Function of TRPM2 in Non-neuronal Inflammatory Components

Chronic and pathologic pain development is largely explained by inflammatory and neuropathic mechanisms. Inflammatory pain mechanisms actively operate in damaged tissues and spinal cord synapses: in both places, immune cells serve essential roles [55]. Upon tissue injury or disease, damaged tissues exude intracellular contents and stimulated residual immune cells secrete peptidergic cytokines and chemokines and lipidergic mediators, resulting in infiltration of additional immune cells by permeabilizing vasculatures and enhancing the cellular migration. Elevated levels of such mediators from increased number of immune cells strongly stimulate nociceptor excitation. Peripheral and central terminals of activated neurons release neuropeptides, which aggravate the pathologic processes [3]. TRPM2 is widely expressed in immune cells including monocytes, macrophages, neutrophils, and dendritic cells (see review, [18]). Oxidative stress-induced TRPM2 activation similarly occurs in monocytes and immune stimulations such as lipopolysaccharide (LPS) exposure promote the signaling paradigm by increasing TRPM2 expression, contributing to chemokine and cytokine production [56, 57]. Genetic deletion or pharmacological inhibition of TRPM2 downregulates the migration and adhesion of neutrophil under ischemic stroke conditions [58, 59]. TRPM2 deficiency diminishes neutrophil infiltration in carrageenan-induced and nerve injury-induced inflammation [17]. ROS-mediated TRPM2 activation promotes NLRP3 inflammasome-mediated interleukin-1β secretion from macrophages [60]. The bactericidal activity of macrophage is improved by TRPM2-induced Ca^{2+} influx in cecal ligation and in a puncture-induced septic model [61]. Interestingly, ROS-mediated TRPM2 activation blocks NADPH oxidase-

mediated ROS production in macrophages as a negative feedback mechanism [62]. Therefore, TRPM2 mediates ROS-sensitive Ca^{2+} signaling in various immune cells.

Roles of TRPM2 in Inflammation-Specific Pain Sensation

Carrageenan Inflammation

Sensory neuronal TRP channels are specific detectors for a certain type of painful stimulation. Stimuli can be categorized as thermal, mechanical, and chemical, and specific TRP channels convey the information on some particular stimuli by transducing the stimulatory energy into cationic flux. For example, TRPV1 responds to thermal (> 43 °C) and chemical (capsaicin) stimuli, TRPM8 to thermal (< 26 °C) and chemical (menthol) ones, and TRPA1 to thermal (< 17 °C), chemical (menthol, cinnamon oil, mustard oil, formalin, reactive lipids, etc.), and mechanical (sting, pinch, etc.) ones [63]. This coverage of the molecular sensitivities is well extrapolated to in vivo pain modality. Because TRPM2 is activated by oxidative stress (usually oxidizing chemicals), it can be assumed that TRPM2 may convey a type of chemical pain modality in in vivo aspect. Alternatively, it can have a wider coverage since it has a relatively extensive expression not only in DRG subsets but also in surrounding immune components, and its activation may affect other modality information processing. In the acute pain analysis, neither of the two assumptions was supported. TRPM2-knockout mice retained normal sensitivity to mechanical stretch based on threshold measurements using von Frey filaments and to thermal stimulation using Hargreaves and hot plate apparatuses, compared with wild-type mice under non-inflamed conditions [17] (Table 1). In addition, there was no difference between wild-type and TRPM2-deficient mice in spontaneous nocifensive behavior following acute intraplantar injection of TRPV1-activating chemical capsaicin or H_2O_2 into the paw [64] (Table 1). The acute phase of nocifensive behavior upon hind paw formalin injection is mediated by TRPA1 activation, which also showed no difference between wild-type and TRPM2-knockout animals [17]. The data indicate that, under normal oxidative balance without inflammation or injury, TRPM2 contribution to nociceptor excitability may be negligible.

