CHANNELS
2025, VOL. 19, NO. 1, 2517109
https://doi.org/10.1080/19336950.2025.2517109

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

OPEN ACCESS Check for updates

The research progress into cellular mechanosensitive ion channels mediating cancer pain

Chang Liu[a], Haiyan Li[b], and Lihua Hang[a,b]

[a]Gusu School, Nanjing Medical University, The First People's Hospital of Kunshan, Suzhou, China; [b]Department of Anesthesiology, Kunshan Hospital Affiliated to Jiangsu University & Kunshan Cancer Pain Prevention and Treatment Key Laboratory, Suzhou, China

ABSTRACT

Cellular mechanotransduction refers to the process through which cells perceive mechanical stimuli and subsequently translate them into biochemical signals. Key mechanosensitive ion channels encompass PIEZO, TREK-1, and TRESK. These mechanosensitive ion channels are crucial in regulating specific pathophysiological conditions, including fibrosis, tumor progression, and cellular proliferation and differentiation. Recent research indicates that PIEZO, TREK-1, and TRESK are significant contributors to various types of cancer pain by sensing mechanical stimuli, which subsequently activate internal signaling pathways. Here concentrates on advancements in research concerning PIEZO, TREK-1, and TRESK in cancer pain research, aiming to lay the groundwork for creating new therapeutic drugs that address mechanosensitive ion channels for treating cancer pain.

ARTICLE HISTORY
Received 26 April 2025
Revised 29 May 2025
Accepted 2 June 2025

KEYWORDS
PIEZO; TREK-1; TRESK; cancer pain; mechanosensitive ion channels

Introduction

Mechanotransduction refers to the biological process through which an organism perceives mechanical stimuli and converts them into chemical signals. This process plays a crucial role in modulating the organism's physiological and pathological states [1]. Mechanosensitive ion channels, including PIEZO, TREK-1, and TRESK, have been found to respond to various mechanical stimuli, such as tensile force and fluid shear stress [2–5]. Their role is notably significant in the realm of cancer pain research. Ni et al demonstrated a positive correlation between PIEZO expression levels and mechanical nociceptive sensitivity in a rat model of bone cancer pain [6]. Similarly, Delanne-Cuménal et al identified the downregulation of TREK-1 as a critical factor contributing to bone cancer pain [7]. Additionally, TRPV4, a member of the transient receptor potential (TRP) family, has been implicated in the development of bone cancer pain through the activation of downstream inflammatory pathways, including interleukin-17A [8]. These findings indicate that mechanosensitive ion channels play a role in the development of cancer pain; however, a comprehensive overview of the relationship between these sensors and cancer pain is currently absent. Therefore, this review seeks to systematically clarify the mechanisms of action of three mechanosensitive ion channels – PIEZO, TREK-1, and TRESK – in the context of cancer pain. Additionally, it aims to establish a scientific foundation for the development of pharmacological agents targeting mechanotransduction sensors.

Cancer pain

Cancer pain is divided into two categories: cancer-related pain and treatment-related pain. Cancer-related pain can be further categorized into neuropathic cancer pain (NCP), cancer-induced bone pain (CIBP), and visceral cancer pain, with these types involving both inflammatory and neuropathic mechanisms. Visceral cancer pain is a chronic pain condition resulting from primary or metastatic tumors invading visceral organs, characterized by vague localization. Currently, research on visceral cancer pain in animal models is limited, highlighting

CONTACT Lihua Hang 18013273169@163.com
Supplemental data for this article can be accessed online at https://doi.org/10.1080/19336950.2025.2517109

it as a significant area for future investigation. Additionally, treatment-related pain results from tissue or nerve damage caused by cancer therapies, including surgery, chemotherapy, and radiotherapy [9].

The transmission mechanism of cancer pain involves a complex, multilevel interaction among neurons. This process mainly involves the sequential activation and synergistic interaction of tertiary neurons. Specifically, Injury sensors located at the terminus of sensory neurons play a crucial role in converting harmful stimuli into electrical signals, known as nerve impulses. These impulses are first transmitted from primary sensory neurons to secondary neurons in the dorsal horn of the spinal cord. Here, they are initially processed through complex neural circuits. Following this, pain signals travel along specific neural pathways, such as the thalamic tract, reaching tertiary neurons in the thalamus and brainstem. Ultimately, these signals are integrated across various functional areas of the cerebral cortex, culminating in the perception of pain. The conduction process is also notably influenced by a downstream neural pathway, which significantly affects the final experience of pain perception [10].

In recent years, extensive research has focused on the molecular mechanisms that contribute to cancer pain. These studies have increasingly highlighted the significance of mechanical signaling in the transmission of cancer pain. Mechanosensitive ion channels within the tumor microenvironment, such as PIEZO, TREK-1, and TRESK, may be activated by persistent mechanical stimuli. These stimuli can arise from the compression of adjacent tissues, the dilation of visceral organs, or fibrotic tugging associated with tumor progression or treatment interventions. Such mechanosensitive ion channels play a critical role in the initiation and progression of cancer-related pain.

PIEZO

PIEZO biological characteristics

In 2010, Coste et al identified a Ca^{2+}-permeable nonselective cation channel, characterized by the permeability sequence $Ca^{2+} > Na^{+} \approx K^{+} > Mg^{2+}$ [11,12]. This channel has been named PIEZO, derived from the Greek term "pi' esi," meaning pressure. The PIEZO family consists of two members, PIEZO1 and PIEZO2, which are highly conserved across species [12].

PIEZO functions as a mechanosensitive ion channel, responding to mechanical stimuli. These stimuli include shear stress, tensile force, hydrostatic pressure, and the stiffness of the extracellular matrix [2]. Its mechanosensitivity is significantly influenced by the integrity of the cytoskeletal network. Actin and myosin II, as fundamental components of the cytoskeleton, modulate the mechanosensitivity of Piezo channels through direct mechanical coupling or indirect signaling pathways [13,14].

In addition to the cytoskeleton's regulatory network, the presence of the lipid microenvironment (e.g. PI (4,5) P_2, cholesterol) plays a critical role [15,16]. Subsequent studies have demonstrated that lipid metabolism exerts bidirectional regulation on PIEZO mechanosensitivity. Specifically, saturated fatty acids, such as C17:0, raise the threshold for mechanical activation by enhancing membrane stiffness. Conversely, polyunsaturated fatty acids, like DHA (C22:6), promote channel activation by reducing membrane structural order and facilitating channel opening [17]. This differential regulation indicates that cells can dynamically control PIEZO mechanosensitivity by precisely modulating membrane lipid composition.

Upon completing mechanosensing, activated PIEZO regulates specific physiopathological activities by initiating the ATP and calpain signaling pathway [18]. PIEZO1 is predominantly expressed in non-sensory tissues, including the lungs, bladder, and skin. It critically regulates vascular tone, embryonic development, inflammation, and tumorigenesis via the aforementioned signaling pathways [12,19]. In contrast, PIEZO2 is selectively distributed in sensory systems such as the dorsal root ganglion (DRG), trigeminal ganglion (TG), and Merkel cells within the skin, where it dominates processes related to tactile and mechanical nociception [20]. Recent studies have shown that the modulation of sensory modalities is closely linked to the membrane transport of PIEZO2 neurons,

which is aided by the intracellular protein EndoA2 [21].

Activators of PIEZO

Among small-molecule activators, Yoda1 is notable for its ability to partially activate PIEZO1 independent of external forces. Additionally, it considerably enhances the mechanosensitivity of PIEZO1 when exposed to mechanical stimuli, resulting in a reduction of the half-maximal activation pressure (P50) by approximately 15 mmHg. Furthermore, Yoda1 slows the inactivation phase of the transient currents and stabilizes the open state of the channel, thereby promoting Ca^{2+} inward [22]. Jedi1/2 functions as an activator of PIEZO1 and remarkably increases its activity in conjunction with Yoda1. However, there exists a spatial distinction between their respective target sites: Yoda1 interacts with the "beam" structural domain in a downstream position, whereas Jedi1/2 exerts its effect on the upstream lobes to modulate PIEZO1 activity [23]. In the investigation of novel activators, cell culture water-soluble extract (ObHEx) was shown to activate PIEZO1 through a myosin light chain kinase (MYLK) dependent pathway. This finding implies that cellular metabolites may play a role in regulating endogenous mechanosensitivity [24]. Conversely, there has been no identification of a specific chemical activator for PIEZO2.

Inhibitors of PIEZO

In studies of the inhibitory regulation of PIEZO channels, various small chemical molecules and endogenous proteins have demonstrated specific or broad-spectrum inhibitory effects. The compounds Dooku1, a structural analog of Yoda1, and tubeimoside I serve as competitive antagonists against PIEZO1, effectively blocking Yoda1-mediated channel activation. In contrast, OB-1 and OB-2 diminish the mechanosensitivity of PIEZO1 [25–27]. Additionally, selective inhibition of PIEZO2 is observed with the styryl dye FM1–43, the transmembrane protein TMEM120A, and phospholipase D (PLD) [28,29]. Broad-spectrum inhibitors, including the spider toxin GsMTx4, ruthenium red, streptavidin, and gadolinium ions (Gd^{3+}), non-selectively inhibit PIEZO isoforms [30]. Notably, GsMTx4 disrupts mechanosensitive current conductance by reducing membrane tension through the relaxation of the lipid outer monolayer [31,32].

In the endogenous regulatory system, PIEZO1 activity is selectively inhibited by sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase and Polycystin-2, while PIEZO2 function is specifically inhibited by Mtmr2 and Pericentrin [33–36]. Furthermore, the transcriptional regulator MDFIC/MDFI exerts cross-subtype activity repression by directly binding to PIEZO channels, illustrating the intricate nature of the endogenous regulatory network [37]. These findings provide a molecular foundation for precision therapy aimed at targeting mechanistic signaling.

The role of PIEZO in cancer pain

The dysregulated expression of PIEZO in tumors is closely correlated with the progression of cancer [38]. Tumor metastasis leads to inflammatory responses and nerve compression, which are primary contributors to cancer pain. Recent studies indicate that the activation of PIEZO correlates with the upregulation of analgesic factors, including TNF-α, IL-6, IL-1β, and bradykinin. Additionally, PIEZO substantially influences the development of inflammatory and neuropathic pain, which are fundamental components of cancer-related pain [39–43]. Its expression in sensory neurons such as DRG and TG suggests its significant role in pain-signaling perception and transduction. Therefore, PIEZO may be implicated in the pathophysiology of cancer pain, potentially influencing both its onset and severity. This mechanism may be linked to alterations in PIEZO expression as well as its regulatory effects on inflammation and neural signaling pathways.

CIBP is a prevalent form of cancer pain, primarily stemming from the metastasis of cancer cells to bone tissue. This metastasis disrupts the homeostatic balance of the skeleton, leading to alterations in the bone microenvironment. During this process, RANKL, released by cancer cells and osteoblasts (OB), interacts with RANK on osteoclasts (OC). This interaction activates the OC, leading to the release of significant amounts of H^+, which in turn triggers osteolytic bone destruction and the associated pain [44]. In addition, bradykinin in the bone microenvironment sensitizes PIEZO channels in neurons,

representing a critical mechanism underlying CIBP [41]. More importantly, as the tumor grows, bone destruction can lead to fractures and inflammatory edema, which increases pressure within the bone microenvironment [45]. This increase can activate PIEZO, a mechanosensitive ion channels located on the periosteal surface of sensory neurons, thereby exacerbating CIBP.

In recent years, epigenetic regulatory mechanisms have offered new insights into the study of CIBP. Investigations have revealed that m6A methylation displays tissue specificity in breast cancer cell-induced CIBP. Specifically, reduced m6A methylation in the spinal cord is implicated in the promotion of pain, while increased m6A methylation levels in the DRG actively drive nociceptive signaling [46,47]. This tissue-specific modulation may involve the targeting of key nociception-related molecules. Further research has shown that the expression of PIEZO is regulated by m6A methylation, suggesting that m6A may function as an upstream regulator that integrates distinct pain signaling pathways between the spinal cord and the DRG via modulating PIEZO expression. This underscores the potential epigenetic basis of CIBP [48,49].

The role of PIEZO1 in cancer pain

In investigating the regulatory mechanisms of CIBP, it was observed that the activity of PIEZO1 in OB, neurons, and macrophages exerts a significant influence on the pathogenesis of CIBP. Wang et al observed that the deletion of PIEZO1 in OB led to a reduction in bone mass, an increase in bone resorption, and a heightened presence of OC on the surface of bone trabeculae in mice (Table 1). Interestingly, the absence of PIEZO1 in OC did not significantly impact bone metabolism [50]. Given that elevated OC activity, identified as a crucial initiator of CIBP, these findings imply that PIEZO1 in OB may regulate bone resorption and CIBP through its influence on OC function [51]. Additionally, subsequent investigations demonstrated that the simultaneous deletion of PIEZO1 and PIEZO2 in OB exacerbated bone resorption [52]. In summary, PIEZO1 and PIEZO2 in OB may collaboratively influence CIBP by modulating bone metabolic processes.

In contrast to the bone homeostatic regulation of PIEZO1 in OB, PIEZO1 in neurons and macrophages promotes nociceptive hypersensitivity via an inflammatory signaling cascade. In a model of cancer-induced CIBP resulting from breast cancer cells, the activation of neuronal PIEZO1 may mediate Ca^{2+} influx and subsequently initiate the STING/TBK1/NF-κB signaling pathway through the release of mitochondrial DNA (Figure 1). This process promotes the expression of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, which drive neuroinflammatory responses and ultimately trigger CIBP [53,54]

Table 1. Effects of mechanosensitive ion channels on cancer pain.

Cellular mechanosensitive ion channels	Types of cancer pain	Cell types	Potential mechanisms of action	Reference
PIEZO1	CIBP	Osteoblast	PIEZO1 deletion→bone resorption→CIBP	[50]
		Sensory neuron	PIEZO1→Ca^{2+}influx→Release of mitochondrial DNA→STING→TBK1→CIBP	[53,54]
			PDGF→PIEZO1→Ca^{2+}influx→AKT→ERK→CIBP	[59–61,64]
			VEGF→PKC→PIEZO1→Ca^{2+}influx→CaMKII→CIBP	[18,62,64]
			PIEZO1→BMP2→BMPR→Samd1→CGRP→CIBP	[58,63]
		Macrophage	LPS→TLR4→PIEZO1→Ca^{2+}influx→CaMKII-Mst1/2-Rac axi→Inflammatory reaction→CIBP	[55–57]
PIEZO2	CIBP	Sensory neuron	NGF→PIEZO2→CIBP	[66,67]
			GPCRS→CAMP→Epac1→NR2B→Ca^{2+}influx→ERK/CaMK→PIEZO2→CIBP	[6]
	NCP	Sensory neuron	PIEZO2 MA↑→NCP	[70]
TREK-1	CIBP		TREK-1↓→CIBP	[7]
	NCP	Sensory neuron	TREK-1/TRAAK/TRESK↓→NCP	[109,110]
TRESK	CIBP	Sensory neuron	VEGF→VEGFR→↓Calcineurin→↓NFAT→↓TRSK→CIBP	[117,142]
	NCP	Sensory neuron	HDAC1→↓H3K9/K14→TRESK↓→NCP	[145]

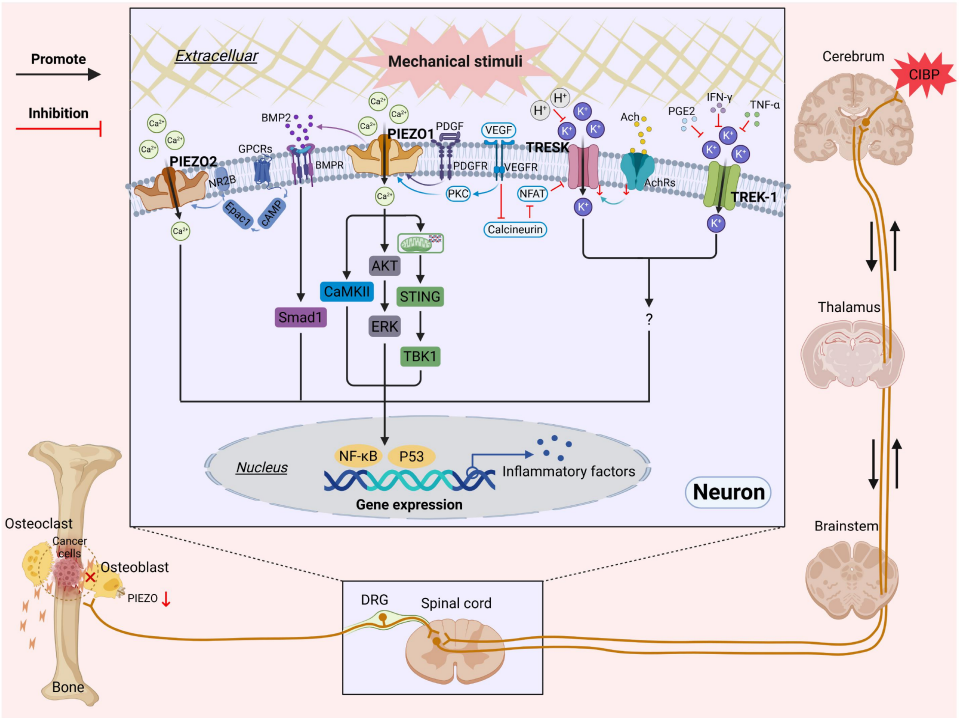

Figure 1. Possible mechanisms of mechanosensitive ion channels in DRG and spinal cord neurons contributing to CIBP. These channels transduce mechanical and biochemical signals from the ECM, activating signaling pathways that regulate transcription factors (e.g. NF-κB and P53), and thereby modulate inflammatory mediator expression and CIBP pathogenesis. Calcium channels (PIEZO1/2): upon mechanical stimulation, activation of PIEZO1/2 facilitates calcium influx and subsequently activates downstream signaling pathways, such as the CaMKII, AKT/ERK, and STING/TBK1, etc. Notably, selective deletion of PIEZO channels in osteoblasts exacerbates bone destruction and CIBP progression. Potassium channels (TREK-1/TRESK): regulated by mechanical and biochemical signals from the ECM, these channels induce neuronal hyperexcitability, leading to nociceptive sensitization and CIBP development. ECM extracellular matrix, platelet-derived growth factor PDGF, vascular endothelial growth factor VEGF, and bone morphogenetic protein 2 BMP2, N-methyl-D-aspartic acid (NMDA) receptor subunit 2B NR2B, exchange protein directly activated by cAMP 1 Epac1.

(Table 1).In macrophages, the LPS-TLR4 signaling axis induces a substantial influx of Ca^{2+} by activating PIEZO1. This activation further stimulates the CaMKII-Mst1/2-Rac pathway, contributing to the release of substantial amounts of inflammatory mediators [55,56]. Moreover, microglia, as specialized macrophages in the central nervous system, further exacerbate in breast cancer-associated CIBP upon TLR4 activation [57] (Table 1). These findings indicate that macrophages may initiate an inflammatory response contributing to CIBP by activating PIEZO1.

The aforementioned cell-specific investigations indicate that, at the cellular level, PIEZO1 plays a role in the genesis of CIBP through a dual pathway, which regulates bone metabolic homeostasis (OB) and neuroinflammatory responses (neurons/macrophages). At the molecular level, PIEZO1 not only affects the CIBP process by regulating multiple pain mediators but also elucidates its pathological mechanisms through interactions with growth factors such as Platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and bone morphogenetic protein 2 (BMP2) [58–64]. PIEZO1 exhibits bidirectional regulatory properties in growth factor-mediated CIBP. It acts both as a direct effector activated downstream of growth factor receptors and as an enhancer of the nociceptive pathway via mechanochemical signaling. This bimodal role positions PIEZO1 as a crucial integrative node within the CIBP mechanistic framework.

PDGF serves as a prominent example of this regulatory mechanism by activating PIEZO1, which subsequently induces Ca^{2+} endocytosis and activates the calcium-dependent AKT-ERK signaling pathway. Importantly, the activation of PIEZO1 not only participates in downstream signaling but also contributes to mechanical nociceptive sensitization by lowering the thresholds of

neuronal action potentials [59,60] (Table 1). Given that PDGF has been implicated in the mediation of CIBP via the AKT-ERK pathway, it is hypothesized that PDGF may work synergistically to promote the development of CIBP through the PIEZO1-Ca^{2+} -AKT/ERK cascade (Figure 1). However, further experiments are required to confirm these molecular interactions [61].

In contrast to the direct channel activation properties of PDGF, the VEGF pathway enhances its functional dimension in CIBP by altering the mechanosensitive domain of PIEZO1.VEGF-A/VEGFR2 signaling facilitates the inward flow of Ca^{2+} by activating protein kinase C (PKC), which subsequently initiates cancer pain transmission dependent on Ca^{2+} and CaMKII [64]. Central to this pathway may be the mechanosensitive ion channels PIEZO1 (Figure 1). Specifically, PKC phosphorylates the S1612 site of PIEZO1, thereby enhancing its mechanosensitivity [62]. Additionally, the Ca^{2+} influx resulting from PIEZO1 activation can create a positive feedback loop that perpetuates CaMKII activation [18]. Collectively, these findings indicate that PIEZO1 May have a role in CIBP via the VEGF-PKC-PIEZO1-Ca^{2+} -CaMKII signaling axis (Table 1).

In addition to its direct activation by growth factors, PIEZO1 May also influence these factors indirectly by sensing mechanical stress within the tumor microenvironment. Activation of PIEZO1 by mechanical stress leads to an upregulation of BMP2 expression [63]. As a member of the TGF-β superfamily, BMP2 directly mediates nociceptive signaling by stimulating the release of calcitonin gene-related peptide (CGRP) from sensory neurons via the BMPR/Smad1 pathway [58] (Table 1) (Figure 1).