Table 1 Difference in nociceptive responses of TRPM2-deficient mice compared with those of wild-type mice in experimental pain models

Animal model	Stimulatory modality	Nociceptive response	Reference
None	Mechanical stimulation (Von Frey filament)	No difference	17
None	Thermal stimulation (Hargreaves test and the hot plate)	No difference	17
Intraplantar injection of H_2O_2 into a hind paw	Chemical injection for oxidative stress	No difference in spontaneous licking and biting behaviors on the paw	17
Intraplantar injection of capsaicin into a hind paw	Chemical injection for TRPV1 activation	No difference in spontaneous licking and biting behaviors on the paw	17
Intraplantar injection of formalin into a hind paw	Chemical injection for TRPA1 activation	No difference in phase 1 spontaneous licking and biting behaviors ↓ Phase 2 behaviors	17
Intraplantar injection of carrageenan into a hind paw	Mechanical stimulation (Von Frey filament) Thermal stimulation (Hargreaves test)	↓ Mechanical allodynia ↓ Thermal hyperalgesia	17
Trinitrobenzene sulfonic acid-induced colitis	Mechanical colorectal distension	↓ Visceral hypersensitivity	43
Incision of paw skin and fascia	Mechanical stimulation (Von Frey filament)	No difference	64
Partial sciatic nerve ligation	Mechanical stimulation (Von Frey filament) Thermal stimulation (Hargreaves test)	↓ Mechanical allodynia ↓ Thermal hyperalgesia	17
Spinal nerve transection	Mechanical stimulation (Von Frey filament) Thermal stimulation (Hargreaves test)	↓ Mechanical allodynia ↓ Thermal hyperalgesia	17
Streptozotocin-induced diabetic neuropathy	Mechanical stimulation (Von Frey filament)	↓ Mechanical allodynia	64
Monoiodoacetate-induced osteoarthritis	Mechanical stimulation (Von Frey filament)	↓ Mechanical allodynia	64
Paclitaxel-induced peripheral neuropathy	Mechanical stimulation (Von Frey filament)	↓ Mechanical allodynia	64
Experimental autoimmune encephalomyelitis	Mechanical stimulation (Von Frey filament)	↓ Mechanical allodynia	64

In contrast, inflamed animals show different phenotypes and the latter hypothesis—that TRPM2 detects a wide range of stimuli—is possibly true according to a study conducted by Haraguchi et al. [17]. TRPM2-deficient mice displayed blunted response in terms of both mechanical and thermal nociception, compared with wild-type mice in the carrageenan-induced inflammation model. Epidermal injection of carrageenan into the hind paw caused sustained elevation of H_2O_2 level in the inflamed paw and increased TRPM2 mRNA in macrophages and neutrophils [17]. There was no difference in carrageenan-induced H_2O_2 level between wild-type and TRPM2-deficient mice, but the knockout animals had significantly reduced neutrophil infiltration in the inflamed paw, probably due to reduced neutrophil generation of C-X-C Motif chemokine ligand 2 (CXCL2), a potent chemoattractant [17]. TRPM2-deficient mice exhibited reduced paw edema, a hallmark of tissue inflammation [17]. Therefore, this study clearly demonstrated that TRPM2 contributes to inflammatory pain with a wide range of sensory modalities at least by promoting the peripheral immune function. However, neuronal TRPM2 involvement in these in vivo aberrant phenotypes under inflammation remains elusive.