In conclusion, PIEZO1 is involved in regulating the pathological process of CIBP through a multifaceted mechanism. At the cellular level, PIEZO1 disrupts bone metabolic homeostasis by affecting OB and mediates neuroinflammatory responses involving neurons and macrophages. At the molecular level, PIEZO1 establishes a functional network with various growth factors. Specifically, PDGF directly activates PIEZO1 through the Ca^{2+} -AKT/ERK pathway, while VEGF enhances PIEZO1's mechanosensitivity by phosphorylating the S1612 site via the Ca^{2+} -CaMKII pathway. Furthermore, mechanical stress stimulates PIEZO1, leading to the upregulation of BMP2 and subsequent release of CGRP. This "mechano-chemical signaling hub" ultimately facilitates the amplification of the cancer pain signaling cascade.

The role of PIEZO2 in cancer pain

Research has demonstrated that the expression of PIEZO2 in skeletal tissues is predominantly localized within Aδ sensory nerve fibers, which likely detect pressure alterations within the skeleton, consequently initiating bone pain [65]. Nencini et al. observed that the intrathecal administration of PIEZO2 antisense oligonucleotide diminished the responsiveness of Aδ bone afferent neurons to pressures in the bone marrow cavity. Moreover, the down-regulation of PIEZO2 expression in DRG nearly abolished the nerve growth factor (NGF)-induced enhancement of mechanosensitivity in bone afferent neurons [66]. Additionally, studies by Jing et al. have shown that anti-NGF antibodies significantly mitigate bone pain associated with CIBP and reduce bone destruction [67]. Collectively, these findings underscore the essential function of PIEZO2 in sensory neurons in the pathogenesis of NGF-induced CIBP (Table 1).

In another model of CIBP, established through the injection of osteosarcoma NCTC 2472 cells into the femoral marrow cavity, the researchers demonstrated that intrathecal administration of antisense oligonucleotides targeting cyclic adenosine monophosphate-binding protein 1 (Epac1-ASODN) alongside the NR2B antagonist ifenprodil effectively alleviated mechanical pain in CIBP mice while simultaneously decreasing PIEZO2 expression in the DRG. In contrast, administration of the Epac1 agonist 8-pCPT via plantar injection and intrathecal injection of the NR2B agonist N-methyl-D-aspartic acid (NMDA) exacerbated mechanical pain and increased PIEZO2 levels in the DRG. Notably, while ifenprodil successfully attenuated pain and the upregulation of PIEZO2 induced by 8-pCPT, Epac1-ASODN did not reverse NMDA's effects. These findings suggest that PIEZO2 may play a critical role in CIBP through the Epac1-NR2B-PIEZO2 signaling pathway [6] (Table 1).

Based on the aforementioned experimental results, the researchers formulate a hypothesis underlying the mechanism of action. Specifically, they proposed that the activation of G protein-coupled receptors (GPCRs) in DRG neurons occurs through mechanical stimulation. This activation facilitates the conversion of ATP to cAMP, which subsequently activates Epac1. Activated Epac1 regulates the NR2B-containing NMDA receptor; The activation of this receptor enhances Ca^{2+} influx, further stimulating ERK and CaMK (Figure 1). This ultimately promotes the expression of PIEZO2 mRNA and its phosphorylation, resulting in heightened neuronal excitability and peripheral nociceptive sensitization [6] (Figure 1). Furthermore, the upregulation of PIEZO2 expression is significantly correlated with increased levels of m6A methylation. This relationship may involve a dual mechanism: Firstly, the m6A-dependent regulatory mechanism may enhance the stability or translational efficiency of PIEZO2 mRNA through the action of reading proteins, such as YTHDF1, which directly promotes its protein expression and facilitates the amplification of cancer pain signals [48]. Secondly, in the CIBP model, elevated m6A modifications within the DRG can upregulate NR2B expression, an upstream regulator of PIEZO2, by inhibiting the demethylase ALKBH5. This mechanism subsequently leads to the transcriptional activation and functional phosphorylation of PIEZO2, thereby intensifying peripheral nociceptive sensitization [46].

In addition to modulating neuronal excitability, PIEZO2 influences the bone microenvironment via transcellular interactions. Recent research demonstrated that the activation of PIEZO2 in sensory neurons enhances OC production via the neural-immune-OC axis [68]. Specifically, PIEZO2 activation elicits the release of neuropeptides, such as calcitonin gene-related peptide (CGRP) and substance P (SP), This neuropeptide release serves to amplify the inflammatory response, recruits immune cells, and promotes the differentiation and activation of OC. Given that increased OC activity is a key contributor to CIBP, PIEZO2 may heighten OC activity through this signaling pathway, consequently exacerbating bone destruction and contributing to the progression of CIBP [68].

In summary, PIEZO2 serves a dual function in CIBP. It enhances neuronal sensitization via the Epac1-NR2B-m6A axis while simultaneously promoting bone destruction through the neural-immune-bone axis. These two mechanisms work together to exacerbate the pain process.

NCP constitutes a distinctive category of cancer pain primarily resulting from nerve damage associated with cancer itself and chemotherapy-induced peripheral neuropathy [69]. Vincristine (VCR), a commonly utilized chemotherapeutic agent, has shown considerable efficacy against various malignant tumors; however, its clinical application is frequently associated with the onset of NCP. Duan et al. demonstrated in the VCR-induced NCP model that microinjections of PIEZO2 small short hairpin RNA (shRNA) into the DRG, subcutaneous injections of Gd3+, and the PIEZO2 mechanically-activated (MA) current inhibitor cytochalasin D (CD) resulted in an increased nociceptive threshold in NCP rats (Table 1) [70]. While VCR treatment reduced the expression level of PIEZO2 in the DRG, it concurrently enhanced the PIEZO2 MA current in DRG neurons, an effect that was inhibited by both PIEZO2 shRNA and CD. The findings indicate that VCR-induced PIEZO2-dependent NCP is not directly linked to PIEZO2 expression levels; rather, it primarily results from the augmentation of PIEZO2 MA currents. Importantly, the VCR group demonstrated notable behavioral differences compared to the PIEZO2 shRNA- and Gd^{3+}-treated groups. This discrepancy may arise from the enhancement of PIEZO2 MA currents induced by VCR, which could obscure the reduction of MA currents associated with decreased PIEZO2 expression [70].

The results of the aforementioned study indicate that the mechanosensitive ion channel PIEZO2 is a pivotal mediator in the pathogenesis of cancer-associated pain, particularly in CIBP and NCP. In sensory neurons, the onset of NCP is linked to increased PIEZO2-mediated currents, which are not directly associated with a decrease in PIEZO2 expression. This contrasts with the critical role of PIEZO2 expression in CIBP, inflammatory pain, and neuropathic pain models. Specifically, in CIBP, PIEZO2 is integral to the Epac1-NR2B-Piezo2 signaling axis. Conversely, in

models of inflammatory and neuropathic pain, the expression of PIEZO2 is upregulated by inflammatory factors such as IL-1β and IL-6, which contribute to pain perception [6,39,40]. These findings highlight the distinct role of PIEZO2 channels in various pain conditions and offer new insights for the treatment of cancer-related pain. Collectively, these findings underscore the distinct roles of PIEZO2 channels across various pain states and offer new insights into the management of cancer-related pain.

TREK-1

TREK-1 biological characteristics

The K2P channel family, also known as two-pore domain potassium channels, represents the newest class of potassium channels by the scientific community in the past two decades [71]. This family can be classified into six subfamilies – TWIK, TREK, TASK, TALK, THIK, and TRESK – comprising a total of 15 distinct members [72]. Among these, TREK-1 is the most extensively studied, having been initially identified in mouse brain tissue [71,73]. This channel comprises two pore structural domains (PD1 and PD2), each featuring two transmembrane helices (TM1-M2 and TM3-M4) interconnected by pore helices (P1 and P2) and selective filters (SF1 and SF2). The distinctive two-pore architecture underlies its ability to generate background currents. Furthermore, TREK-1 possesses intracellular N-terminal and C-terminal regulatory domains, which are crucial for modulating channel activity and signaling [74].

TREK-1 channel activation is modulated by a diverse array of stimuli, including mechanical forces, temperature (32–37°C), intracellular acidification, and specific membrane lipids, such as low concentrations of phosphatidylinositol [71,75]. Mechanosensitivity is its primary function, facilitating the transduction of mechanical forces through lipid bilayers. This activation can occur in response to cellular stretch, hypotonic swelling, and laminar shear stress, a process that is contingent upon the C-terminal Val298-Thr322 amino acid sequence [3,5]. In addition to direct mechanical activation, the activity of TREK-1 is dynamically regulated by mechanosensitive cytoskeletal proteins. In addition to direct mechanical activation, the activity of TREK-1 is dynamically regulated by mechanosensitive cytoskeletal proteins. The scaffolding protein AKAP150 binds to the cytoplasmic C-terminal sites 298–311, directly activating the channel. Meanwhile, the microtubule-associated protein Mtap2 enhances membrane expression and current by binding to sites 335–360. Both proteins exhibit synergistic effects in modulating TREK-1 activity [76]. Conversely, actin and microtubule proteins may inhibit TREK-1 mechanosensitivity by restricting membrane deformation [71,77]. This suggests that the cytoskeletal network plays a crucial role in maintaining the dynamic balance of TREK-1 function through a bidirectional mechanism of "activation-inhibition."

TREK-1 demonstrates a widespread presence in the central nervous system, including the basal ganglia, cerebral cortex, and dorsal root ganglia, as well as in peripheral organs such as the heart and kidneys [71]. This extensive distribution underpins its multifunctional roles. TREK-1 is critically involved in nociception, neuroprotection, and epileptogenesis through its modulation of neuronal excitability. Furthermore, it mediates the biological effects of volatile anesthetics and is implicated in inflammatory responses by affecting immune cell function and the secretion of inflammatory mediators [71]. Moreover, TREK-1 is involved in inflammatory responses by influencing immune cell function and the secretion of inflammatory factors [78,79].

Activators of TREK-1

The activation mechanism of TREK-1 channels is marked by notable ligand diversity. For instance, volatile anesthetics, such as chloroform, halothane, isoflurane, chloromethane, and ether, activate TREK-1 through specific interactions with the channel's C-terminal structural domain [80]. In contrast, nonvolatile anesthetics, including nitrous oxide, xenon, and cyclopropane, do not depend on C-terminal binding at clinically effective concentrations; however, they enhance channel activity by interacting with the residue Glu306 [81].

Notably, a range of clinical therapeutic agents have been shown to regulate TREK-1. For

instance, riluzole, an approved treatment for amyotrophic lateral sclerosis, exerts a bidirectional regulatory impact on TREK-1 by increasing cAMP levels. This increase initially results in the transient activation of the channel, which is then followed by negative feedback inhibition as cAMP accumulates [82,83]. Additionally, opioids, non-steroidal anti-inflammatory drugs such as flufenamic acid, mefenamic acid, and niflumic acid, along with cardiac stabilizers including lithium chloride, gabapentin, valproic acid, and carbamazepine, have been shown to directly activate TREK-1, with lithium chloride and carbamazepine also upregulating its expression [5,84].

In the realm of synthetic compounds, BL-1249, PD-118057, and DCPIB, which possess negatively charged groups, alongside ML analogs (ML335 and ML402), interact with the SF region to facilitate the opening of channel gates [84,85]. Recent discoveries of novel TREK-1 activators, specifically E1, B3, and A2, potentially operate through a comparable mechanism [86]. Notably, caffeic acid derivatives have demonstrated significant analgesic effects by enhancing TREK-1 activity, thereby indicating a promising direction for the development of new analgesic agents [5].