Visceral Hypersensitivity

Visceral hypersensitivity occurs in gastrointestinal disorders such as dyspepsia, irritable bowel syndrome, and inflammatory bowel disease [65]. Studies have consistently shown that many types of visceral hypersensitivities are pathologically derived from altered activation of visceral afferent nociceptors innervating the gastrointestinal tract (see reviews, [66, 67]). TRPM2 seems to pathologically contribute to visceral hypersensitivity as it does to somatosensory pain. In detail, TRPM2 is shown to be highly expressed in lumbar 6/sacral 1 DRG, which are composed of spinal afferents innervating the distal colon. Its expression was upregulated in mucosal nerve fibers of the distal colon in a trinitrobenzene sulfonic acid (TNBS)-induced colitis model [43]. Unlike in DRG, TRPM2 failed to be upregulated in the intrinsic nerve plexus. In this colitis model, colorectal distention using pressure-controlled air inflation caused enhanced visceromotor reflexes in electromyographic recordings, indicating that the inflammation model induced visceral hypersensitivity [43]. Oral administration of the TRPM2 inhibitor econazole normalized this pathological reflex [43]. Similarly, this sensorimotor function of TRPM2-deficient mice was highly resistant to TNBS inflammation. Because this study employed mechanical distension to stimulate the colon, which is conventionally settled in the field but does not cover the molecular sensitivity of TRPM2 (oxidative stress and ADPR), TRPM2 may be involved in the general pathology, for example by conveying oxidative information caused by TNBS inflammation to neuronal firing.

Interestingly, at an intense range of stimulation, both pharmacological and genetic antagonisms of TRPM2 reduced baseline reflexes in uninflamed animals although the data were statistically marginal [43]. The former could have been due to a nonspecific nature of econazole action on other receptors and the latter due to an unknown molecular modality of TRPM2, but further studies are required to clarify whether these are reproducible events. Together with the marginal shift of the basal reflexes, the contribution to the aberrant mechanosensitivity that TRPM2 intrinsically lacks in the molecular level may lead to a hypothesis that certain immune components also intervene in this process, as in somatosensory pathologic pain. However, Matsumoto et al. provided negative evidence for this hypothesis by demonstrating only limited TRPM2 expression in mucosal macrophages [43]. Collectively, neuronal TRPM2 appears to mediate visceral hypersensitivity under intestinal inflammation.

Postoperative Pain

Unexpected results have been obtained from observation of TRPM2 roles in a postoperative pain model. Although postoperative incision pain has been considered acute nociceptive pain, its inflammatory aspects also currently attract strong attention [68]. For example, sustained firing of nociceptors during and after surgery can promote spinal synaptic plasticity, probably accompanied by interaction with activated spinal microglia, besides other cases where damaged tissue can undergo inflammation after surgery to an extent that abnormally heightens nociceptor firing [69]. However, So et al. did not detect a difference between wild-type and TRPM2-knockout mice in terms of mechanical allodynia using a hind paw skin/fascia incision model [64]. It is possible that this model-induced pain depends more on acute nociceptive mechanisms to which TRPM2 generally failed to significantly contribute [17]. The authors raised another possibility that sensory fibers innervating muscle, which is typically damaged during fascia incision in this model, might specifically be related to the minimal TRPM2 function [64].

Roles of TRPM2 in Neuropathic Pain

Traumatic Nerve Injury Models

In addition to peripheral inflammation, neuropathic pathology and central neuroinflammation contribute to neuropathic pain development, its exacerbation, and chronicity. Oxidative stress, which stimulates TRPM2, is a pathogenic signature after trauma in spinal cord injury (SCI) and sciatic nerve injury (SNI) models and is closely associated with the severity of neuropathic pain [10, 11]. Overloaded ROS induce Ca^{2+} influx in rodent DRG neurons in both experimental SCI and SNI

models to a greater extent than in uninjured ones although basal intracellular Ca^{2+} levels were not different among one another [45, 70, 71]. Surprisingly, treatment with the TRPM2 inhibitor ACA significantly reversed the increased intracellular Ca^{2+} in DRG neurons of rats with SCI and SNI neuropathies [45, 70, 71]. Indeed, DRG neurons from rats with SCI displayed a higher current density responding to H_2O_2 compared to control neurons in a whole-cell patch-clamp mode, which was suppressed by the treatment of 2-APB and ACA [70]. Similarly, DRG neurons from rats with SNI showed a higher current density responding to ADPR compared to control neurons, which was blunted in the same way when treated with TRPM2 antagonist [71]. These data suggest that neuronal upregulation of TRPM2 occurs in neuropathies. Furthermore, DRG neurons from rats with SNI were more vulnerable to neuropathic cell death by exposure to ROS. SNI neurons displayed lower viability, higher apoptotic rates, and greater increase in caspase activity than neurons from healthy control rats. ACA treatment improved these parameters in SNI neurons [71].

In a neuropathic state, mobilization and function of centrally localized immune cells increase near synaptic areas of injured nerves, wherein activated immune cells release nociceptive inflammatory mediators that typically aggravate nociceptive synaptic transmission [72, 73]. As well as rodent SCI and SNI models, murine partial sciatic nerve ligation (pSNL) and spinal nerve transection (SNT) models are well reproducible for observing neuropathic pain, which sensitizes nociceptive perception and behavioral response to the mechanical or thermal stimulations to the injured side, termed as mechanical allodynia and thermal hyperalgesia. In the pSNL model, mechanical allodynia and thermal hyperalgesia of TRPM2-knockouts were blunted compared with wild-type mice. In the SNT model, reduced mechanical allodynia was observed in TRPM2-deficient mice [17]. Chemokines secreted from spinal glial cells appear to be a critical cue to attract other immune cells and promote synaptic strength in spinal cord synapses of damaged sensory neurons. The intracellular signaling paradigm that TRPM2-mediated Ca^{2+} influx upon oxidative stress and LPS/interferon-γ stimulation causes the generation of the chemokine CXCL2 in cultured monocytes, macrophages, and microglia has been successfully repeated in those two neuropathy models [17, 37, 56]. In pSNL mouse spinal cord, microglial mRNA of TRPM2 was upregulated at 8 and 24 h with increased production of CXCL2 as well as elevated immune infiltration [17]. In contrast, genetic disruption of TRPM2 reduced these parameters [17]. Decreases in infiltrated neutrophils and macrophages at injured sites and in the spinal dorsal horn of the ipsilateral sides where nociceptive synapses with injured neurons are located were observed in TRPM2-deficient mice compared to wild-type following pSNL or SNT surgery [17, 74] (Table 1).

Although the relative contributions of neuronal and immune TRPM2 to pain have not been thoroughly compared in a quantitative manner, interesting data have been produced by Kaneko laboratory. When wild-type mice were treated intraplantarily with LPS-stimulated macrophages from either wild-type mice or TRPM2-deficient mice, the mice developed less severe mechanical allodynia when receiving cells from the knockout mice [17]. More interestingly, mechanical allodynia was only greatly attenuated in animals with bone marrow-specific depletion of TRPM2-positive cells, most of which are predicted as immune cells, but it was seriously developed in TRPM2-deficient animals transplanted with wild-type bone marrow [17, 74]. These two results implicate the critical contribution of TRPM2-positive immune cells. Taken together, in traumatic nerve injury models, TRPM2 contribution may be emphasized regarding CXCL2 secretion and recruitment of peripheral and spinal immune cells and the excitability and pathologic Ca^{2+} increase of injured neurons, all of which exacerbate pathologic pain.

Diabetic Neuropathy

Diabetic neuropathy is one of the most common complications of diabetes, occurring in 15–25% of type 1 diabetic patients and in 30–40% of type 2 diabetic patients. Diabetic neuropathy generally leads to hyperalgesia and allodynia as in traumatic nerve injuries [75]. In pathogenic pathways implicated in diabetic neuropathy, high glucose is converted into sorbitol through the activity of aldose reductase. It is hypothesized that the increased sorbitol may cause an osmotic imbalance with resultant osmotic stress and loss of aldose reductase activity, elevating intracellular ROS levels due to NADPH depletion [12]. Indeed, DRG neurons from transgenic type 2 diabetic mice (BKS.Cg-mC/CLeprdb; db/db) showed increased oxidation of proteins and lipids with an increase in oxidative stress [76]. The sensory neuronal redox state can be further deteriorated in this disease since streptozotocin (STZ)-induced diabetic rats were reported to have reduced levels of antioxidant GSH and GSH peroxidase in DRG neurons compared to control rats [13]. In the same study and a subsequent one, H_2O_2 response (putatively by TRPM2) in the DRG neurons of STZ-induced diabetic rats was exaggerated compared with those of control neurons. However, it remains to be clarified whether diabetic oxidative burden or other upstream signaling pathways activated by diverged pathologies sensitize TRPM2 activity [13, 77]. Such enhanced TRPM2 responses might be extrapolated to actual pain. A consistent result has once been obtained that TRPM2-deficient mice exhibited reduced allodynia to mechanical stimuli based on measurements using von Frey filaments compared to wild-type mice in an STZ-induced diabetic model [64] (Table 1).