The activation mechanism of TREK-1 is not confined to the binding of chemical ligands; it also encompasses the regulation of physical-mechanical forces. Cytoskeletal modulators, including colchicine, latrunculin A, and cytochalasin D, activate TREK-1 channels by inhibiting the polymerization of microtubules and actin. This inhibition induces localized deformation of the cell membrane, thereby disrupting the inhibitory effects on the TREK-1 C-terminus [71].

Inhibitors of TREK-1

Numerous studies have elucidated that diverse clinical agents inhibit TREK-1 through distinct mechanisms. For instance, the antidepressants fluoxetine (IC50 = 19 μM) and desmethyl fluoxetine (IC50 = 9 μM) interfere with TREK-1 by binding to the E306 site located at the C-terminus [87]. Similarly, SID1900 and Spadin, along with their derivatives, demonstrate comparable inhibitory effects [88,89]. Furthermore, newly identified 2-hydroxy-3-phenoxypropylpiperidine derivatives, which also exhibit antidepressant activity, have emerged as potent TREK-1 inhibitors, showing IC50 values ranging from 17 to 45 nM [90].

Antipsychotic medications, including phenothiazines (e.g. chlorpromazine) and butyrophenazines (e.g. haloperidol), directly dose-dependently inhibit TREK-1 currents with an IC50 ranging from 1 to 20 μM, and do not utilize the phosphorylation pathway for their action [91]. Rather, local anesthetics such as lidocaine and bupivacaine indirectly modulate TREK-1 activity by inhibiting phospholipase D2 [92].

Calcium channel blockers, such as amlodipine and nicardipine, have been shown to decrease the opening rate of TREK-1 channels by influencing their gating mechanisms. In contrast, class I antiarrhythmics, including mexiletine, propafenone, and quinidine, inhibit TREK-1 activity; however, the precise mechanisms underlying this inhibition remain inadequately understood [3,93,94]. In the domain of natural medicines, the Japanese formulation KKT, comprised of 14 components, induces neuronal activation through the inhibition of TREK-1 channels. Notably, six of these ingredients, such as Poria and Longan meat, have demonstrated individual inhibitory activity. This suggests that the overall efficacy of KKT may result from the synergistic interactions among its ingredients [95].

The role of TREK-1 in cancer pain

TREK-1 is extensively expressed in pain-associated sensory neurons, including those found in the DRG and thalamus. It colocalizes with C-fibers and injury-related receptors, such as TRPV1. By inducing hyperpolarization of the membrane potential, TREK-1 effectively inhibits neuronal excitability, thereby exerting analgesic effects [71,96]. Knockout studies have demonstrated that the absence of TREK-1 results in hypersensitivity to mechanical and thermal stimuli, underscoring its essential role in the modulation of nociceptive processes [96].

In the cancer microenvironment, the activity of TREK-1 may be modulated by various mediators, with implications for the pathogenesis of cancer-related pain. For instance, inflammatory factors such as PGE2, IFN-γ, TNF-α, and bradykinin can

enhance neuronal excitability through the inhibition of TREK-1 (Figure 1). Additionally, acidic pH and lysophosphatidic acid may also impede TREK-1 channel activity [96–99]. Moreover, TREK-1 dysfunction may exacerbate pain by facilitating the release of CGRP [100]. These regulatory mechanisms are relevant not only in basal nociceptive pathways but may also be significant leading to the context of cancer pain.

In cancer, TREK-1 expression is intricately linked to the manifestation of cancer-related pain. Notably, its expression exhibits distinct patterns across various cancer types. For instance, low levels of TREK-1 in esophageal squamous, pancreatic, and thyroid cancers are associated with enhanced tumor progression [101–103]. Conversely, elevated TREK-1 expression in breast cancer facilitates invasion and bone metastasis, with its activity positively correlating with integrin αv/β3. This correlation implies that mechanical stress could modulate pain signaling via the integrin-TREK-1 axis [104]. It is hypothesized that various mechanisms, including nerve compression, the release of inflammatory factors, and the occurrence of bone metastasis during cancer progression, may contribute to nociceptive sensitization through the TREK-1 pathway. Consequently, TREK-1 presents a promising therapeutic target for cancer-related pain; however, its specific regulatory mechanisms in this context warrant further investigation.

To elucidate the effect of TREK-1 in cancer-related pain, researchers established a CIBP model by injecting PC3 prostate cancer cells into the tibia of immunodeficient mice. The study documented the onset of spontaneous pain on day 14 and mechanical nociceptive hypersensitivity on day 21. Administration of riluzole, a TREK-1 activator, resulted in substantial pain relief; however, this effect was diminished by spadin, indicating that pain relief is dependent on the TREK-1 signaling pathway [7] (Table 1). Furthermore, a separate study indicates that Piezo1 may facilitate the nociceptive sensitization previously described by increasing the mechanosensitivity of TREK-1, a process that appears to be influenced by cholesterol-dependent membrane tension [105]. Riluzole has been shown to exhibit comparable analgesic effects in both inflammatory and neuropathic pain; however, the underlying mechanism remains unclear [106,107]. Given the crucial role of bone destruction in the progression of CIBP, researchers have posited that riluzole might mitigate CIBP by activating TREK-1 to inhibit bone destruction. Nonetheless, computed tomography (CT) and bone scintigraphy findings indicate that riluzole does not significantly impact cancer cell-induced bone destruction and remodeling [7]. Further studies revealed that riluzole treatment decreased the resting membrane potential of PC3 cells from −30 mV to −47.7 mV while inhibiting cellular proliferation. This indicates that the reduction of cellular resting membrane potential induced by TREK-1 is a critical mechanism via which riluzole exerts its antiproliferative effects. In conclusion, TREK-1 mediates the dual analgesic and antiproliferative effects of riluzole in mice with CIBP [7]. Unlike the traditional analgesic morphine, riluzole does not exacerbate bone destruction and elicits a synergistic effect on analgesia and anti-tumor proliferation through the activation of TREK-1. This positions riluzole as a highly promising analgesic for CIBP [7,108]. Additionally, the mechanical signal regulation of TREK-1 by PIEZO1 offers a theoretical framework for understanding the regulation of multiple mechanosensitive ion channels in CIBP.

Research has demonstrated that oxaliplatin downregulates the expression of TREK-1, TRAAK, and TRESK in mouse DRG neurons through epigenetic mechanisms (Table 1). Specifically, the neural restriction silencing factor binds to regulatory sequences of K2P genes and recruits histone deacetylases, resulting in chromatin condensation and subsequent gene silencing [109]. The coordinated down-regulation of these three mechanosensitive ion channels implies a potential integrative regulation of the mechanical signal network within the nociceptive pathways.

In alignment with previous research, oxaliplatin administration reduced TREK-1/TRAAK expression, which in turn led to mechanical nociceptive hypersensitivity and cold sensitization. However, this effect was not observed in TREK-1-TRAAK double-knockout mice, indicating that these channels may synergistically modulate NCP [110] (Table 1). Furthermore, the regulation of TREK-1 exhibits spatiotemporal dependence; during the early stages, compensatory upregulation of TREK-1 expression through cytoplasmic

acidification mitigates neuronal damage, while in later stages, it exacerbates NCP through functional inhibition [111].

In the C57Bl/6JRj mouse model, oxaliplatin-induced mechanical pain, cold nociception, and nerve damage – characterized by decreased conduction velocity and mitochondrial degradation – could be reversed by riluzole. The efficacy of riluzole was found to depend on the activation of TREK-1, as evidenced by the ineffectiveness of treatments in TREK1-/- mice or spadin-treated mice, while TRAAK-/- mice still responded positively to riluzole [108]. Moreover, the broad inhibition of multiple potassium channels – including TREK-1, TRAAK, and TRESK – by oxaliplatin indicates that TREK-1 activation might synergistically collaborate with other potassium channels to restore neuronal excitatory and, ultimately, mitigate NCP [108,109].

TREK-1 modulates cancer pain via its dual function by regulating the excitatory balance in neurons. Its functional inhibition, instigated by inflammatory mediators, acidic microenvironments, and silencing effects from oxaliplatin, exacerbates nociceptive sensitization and promotes tumor progression. Conversely, activating TREK-1, for instance, through riluzole, alleviates pain and inhibits cancer cell proliferation by reducing glutamatergic toxicity and maintaining a hyperpolarized membrane potential. As a K^+ channel operating downstream of the mu-opioid receptor, TREK-1 contributes to morphine-induced analgesia with fewer side effects [112]. Recent studies have identified the novel activator C3001a, which targets the P1-TM4 structural domain, demonstrating significant analgesic efficacy in both inflammatory and neuropathic pain without the adverse effects typical of opioids [113]. These findings highlight the potential of TREK-1 in cancer pain management and provide a crucial pathway for the development of next-generation targeted therapies.

TRESK

Biological characteristics of TRESK

In 2003, the KCNK18 gene, located on human chromosome 10, was successfully cloned. The gene encodes TRESK (TWIK-related spinal cord K^+ channel), a member of the K2P potassium channel family; however, it exhibits only 19% homology with other family members [114]. Subsequent research has classified the TRESK family into two subtypes: TRESK-1 and TRESK-2 [115]. Notably, TRESK channels exhibit the highest activity levels among K2P channels within rodent sensory neurons and constitute the primary determinant of the background K^+ current in the DRG [114,116]. Unlike TREK-1, TRESK does not significantly influence the resting membrane potential [116].

TRESK functions as a mechanosensitive ion channel, exhibiting exceptional sensitivity to various stimuli. Specifically, hypotonic-induced cell swelling enhances its current by approximately 40%, while shear stress increases the current by about 30%. Additionally, tensile force elevates the channel opening rate by 1.51-fold. These mechanical stimuli likely induce conformational changes in TRESK channel proteins by modifying membrane tension, thereby increasing their opening probability [4]. In contrast to TREK-1, TRESK exhibited insensitivity to temperature variations but demonstrated a pronounced response to changes in pH. Both intracellular and extracellular acidification influenced TRESK's activity; however, intracellular acidification had a more pronounced effect, resulting in a 39% inhibition of current at pH 5.6. TREK-1, on the other hand, was activated by intracellular acidification but inhibited by extracellular acidification [114]. This divergence in behavior may be attributed to the distinct molecular structures of the two channels, which dictate their respective responses to environmental stimuli. Furthermore, TRESK activity is modulated not only by mechanical stimuli and pH levels but also by calcium concentration; specifically, an increase in intracellular calcium concentration enhances its activity through the activation of calcium-dependent phosphatases [117].

TRESK is extensively distributed in the central nervous system, including the dorsal root ganglia, trigeminal ganglia, cortex, and spinal cord, as well as in peripheral organs such as the liver, spleen, kidney, and thymus [118]. Dysfunction of TRESK has been implicated in various neurological disorders. For instance, in epilepsy, reduced expression

of TRESK has been shown to directly induce neuronal hyperexcitability, which can precipitate seizures [118]. Importantly, the consequences of diminished TRESK activity extend beyond epilepsy; it also plays a critical role in pain modulation. Current evidence indicates a significant association between TRESK dysfunction and neuropathic, inflammatory, and cancer-related pain [118–120].

Activators of TRESK

The activity of TRESK channels is modulated by various exogenous substances and endogenous signaling pathways. Notably, volatile anesthetics, such as desflurane, halothane, isoflurane, and sevoflurane, significantly enhance the TRESK current by approximately threefold, with IC50 values ranging from 162 μM (isoflurane)to 658 μM (desflurane) [121]. In contrast, alcohols, including ethanol, 2-butanol, 2-pentanol, and 2-hexanol, exhibit lower potency [118]. Furthermore, compounds such as cloxyquin, A2797, nitroxoline, flufenamic acid, and its derivative BL-1249 enhance TRESK activity by stabilizing its open conformation [118].

At the signaling pathway level, Gq-coupled receptor activators, such as acetylcholine, glutamate, and histamine, along with muscarinic M1 receptor agonists like acetyl-β-methyl-choline and betaine, enhance the activity of calmodulin phosphatases through elevated intracellular Ca^{2+} concentrations. Calmodulin subsequently targets the TRESK PQIIIS, LQLP, and PQIVID (NFAT-like docking site) sequences, culminating in channel activation [117,122,123]. Additionally, PKC receptor activators, such as 12-myristate-13-acetate, facilitate the activation of TRESK through the dephosphorylation of S264 residues. This process may involve the PKC-dependent inhibition of the kinase responsible for S264 phosphorylation, thereby unveiling Ca^{2+} - Ca^{2} -independent regulatory pathways [124].

The intracellular macrocyclic region of human TRESK, spanning amino acids 163 to 177, features a PIP2-binding site comprised of positively charged residues. This structural motif markedly enhances channel activity through its interaction with anionic phospholipids, such as PIP2, via a mechanism that operates independently of the Ca^{2+}/calmodulin phosphatase pathway. In contrast, rodent TRESK lacks this binding site and thus exhibits no response to PIP2 [125].

Inhibitors of TRESK

TRESK inhibitors encompass a diverse array of chemical agents and drug classes. Among the broad-spectrum potassium channel blockers, non-selective inhibitors such as Ba^{2+}, propafenone, and quinidine directly impair TRESK function [114]. However, DCPIB serves as a highly selective inhibitor with an IC50 of 0.14 μM, achieving 82% inhibition while simultaneously activating the TREK-1 channel. This bidirectional regulation implies that the action site may reside within a structurally distinct region of the channel [85]. Furthermore, fatty acids, including arachidonic acid and docosahexaenoic acid, can also inhibit TRESK channel function directly [114]].

Among clinically relevant drugs, bupivacaine, a local anesthetic, demonstrates the highest TRESK inhibitory potency (IC_{50} = 80.4 μM), in contrast to lidocaine, which requires substantially higher concentrations to achieve similar effects (IC_{50} = 3400 μM) [121]. Subsequent investigations have identified additional TRESK inhibitors, including the antihistamine loratadine, certain antidepressants such as amitriptyline and fluoxetine, as well as analgesics like acetaminophen and ibuprofen [118,126,127]. Notably, the inhibition of TRESK by calcium channel blockers, such as verapamil and nifedipine, occurs independently of Ca^{2+} influx, and the precise molecular mechanisms remain unclear [128]. However, Immunosuppressants, including cyclosporine A, FK506, and tacrolimus, indirectly regulate TRESK by inhibiting the calmodulin phosphatase-NFAT pathway [117,129]. Additionally, the functional regulation of TRESK involves multisite phosphorylation, with PKA targeting the Ser-264 site and 14–3–3 protein/MARK kinase acting on the Ser-274/276/279 sites, creating a dynamic phosphorylation regulatory system [130,131].

The role of TRESK in cancer pain

TRESK channels are prominently expressed in key sites of nociceptive transmission, particularly in

A-δ and C fibers, as well as in TG and DRG neurons. The functional downregulation of TRESK enhances neuronal excitability, thereby facilitating the onset of pain [132–134]. Preclinical studies indicate that the diminished expression of TRESK in DRG constitutes a fundamental mechanism underlying nerve-injurious pain [133]. The inhibition of TRESK function leads to an increased release of pro-inflammatory factors, such as IL-1β and IL-6, while simultaneously reducing the secretion of anti-inflammatory factors, including IL-10. This ultimately triggers a neuroinflammatory response [135]. Consequently, it can be inferred that nerve infiltration may exacerbate cancer pain via analogous pathways. Importantly, cancer pain encompasses both neuropathic and inflammatory components, with downregulation of TRESK expression observed in both contexts [120,136]. This evidence indicates that TRESK may play a pivotal role in the development of cancer-related pain through the multiple mechanisms delineated above.

The multi-mechanistic role of TRESK in cancer pain appears to be intricately linked to its dynamic reaction to factors within the tumor microenvironment. While pro-nociceptive mediators such as histamine, glutamate, and lysophosphatidic acid (LPA) can directly activate TRESK to modulate neuronal excitability, their overall impact on cancer pain remains pro-nociceptive [122,137–140]. This suggests that TRESK's function may be overshadowed by other mechanisms. Potential explanations for this phenomenon include: (i) significant down-regulation of TRESK expression, which masks its physiological analgesic effects; (ii) the generation of strong pro-nociceptive signals by these mediators through alternative molecular pathways, with their strength surpassing the analgesic potential of TRESK activation; and (iii) the predominance of histamine, glutamate, and LPA in the context of cancer pain, indicating that TRESK activation may play a secondary role. Further investigation is warranted to determine whether TRESK activation is involved in the modulation of bone cancer pain.

In addition to being modulated by pro-nociceptive mediators, alterations in TRESK activity can significantly influence the progression of cancer pain. Functional studies indicate that the overexpression of TRESK substantially decreases the release of cancer pain-related mediators, such as substance P, CGRP, TNF-α, and IL-1β, underscoring its potential analgesic properties [141]. Moreover, while acetylcholine (ACh) has been found to activate TRESK channels, a positive correlation exists between α7-nicotinic acetylcholine receptors (α7-nAChRs) and the downregulation of TRESK expression, as well as nociceptive sensitization in a bone cancer pain model [122,142,143]. This suggests that the functional inhibition of the ACh-α7-nAChRs-TRESK pathway may serve as a central mechanism underlying nociceptive sensitization (Figure 1); however, further investigation is essential to validate this hypothesis.

To further elucidate TRESK involvement in cancer pain, a CIBP model was developed by researchers using tibial inoculation of Walker 256 breast cancer cells. Their findings revealed that the expression of TRESK was primarily concentrated in the dorsal horn region of the spinal cord; however, it exhibited a marked downregulation in this area [144]. In a parallel study, Yang et al found a similar decrease in TRESK expression in the rats suffering from CIBP, thereby confirming a consistent alteration of TRESK expression across both peripheral and central nervous systems [142]. The researchers utilized lentivirus-mediated TRESK overexpression (LV-TRESK) and siRNA knockdown techniques to investigate the functional implications of TRESK modulation. The findings indicated that LV-TRESK transfection significantly enhanced outward potassium current density and reduced the excitability of DRG neurons, effectively alleviating both mechanical and spontaneous pain behaviors in rats [142]. Conversely, TRESK knockdown expedited nociceptive sensitization, resulting in spontaneous nociception at 24 hours post-surgery and mechanical nociceptive sensitization at 48 hours. Collectively, these results confirm that the downregulation of TRESK expression contributes to peripheral and central sensitization by impairing potassium current-mediated inhibitory effects in neurons, thus representing a fundamental pathological mechanism underlying CIBP [142].

In-depth mechanistic investigations have elucidated that the abnormal activation of the VEGF-VEGFR2-calcineurin-NFAT signaling pathway plays a pivotal role in the downregulation of TRESK expression in CIBP (Figure 1). It has been verified that the expression levels of VEGF and its receptor VEGFR2 are significantly elevated in the DRG of CIBP rats. This elevation contributes to the inhibition of calcineurin activity via VEGFR2 activation, subsequently blocking the dephosphorylation of NFAT. As a result, NFAT is unable to translocate into the nucleus to initiate the transcription of the TRESK gene, leading to a reduction in TRESK protein expression, ultimately contributing to the pathogenesis of CIBP [117,142] (Table 1).

In addition to alterations in expression, differential distribution of TRESK in nerve fibers modulates pain phenotypes in breast cancer-associated CIBP equally. A study revealed a significant reduction in TRESK expression, specifically in the skin of the hind paw and in the periosteal nerve fibers of the tibia in CIBP rats. The overexpression of TRESK resulted in a relief of spontaneous pain at 14 days and evoked pain at 18 days postoperatively; conversely, the knockdown of TRESK swiftly elicited pain phenotypes, with spontaneous pain appearing at 24 hours and evoked pain at 48 hours [119]. These observations align with previous research findings [142]. The analysis of pain modalities indicates that low expression of TRESK in periosteal nerve fibers (CGRP+ only) is associated with spontaneous pain. In contrast, the reduction of TRESK expression in cutaneous nerve fibers (CGRP+/IB4+) correlates with evoked pain. This discrepancy likely accounts for the observed behavioral differences between spontaneous and evoked pain. Thus, variations in TRESK distribution and its pathological downregulation play a critical role in defining nociceptive specificity, underpinning the molecular mechanisms of pain heterogeneity in CIBP [119].

Inhibition of TRESK expression is observed not only in CIBP but also in NCP induced by chemotherapeutic agents such as oxaliplatin. Consistent with previous studies [109], the oxaliplatin-induced NCP model demonstrated a significant reduction in TRESK expression in the DRG, which was accompanied by an abnormal increase in histone deacetylase 1 (HDAC1). Electrophysiological assessments revealed that the diminished TRESK currents contribute to neuronal hyperexcitability, suggesting that the functional inhibition of TRESK serves as a central mechanism underlying NCP. Further studies established that HDAC1 epigenetically suppresses TRESK expression by lowering the acetylation of histone H3 at lysines 9 and 14, which in turn exacerbates neuronal excitability and pain phenotypes [145] (Table 1). In contrast, research on neuropathic pain indicates that the silencing of TRESK enhances neuronal apoptosis through the upregulation of the Gm11874/ATP5i gene [136]. This mechanistic distinction underscores a crucial foundation for the formulation of targeted analgesic strategies.

Discussion

Recent research has progressively clarified the role of mechanosensitive ion channels in cancer pain, especially those represented by PIEZO, TREK-1, and TRESK. These mechanosensitive ion channels may influence nuclear factors such as NF-κB and P53 by activating various signaling pathways, thereby enhancing the production of inflammatory mediators [1] (Table 1). This process significantly influences the progression of cancer pain. Importantly, cross-talk of mechanosensitive ion channels with other nociceptive pathways, such as TRPV1 May 2001amplify cancer pain signals. For instance, Piezo1 enhances the sensitization of TRPV1 through a mechanism dependent on calcium ion influx [146]. This suggests that targeting shared nodes, particularly calcium signaling, could prove more effective in managing cancer-induced bone pain that arises from multiple factors.