Osteoarthritic Pain

Osteoarthritis, a degenerative joint disease involving collapse of joint cartilage, is generally accompanied by severe and chronic pain and stiffness. Models using intra-articular injection of monoiodoacetate (MIA) into a knee joint mimic such disruption and osteoarthritic pain with a neuropathic nature [78]. In such an MIA-induced osteoarthritis model, there was no significant difference in the incidence rate of osteoarthritis between WT and TRPM2-deficient mice [64]. However, TRPM2-deficient mice showed attenuated mechanical allodynia compared with wild-type [64] (Table 1). Evidence is accumulating that inflammatory components and ROS in the periphery and microglial activation of the spinal synapses are involved in the disease pathology [79–81]. Thus, TRPM2-expressing DRG neurons and infiltrated TRPM2-positive immune cells might play the same role as demonstrated in other inflammatory pain diseases, which needs further experimental confirmation. Depending on whether the osteoarthritis is either of a neuropathic nature or of a simple nociceptive, TRPM2 contribution can be quantified in the future studies [82].

Chemotherapy-Induced Pain

Some chemotherapeutic agents often induce neuropathy as a side effect. The paclitaxel-induced peripheral neuropathy model is frequently used to study the pathogenic mechanism and suggest preventive strategies. Interestingly, the neuropathic pathology caused by paclitaxel appears to involve oxidative stress [83]. Paclitaxel induces mitochondrial destruction and dysfunction, which generate oxidative stress and result in neurotoxicity including axonal degeneration of primary afferent neurons. Inflammatory reactions by sustained exposure to oxidative stress can also occur, and the oxidative stress, neuropathy, and inflammation all can contribute to pathologic pain development [84]. It is assumed that TRPM2 plays a role because TRPM2 in nociceptors and immune cells participates in all of these processes. Indeed, TRPM2-deficient mice displayed attenuated mechanical allodynia in the paclitaxel model [64].

Multiple Sclerosis

Multiple sclerosis is an inflammatory disease that results from disruption of the myelin insulating neuronal axons in the brain and spinal cord, causing symptoms of paralysis, tremor, and pain. Subsequent neuronal degeneration due to demyelination indicates that it also has neuropathic nature. The experimental autoimmune encephalomyelitis (EAE) model is the most commonly used animal model of multiple sclerosis [85]. In the EAE model, TRPM2-deficient mice displayed decreases in both paralytic symptoms and demyelination compared with wild-type mice [64, 85, 86]. Based on TRPM2 upregulation in $CD4^+$ T cells, this cell type can be predicted in contribution to the pathology. The TRPM2 knockout mice also exhibited lesser mechanical allodynia compared with wild-type [64] (Table 1). Because TRPM2 deficiency improved the disease pathology and clinical problems typically originate from the