Targeted interventions employing mechanosensitive ion channels present promising strategies for the management of cancer-related pain. For example, low-intensity focused ultrasound has demonstrated efficacy in achieving noninvasive analgesia in murine models by selectively activating TREK-1 to inhibit neuronal hyperexcitability [147]. Notably, recent studies have identified that elevated levels of PIEZO1 in breast cancer cells enhance cancer cell invasion and metastasis [148]. Furthermore, the mechanistic modulation

of PIEZO1 by ultrasound has been shown to induce apoptosis in cancer cells, suggesting a promising avenue for mechanical interventions in the management of cancer pain [149]. However, the current study encounters two significant challenges. First, the functional heterogeneity of certain mechanosensitive ion channels family members, such as TREK-1 and TRESK, within the bone metabolic microenvironment remains poorly understood. Further research is necessary to clarify how these mechanosensitive ion channels affect CIBP by regulating the OB-OC balance. Second, the interplay between mechanosensitive ion channels and chemical signals, including cytokines and chemokines, in the tumor microenvironment warrants further investigation.

Acknowledgments

Chang Liu: Conceptualization, conducted the literature search, writing, original manuscript preparation; Haiyan Li: Conceptualization, conducted the literature search; Lihua Hang: Conceptualization, supervised the project, revised the final version, funding. All the authors read and approved the final manuscript.

Author contributions

CRediT: **Chang Liu:** Writing – original draft, Writing – review & editing; **Haiyan Li:** Investigation, Resources, Writing – review & editing; **Lihua Hang:** Supervision, Writing – review & editing.

Data availability statement

No datasets were generated or analyzed during the current study.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was financed by the Medical Scientific Research Project of Jiangsu Provincial Health Commission in 2021 [M2021072], Suzhou Applied Basic Research (medical and health) of Science and Technology Innovation Project [SYWD2024021], Kunshan High-level Medical Talents Project [Ksgccrc2004], and Medical Health Science and Technology Project of Kunshan First People's Hospital [CXTD24-B03, KSKFQYLWS2023005, KRY-YN007].

References

[1] Cao R, Tian HM, Tian Y, et al. A hierarchical mechanotransduction system: from macro to micro. Adv Sci. 2024;11(11):202302327. doi: 10.1002/advs.202302327

[2] Di XP, Gao XS, Peng L, et al. Cellular mechanotransduction in health and diseases: from molecular mechanism to therapeutic targets. Signal Transduct Target Ther. 2023;8(8):3705–3736. doi: 10.1038/s41392-023-01501-9

[3] Patel AJ, Honoré E, Maingret F, et al. A mammalian two pore domain mechano-gated S-like K+ channel. Embo J. 1998;17(15):4283–4290. doi: 10.1093/emboj/17.15.4283

[4] Callejo G, Giblin JP, Gasull X, et al. Modulation of TRESK background K^+ channel by membrane stretch. PLOS ONE. 2013;8(5):e64471. doi: 10.1371/journal.pone.0064471

[5] Djillani A, Mazella J, Heurteaux C, et al. Role of TREK-1 in health and disease, focus on the central nervous system. Front Pharmacol. 2019;10:379. doi: 10.3389/fphar.2019.00379

[6] Ni K, Zhang W, Ni Y, et al. Dorsal root ganglia NR2B-mediated Epac1-Piezo2 signaling pathway contributes to mechanical allodynia of bone cancer pain. Oncol Lett. 2021;21(4):338. doi: 10.3892/ol.2021.12599

[7] Delanne-Cumenal M, Lamoine S, Meleine M, et al. The TREK-1 potassium channel is involved in both the analgesic and anti-proliferative effects of riluzole in bone cancer pain. Biomed Pharmacother. 2024;176:116887. doi: 10.1016/j.biopha.2024.116887

[8] Wang JY, Zhang RX, Dong CS, et al. Transient receptor potential channel and interleukin-17A involvement in LTTL gel inhibition of bone cancer pain in a rat model. Integr Cancer Ther. 2015;14(4):381–393. doi: 10.1177/1534735415580677

[9] Bennett MI, Kaasa S, Barke A, et al. The IASP classification of chronic pain for ICD-11: chronic cancer-related pain. Pain. 2019;160(1):38–44. doi: 10.1097/j.pain.0000000000001363

[10] Nwonu CNS. Neuronal cell mechanisms of pain. West Afr J Med. 2022;39(10):1075–1983.

[11] Szczot M, Pogorzala LA, Solinski HJ, et al. Cell-type-specific splicing of Piezo2 regulates mechanotransduction. Cell Rep. 2017;21(10):2760–2771. doi: 10.1016/j.celrep.2017.11.035

[12] Coste B, Mathur J, Schmidt M, et al. Piezo1 and Piezo2 are essential components of distinct mechanically activated cation channels. Science. 2010;330(6000):55–60. doi: 10.1126/science.1193270

[13] Ellefsen KL, Holt JR, Chang AC, et al. Myosin-II mediated traction forces evoke localized Piezo1-dependent Ca2+ flickers. Commun Biol. 2019;2:298. doi: 10.1038/s42003-019-0514-3

[14] Wang J, Jiang J, Yang X, et al. Tethering piezo channels to the actin cytoskeleton for mechanogating via

the cadherin-β-catenin mechanotransduction complex. Cell Rep. 2022;38(6):110342. doi: 10.1016/j.celrep.2022.110342

[15] Borbiro I, Badheka D, Rohacs T. Activation of TRPV1 channels inhibits mechanosensitive piezo channel activity by depleting membrane phosphoinositides. Sci Signal. 2015;8(363):ra15. doi: 10.1126/scisignal.2005667

[16] Ridone P, Pandzic E, Vassalli M, et al. Disruption of membrane cholesterol organization impairs the activity of PIEZO1 channel clusters. J Gen Physiol. 2020;152(8):e201912515. doi: 10.1085/jgp.201912515

[17] Romero LO, Massey AE, Mata-Daboin AD, et al. Dietary fatty acids fine-tune Piezo1 mechanical response. Nat Commun. 2019;10(1):1200. doi: 10.1038/s41467-019-09055-7

[18] Lai A, Cox CD, Sekar NC, et al. Mechanosensing by Piezo1 and its implications for physiology and various pathologies. Biol Rev Camb Philos Soc. 2022;97(2):604–614. doi: 10.1111/brv.12814

[19] Fang XZ, Zhou T, Xu JQ, et al. Structure, kinetic properties and biological function of mechanosensitive piezo channels. Cell Biosci. 2021;11(1):13. doi: 10.1186/s13578-020-00522-z

[20] Szczot M, Nickolls AR, Lam RM, et al. The form and function of PIEZO2. Annu Rev Biochem. 2021;90(1):507–534. doi: 10.1146/annurev-biochem-081720-023244

[21] Xie MX, Lai RC, Xiao YB, et al. Endophilin A2 controls touch and mechanical allodynia via kinesin-mediated Piezo2 trafficking. Mil Med Res. 2024;11(1):17. doi: 10.1186/s40779-024-00520-z

[22] Syeda R, Xu J, Dubin AE, et al. Chemical activation of the mechanotransduction channel Piezo1. Elife. 2015;4:e07369. doi: 10.7554/eLife.07369

[23] Wang YF, Chi SP, Guo HF, et al. A lever-like transduction pathway for long-distance chemical- and mechano-gating of the mechanosensitive Piezo1 channel. Nat Commun. 2018;9(1):1300. doi: 10.1038/s41467-018-03570-9

[24] Tito A, Niespolo C, Monti MC, et al. Oenothera biennis cell culture produce lignans activating Piezo1 triggering the myosin light chain kinase depending pathways. Biochem Biophys Res Commun. 2023;681:36–40. doi: 10.1016/j.bbrc.2023.09.056

[25] McCubbin S, Jeoung A, Waterbury C, et al. Pharmacological profiling of stretch activated channels in proprioceptive neurons. Comp Biochem Physiol C Toxicol Pharmacol. 2020;233:108765. doi: 10.1016/j.cbpc.2020.108765

[26] Liu SL, Pan XM, Cheng WB, et al. Tubeimoside I antagonizes Yoda1-evoked Piezo1 channel activation. Front Pharmacol. 2020;11:768. doi: 10.3389/fphar.2020.00768

[27] Evans EL, Cuthbertson K, Endesh N, et al. Yoda1 analogue (Dooku1) which antagonizes Yoda1-evoked activation of Piezo1 and aortic relaxation. Br J Pharmacol. 2018;175(10):1744–1759. doi: 10.1111/bph.14188

[28] Gabrielle M, Yudin Y, Wang Y, et al. Phosphatidic acid is an endogenous negative regulator of PIEZO2 channels and mechanical sensitivity. Nat Commun. 2024;15(1):7020. doi: 10.1038/s41467-024-51181-4

[29] Suttinont C, Maeno K, Yano M, et al. Role of Piezo2 in Schwann cell volume regulation and its impact on neurotrophic release regulation. Cell Physiol Biochem. 2024;58(4):292–310. doi: 10.33594/000000713

[30] Xu X, Liu SY, Liu H, et al. Piezo channels: awesome mechanosensitive structures in cellular mechanotransduction and their role in bone. Int J Mol Sci. 2021;22(12):6429. doi: 10.3390/ijms22126429

[31] Gnanasambandam R, Ghatak C, Yasmann A, et al. GsMTx4: mechanism of inhibiting mechanosensitive ion channels. Biophys J. 2017;112(1):31–45. doi: 10.1016/j.bpj.2016.11.013

[32] Bae C, Sachs F, Gottlieb PA. The mechanosensitive ion channel Piezo1 is inhibited by the peptide GsMTx4. Biochemistry. 2011;50(29):6295–6300. doi: 10.1021/bi200770q

[33] Narayanan P, Hütte M, Kudryasheva G, et al. Myotubularin related protein-2 and its phospholipid substrate PIP2 control Piezo2-mediated mechanotransduction in peripheral sensory neurons. Elife. 2018;7:e32346. doi: 10.7554/elife.32346

[34] Narayanan P, Sondermann J, Rouwette T, et al. Native Piezo2 interactomics identifies Pericentrin as a novel regulator of Piezo2 in somatosensory neurons. J Proteome Res. 2016;15(8):2676–2687. doi: 10.1021/acs.jproteome.6b00235

[35] Peyronnet R, Martins JR, Duprat F, et al. Piezo1-dependent stretch-activated channels are inhibited by polycystin-2 in renal tubular epithelial cells. EMBO Rep. 2013;14(12):1143–1148. doi: 10.1038/embor.2013.170

[36] Zhang TX, Chi SP, Jiang F, et al. A protein interaction mechanism for suppressing the mechanosensitive Piezo channels. Nat Commun. 2017;8(1):1797. doi: 10.1038/s41467-017-01712-z

[37] Zhou ZJ, Ma XN, Lin YC, et al. MyoD-family inhibitor proteins act as auxiliary subunits of Piezo channels. Science. 2023;381(6659):799–804. doi: 10.1126/science.adh8190

[38] De Felice D, Alaimo A. Mechanosensitive piezo channels in cancer: focus on altered calcium signaling in cancer cells and in tumor progression. Cancers (Basel). 2020;12(7):1780. doi: 10.3390/cancers12071780

[39] Jo MJ, Son JY, Kim YM, et al. Blockade of Piezo2 pathway attenuates inflammatory and neuropathic pain in the orofacial area. Pain Res Manag. 2024;2024(1):9179928. doi: 10.1155/2024/9179928

[40] Liu M, Li Y, Zhong J, et al. The effect of IL-6/Piezo2 on the trigeminal neuropathic pain. AGING-Us. 2021;13(10):13615–13625. doi: 10.18632/aging.202887

[41] Dubin AE, Schmidt M, Mathur J, et al. Inflammatory signals enhance Piezo2-mediated mechanosensitive currents. Cell Rep. 2012;2(3):511–517. doi: 10.1016/j.celrep.2012.07.014

[42] Guo TW, Chen G, Yang L, et al. Piezo1 inhibitor isoquercitrin rescues neural impairment mediated by NLRP3 after intracerebral hemorrhage. Exp Neurol. 2024;379:114852. doi: 10.1016/j.expneurol.2024.114852
[43] Xiao YG, Zhang Y, Yuan WJ, et al. Piezo2 contributes to traumatic brain injury by activating the RhoA/ROCK1 pathways. Mol Neurobiol. 2024;61(10):7419–7430. doi: 10.1007/s12035-024-04058-y
[44] Zajaczkowska R, Kocot-Kepska M, Leppert W, et al. Bone pain in cancer patients: mechanisms and current treatment. Int J Mol Sci. 2019;20(23):6047. doi: 10.3390/ijms20236047
[45] Kapoor R, Saxena AK, Vasudev P, et al. Cancer induced bone pain: current management and future perspectives. Med Oncol. 2021;38(11):134. doi: 10.1007/s12032-021-01587-7
[46] Song K, Cao Q, Yang Y, et al. ALKBH5 modulates bone cancer pain in a rat model by suppressing NR2B expression. Biotechnol Appl Biochem. 2024;71(5):1105–1115. doi: 10.1002/bab.2601
[47] Liu B, Meng D, Luo M, et al. Fat mass and obesity-related protein contributes to the development and maintenance of bone cancer pain in rats by abrogating m6A methylation of RNA. Mol Pain. 2024;20:17448069241295987. doi: 10.1177/17448069241295987
[48] Ding J-F, Tu B, Song K, et al. Epitranscriptomic regulation of cardiac fibrosis via YTHDF1-dependent PIEZO2 mRNA m6A modification. Cardiovasc Res. 2024;120(17):2236–2248. doi: 10.1093/cvr/cvae239
[49] Han N, Yu N, Yu L. The mRNA stability of PIEZO1, regulated by Methyltransferase-like 3 via N6-methylation of adenosine modification in a YT521-B homology domain family 2-dependent manner, facilitates the progression of diabetic retinopathy. Am J Pathol. 2025;195(2):265–280. doi: 10.1016/j.ajpath.2024.10.007
[50] Wang LJ, You XL, Lotinun S, et al. mechanical sensing protein PIEZO1 regulates bone homeostasis via osteoblast-osteoclast crosstalk. Nat Commun. 2020;11(1):282. doi: 10.1038/s41467-019-14146-6
[51] Zhang X, Yuan X, Li X, et al. Sodium Danshensu alleviates bone cancer pain by inhibiting the osteoclast differentiation and CGRP expression. Eur J Pharmacol. 2025;992:177296. doi: 10.1016/j.ejphar.2025.177296
[52] Zhou TF, Gao B, Fan Y, et al. Piezo1/2 mediate mechanotransduction essential for bone formation through concerted activation of NFAT-YAP1-ss-satenin. Elife. 2020;9:e52779. doi: 10.7554/eLife.52779
[53] Zhang Y, Wang W, Gong Z, et al. Activation of the STING pathway induces peripheral sensitization via neuroinflammation in a rat model of bone cancer pain. Inflamm Res. 2023;72(1):117–132. doi: 10.1007/s00011-022-01663-2
[54] Sun L, Wang Y, Kan T, et al. Elevated expression of Piezo1 activates the cGAS-STING pathway in chondrocytes by releasing mitochondrial DNA. Osteoarthritis Cartilage. 2025;33(5):601–615. doi: 10.1016/j.joca.2025.02.778
[55] Xie YF, Hang LH. Mechanical gated ion channel Piezo1: function, and role in macrophage inflammatory response. Innate Immun. 2024;30(2–4):32–39. doi: 10.1177/17534259241249287
[56] Geng J, Shi YR, Zhang JJ, et al. TLR4 signalling via Piezo1 engages and enhances the macrophage mediated host response during bacterial infection. Nat Commun. 2021;12(1):3519. doi: 10.1038/s41467-021-23683-y
[57] Meng XW, Gao JL, Zuo JL, et al. Toll-like receptor-4/p38 MAPK signaling in the dorsal horn contributes to P2X4 receptor activation and BDNF over-secretion in cancer induced bone pain. Neurosci Res. 2017;125:37–45. doi: 10.1016/j.neures.2017.06.006
[58] Wang W, Gong ZH, Wang K, et al. Activation of the BMP2-SMAD1-CGRP pathway in dorsal root ganglia contributes to bone cancer pain in a rat model. Heliyon. 2024;10(6):e27350. doi: 10.1016/j.heliyon.2024.e27350
[59] Wang ZY, Chen JY, Babicheva A, et al. Endothelial upregulation of mechanosensitive channel Piezo1 in pulmonary hypertension. Am J Physiol Cell Physiol. 2021;321(6):C1010–C1027. doi: 10.1152/ajpcell.00147.2021
[60] Lopez-Bellido R, Puig S, Huang PJ, et al. Growth factor signaling regulates mechanical nociception in flies and vertebrates. J Neurosci. 2019;39(30):6012–6030. doi: 10.1523/JNEUROSCI.2950-18.2019
[61] Xu Y, Liu J, He M, et al. Mechanisms of PDGF siRNA-mediated inhibition of bone cancer pain in the spinal cord. Sci Rep. 2016;6(1):27512. doi: 10.1038/srep27512
[62] Zhang TX, Bi C, Li YR, et al. Phosphorylation of Piezo1 at a single residue, serine-1612, regulates its mechanosensitivity and in vivo mechanotransduction function. Neuron. 2024;112(21):3618–3633.e6. doi: 10.1016/j.neuron.2024.08.009
[63] Sugimoto A, Miyazaki A, Kawarabayashi K, et al. Piezo type mechanosensitive ion channel component 1 functions as a regulator of the cell fate determination of mesenchymal stem cells. Sci Rep. 2017;7(1):17696. doi: 10.1038/s41598-017-18089-0
[64] Fan LJ, Kan HM, Chen XT, et al. Vascular endothelial growth factor-A/vascular endothelial growth factor 2 signaling in spinal neurons contributes to bone cancer pain. Mol Pain. 2022;18:17448069221075891. doi: 10.1177/17448069221075891
[65] Nencini S, Ivanusic J. Mechanically sensitive Aδ nociceptors that innervate bone marrow respond to changes in intra-osseous pressure. J Physiol. 2017;595(13):4399–4415. doi: 10.1113/JP273877
[66] Nencini S, Morgan M, Thai J, et al. Piezo2 knockdown inhibits noxious mechanical stimulation and

NGF-induced sensitization in A-delta bone afferent neurons. Front Physiol. 2021;12:644929. doi: 10.3389/fphys.2021.644929

[67] Jing D, Zhao Q, Zhao Y, et al. Management of pain in patients with bone metastases. Front Oncol. 2023;13:1156618. doi: 10.3389/fonc.2023.1156618

[68] Wang S, Nie X, Parastooei G, et al. Nociceptor neurons facilitate orthodontic tooth movement via Piezo2 in mice. J Dent Res. 2025. doi: 10.1177/00220345251317429

[69] Moloney NA, Lenoir D. Assessment of neuropathic pain following cancer treatment. Anat Rec (Hoboken). 2024;307(2):309–319. doi: 10.1002/ar.25161

[70] Duan ML, Jia YR, Huo LF, et al. Potentiation of PIEZO2 mechanically-activated currents in sensory neurons mediates vincristine-induced mechanical hypersensitivity. Acta Pharm Sin B. 2023;13(8):3365–3381. doi: 10.1016/j.apsb.2023.05.010

[71] Vivier D, Bennis K, Lesage F, et al. Perspectives on the two-pore domain potassium channel TREK-1 (TWIK-Related K(+) channel 1). A novel therapeutic target? J Med Chem. 2016;59(11):5149–5157. doi: 10.1021/acs.jmedchem.5b00671

[72] Verkest C, Häfner S, Prado PA, et al. Migraine and two-pore-domain potassium channels. Neuroscientist. 2021;27(3):268–284. doi: 10.1177/1073858420940949

[73] Fink M, Duprat F, Lesage F, et al. Cloning, functional expression and brain localization of a novel unconventional outward rectifier K+ channel. Embo J. 1996;15(24):6854–6862. doi: 10.1002/j.1460-2075.1996.tb01077.x

[74] Natale AM, Deal PE, Minor DL. Structural insights into the mechanisms and pharmacology of K2P potassium channels. J Mol Biol. 2021;433(17):166995. doi: 10.1016/j.jmb.2021.166995

[75] Chemin J, Patel AJ, Duprat F, et al. Up- and down-regulation of the mechano-gated K(2P) channel TREK-1 by PIP (2) and other membrane phospholipids. Pflugers Arch. 2007;455(1):97–103. doi: 10.1007/s00424-007-0250-2

[76] Sandoz G, Tardy MP, Thümmler S, et al. Mtap2 is a constituent of the protein network that regulates twik-related K+ channel expression and trafficking. J Neurosci. 2008;28(34):8545–8552. doi: 10.1523/JNEUROSCI.1962-08.2008

[77] Lauritzen I, Chemin J, Honoré E, et al. Cross-talk between the mechano-gated K2P channel TREK-1 and the actin cytoskeleton. EMBO Rep. 2005;6(7):642–648. doi: 10.1038/sj.embor.7400449

[78] Fang Y, Tian Y, Huang Q, et al. Deficiency of TREK-1 potassium channel exacerbates blood-brain barrier damage and neuroinflammation after intracerebral hemorrhage in mice. J Neuroinflammation. 2019;16(1):96. doi: 10.1186/s12974-019-1485-5

[79] Zhang Y, Fu J, Han Y, et al. Two-pore-domain potassium channel TREK-1 mediates pulmonary fibrosis through macrophage M2 polarization and by direct promotion of fibroblast differentiation. Biomedicines. 2023;11(5):1279. doi: 10.3390/biomedicines11051279

[80] Patel AJ, Honoré E, Lesage F, et al. Inhalational anesthetics activate two-pore-domain background K+ channels. Nat Neurosci. 1999;2(5):422–426. doi: 10.1038/8084

[81] Gruss M, Bushell TJ, Bright DP, et al. Two-pore-domain K+ channels are a novel target for the anesthetic gases xenon, nitrous oxide, and cyclopropane. Mol Pharmacol. 2004;65(2):443–452. doi: 10.1124/mol.65.2.443

[82] Lacomblez L, Bensimon G, Leigh PN, et al. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Amyotrophic lateral sclerosis/riluzole study group II. Lancet. 1996;347(9013):1425–1431. doi: 10.1016/S0140-6736(96)91680-3

[83] Duprat F, Lesage F, Patel AJ, et al. The neuroprotective agent riluzole activates the two P domain K(+) channels TREK-1 and TRAAK. Mol Pharmacol. 2000;57(5):906–912. doi: 10.1016/S0026-895X(24)26499-3