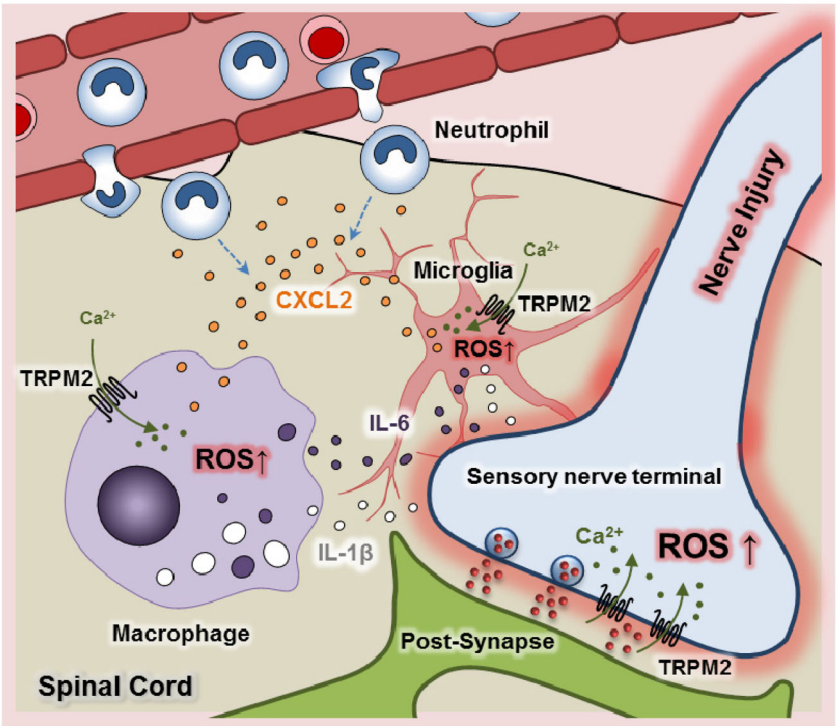

Fig. 2 TRPM2 activation promotes the function and recruitment of spinal glial cells, which may strengthen nociceptive synaptic transmissions that originate from DRG neurons

central nervous system, the dominant mechanism might operate during immune reactions rather than in nociceptor excitation.

Unsolved Issues and Conclusion

Although multiple models of pathologic pain appear to employ functional upregulation of TRPM2 in the development or exacerbation of pain, much of this information is immature and certain aspects remain unclear. For example, while TRPM2 function in in vitro cultured DRG neurons and immune cells has been explored, the majority of in vivo TRPM2 studies have focused only on peripheral or spinal immune contribution but not nerve excitability. It needs to be determined whether the in vitro data from neurons extrapolate well to in vivo outcomes in terms of excitability. This effort will provide clearer standards for quantitative measure of neuronal, immune, and glial contributions to pain pathology. Comparison with other TRP components is also required in terms of pain contribution. Nociceptor-specific and thermosensitive TRPs including TRPV1 and TRPA1 are also known to receive oxidative modulation despite heterogeneous mechanisms for individual TRPs [8, 9]. Conversely, recent studies have demonstrated that TRPM2 is also thermosensitive [37, 39]. Such functional overlap should be carefully handled both to update the understanding of the basic thermosensory mechanism and to validate those channels as painkilling targets. One of the biggest future assignments is to explore the role of TRPM2 in various regions of the central nervous system. Multiple brain circuits can intricately process pain perception, and regions responsible for other functions such as mood control may closely communicate with pain control centers [87–89]. Currently, only infraspinal information is available for TRPM2 function in pain perception. A hypothesis of region-specific TRPM2 control could be important in pain physiology and pathology, but remains unexplored.

In the relatively peripheral regions, TRPM2 has been shown to be tightly associated with pathologic pain. The cellular components in inflammation including sensory neurons, peripheral immune cells, and spinal glial cells are inevitably accompanied by ROS overload. ROS-sensitive TRPM2 is commonly functional in all of these cell types that tightly interact with each other by forming a communication network using inflammatory mediators such as cytokines and chemokines. This review presents an overview of the importance of TRPM2-mediated functions of these cells under various inflammatory and neuropathic pain models and discusses the outcomes in terms of the function of this ion channel (Fig. 2). It appears that TRPM2 is not critically involved in the acute pain. However, in many studies of inflammatory and neuropathic pain models, TRPM2 gene deletion led to alleviated pain phenotypes compared with wild-type mice (Table 1). Taken together, these findings suggest that TRPM2 contributes to the pathogenesis of inflammatory and neuropathic pain where one of the key pathologic processes is elevated oxidative stress that activates TRPM2. In this regard, TRPM2 represents a future challenge that might lead to new therapeutic strategies for pathologic pain.

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