[84] Decher N, Rinne S, Bedoya M, et al. Molecular pharmacology of K2P potassium channels. Cell Physiol Biochem. 2021;55(S3):87–107. doi: 10.33594/000000339

[85] Lv JY, Liang YM, Zhang SQ, et al. DCPIB, an inhibitor of volume-regulated anion channels, distinctly modulates K2P channels. ACS Chem Neurosci. 2019;10(6):2786–2793. doi: 10.1021/acschemneuro.9b00010

[86] Schroeter CB, Nelke C, Schewe M, et al. Validation of TREK1 ion channel activators as an immunomodulatory and neuroprotective strategy in neuroinflammation. Biol Chem. 2023;404(4):355–375. doi: 10.1515/hsz-2022-0266

[87] Kennard LE, Chumbley JR, Ranatunga KM, et al. Inhibition of the human two-pore domain potassium channel, TREK-1, by fluoxetine and its metabolite norfluoxetine. Br J Pharmacol. 2005;144(6):821–829. doi: 10.1038/sj.bjp.0706068

[88] Pietri M, Djillani A, Mazella J, et al. First evidence of protective effects on stroke recovery and post-stroke depression induced by sortilin-derived peptides. Neuropharmacology. 2019;158:107715. doi: 10.1016/j.neuropharm.2019.107715

[89] Ye DQ, Li Y, Zhang XR, et al. TREK1 channel blockade induces an antidepressant-like response synergizing with 5-HT1A receptor signaling. Eur Neuropsychopharmacol. 2015;25(12):2426–2436. doi: 10.1016/j.euroneuro.2015.09.007

[90] Lee EH, Park JE, Gotina L, et al. Novel potent blockers for TWIK-1/TREK-1 heterodimers as potential antidepressants. Biomed Pharmacother. 2023;165:115139. doi: 10.1016/j.biopha.2023.115139

[91] Thümmler S, Duprat F, Lazdunski M. Antipsychotics inhibit TREK but not TRAAK channels. Biochem Biophys Res Commun. 2007;354(1):284–289. doi: 10.1016/j.bbrc.2006.12.199

[92] Pavel MA, Chung HW, Petersen EN, et al. Polymodal mechanism for TWIK-Related K+ channel inhibition by local anesthetic. Anesth Analg. 2019;129 (4):973–982. doi: 10.1213/ANE.0000000000004216
[93] Schmidt C, Wiedmann F, Schweizer PA, et al. Class I antiarrhythmic drugs inhibit human cardiac two-pore-domain K(+) (K2 ₂p) channels. Eur J Pharmacol. 2013;721(1–3):237–248. doi: 10.1016/j.ejphar.2013.09.029
[94] Liu HY, Enyeart JA, Enyeart JJ. Potent inhibition of native TREK-1 K+ channels by selected dihydropyridine Ca2+ channel antagonists. J Pharmacol Exp Ther. 2007;323(1):39–48. doi: 10.1124/jpet.107.125245
[95] Miyano K, Nonaka M, Sakamoto M, et al. The inhibition of TREK-1 K+ channels via multiple compounds contained in the six Kamikihito components, potentially stimulating oxytocin neuron pathways. Int J Mol Sci. 2024;25(9):4907. doi: 10.3390/ijms25094907
[96] Alloui A, Zimmermann K, Mamet J, et al. TREK-1, a K+ channel involved in polymodal pain perception. Embo J. 2006;25(11):2368–2376. doi: 10.1038/sj.emboj.7601116
[97] Cohen A, Sagron R, Somech E, et al. Pain-associated signals, acidosis and lysophosphatidic acid, modulate the neuronal K(2P)2.1 channel. Mol Cell Neurosci. 2009;40(3):382–389. doi: 10.1016/j.mcn.2008.12.004
[98] Rivas-Ramírez P, Reboreda A, Rueda-Ruzafa L, et al. PIP2 mediated inhibition of TREK potassium currents by bradykinin in mouse sympathetic neurons. Int J Mol Sci. 2020;21(2):389. doi: 10.3390/ijms21020389
[99] Maingret F, Lauritzen I, Patel AJ, et al. TREK-1 is a heat-activated background K(+) channel. Embo J. 2000;19(11):2483–2491. doi: 10.1093/emboj/19.11.2483
[100] Prado PA, Landra-Willm A, Verkest C, et al. TREK channel activation suppresses migraine pain phenotype. iScience. 2021;24(9):102961. doi: 10.1016/j.isci.2021.102961
[101] Lin X, Wu JF, Wang DM, et al. The correlation and role analysis of KCNK2/4/5/15 in human papillary thyroid carcinoma microenvironment. J Cancer. 2020;11(17):5162–5176. doi: 10.7150/jca.45604
[102] Wang J, Li JQ, Cheng D, et al. miR-132-3p promotes heat stimulation-induced esophageal squamous cell carcinoma tumorigenesis by targeting KCNK2. Mol Carcinog. 2023;62(5):583–597. doi: 10.1002/mc.23504
[103] Sauter DRP, Sorensen CE, Rapedius M, et al. pH-sensitive K+ channel TREK-1 is a novel target in pancreatic cancer. Biochim Biophys Acta. 2016;1862 (10):1994–2003. doi: 10.1016/j.bbadis.2016.07.009
[104] Wang L, Song LJ, Li J, et al. Bone sialoprotein-αvβ3 integrin axis promotes breast cancer metastasis to the bone. Cancer Sci. 2019;110(10):3157–3172. doi: 10.1111/cas.14172
[105] Glogowska E, Arhatte M, Chatelain FC, et al. Piezo1 and Piezo2 foster mechanical gating of K2P channels. Cell Rep. 2021;37(9):110070. doi: 10.1016/j.celrep.2021.110070
[106] Xie W, Strong JA, Kim D, et al. Bursting activity in myelinated sensory neurons plays a key role in pain behavior induced by localized inflammation of the rat sensory ganglion. Neuroscience. 2012;206:212–223. doi: 10.1016/j.neuroscience.2012.01.007
[107] Coderre TJ, Kumar N, Lefebvre CD, et al. A comparison of the glutamate release inhibition and anti-allodynic effects of gabapentin, lamotrigine, and riluzole in a model of neuropathic pain. J Neurochem. 2007;100(5):1289–1299. doi: 10.1111/j.1471-4159.2006.04304.x
[108] Poupon L, Lamoine S, Pereira V, et al. Targeting the TREK-1 potassium channel via riluzole to eliminate the neuropathic and depressive-like effects of oxaliplatin. Neuropharmacology. 2018;140:43–61. doi: 10.1016/j.neuropharm.2018.07.026
[109] Pereira V, Lamoine S, Cuménal M, et al. Epigenetics involvement in oxaliplatin-induced potassium channel transcriptional downregulation and hypersensitivity. Mol Neurobiol. 2021;58(7):3575–3587. doi: 10.1007/s12035-021-02361-6
[110] Descoeur J, Pereira V, Pizzoccaro A, et al. Oxaliplatin-induced cold hypersensitivity is due to remodelling of ion channel expression in nociceptors. EMBO Mol Med. 2011;3(5):266–278. doi: 10.1002/emmm.201100134
[111] Dionisi M, Ruffinatti FA, Riva B, et al. Early stimulation of TREK channel transcription and activity induced by oxaliplatin-dependent cytosolic acidification. Int J Mol Sci. 2020;21(19):7164. doi: 10.3390/ijms21197164
[112] Devilliers M, Busserolles J, Lolignier S, et al. Activation of TREK-1 by morphine results in analgesia without adverse side effects. Nat Commun. 2013;4 (1):2941. doi: 10.1038/ncomms3941
[113] Qiu YG, Huang L, Fu J, et al. TREK channel family activator with a well-defined structure-activation relationship for pain and neurogenic inflammation. J Med Chem. 2020;63(7):3665–3677. doi: 10.1021/acs.jmedchem.9b02163
[114] Sano Y, Inamura K, Miyake A, et al. A novel two-pore domain K+ channel, TRESK, is localized in the spinal cord. J Biol Chem. 2003;278(30):27406–27412. doi: 10.1074/jbc.M206810200
[115] Kang D, Mariash E, Kim D. Functional expression of TRESK-2, a new member of the tandem-pore K+ channel family. J Biol Chem. 2004;279 (27):28063–28070. doi: 10.1074/jbc.M402940200
[116] Dobler T, Springauf A, Tovornik S, et al. TRESK two-pore-domain K+ channels constitute a significant component of background potassium currents in murine dorsal root ganglion neurones. J Physiol. 2007;585 (3):867–879. doi: 10.1113/jphysiol.2007.145649
[117] Han J, Kang D. TRESK channel as a potential target to treat T-cell mediated immune dysfunction. Biochem Biophys Res Commun. 2009;390(4):1102–1105. doi: 10.1016/j.bbrc.2009.10.076

[118] Schreiber JA, Dufer M, Seebohm G. The special one: architecture, physiology and pharmacology of the TRESK channel. Cell Physiol Biochem. 2022;56 (6):663–684. doi: 10.33594/000000589

[119] Liu JP, Jing HB, Xi K, et al. Contribution of TRESK two-pore domain potassium channel to bone cancer-induced spontaneous pain and evoked cutaneous pain in rats. Mol Pain. 2021;17:17448069211023230. doi: 10.1177/17448069211023230

[120] Marsh B, Acosta C, Djouhri L, et al. Leak K^+ channel mRNAs in dorsal root ganglia: relation to inflammation and spontaneous pain behaviour. Mol Cell Neurosci. 2012;49(3):375–386. doi: 10.1016/j.mcn.2012.01.002

[121] Liu CH, Au JD, Zou HL, et al. Potent activation of the human tandem pore domain K channel TRESK with clinical concentrations of volatile anesthetics. Anesth Analg. 2004;99(6):1715–1722. doi: 10.1213/01.ANE.0000136849.07384.44

[122] Kang D, Kim GT, Kim EJ, et al. Lamotrigine inhibits TRESK regulated by G-protein coupled receptor agonists. Biochem Biophys Res Commun. 2008;367 (3):609–615. doi: 10.1016/j.bbrc.2008.01.008

[123] Czirják G, Enyedi P. The LQLP calcineurin docking site is a major determinant of the calcium-dependent activation of human TRESK background K+ channel. J Biol Chem. 2014;289(43):29506–29518. doi: 10.1074/jbc.M114.577684

[124] Pergel E, Lengyel M, Enyedi P, et al. TRESK (K2P18.1) background potassium channel is activated by novel-type protein kinase C via dephosphorylation. Mol Pharmacol. 2019;95(6):661–672. doi: 10.1124/mol.119.116269

[125] Giblin JP, Etayo I, Castellanos A, et al. Anionic phospholipids bind to and modulate the activity of human TRESK background K+ channel. Mol Neurobiol. 2019;56(4):2524–2541. doi: 10.1007/s12035-018-1244-0

[126] Park H, Kim EJ, Han J, et al. Effects of analgesics and antidepressants on TREK-2 and TRESK currents. Korean J Physiol Pharmacol. 2016;20(4):379–385. doi: 10.4196/kjpp.2016.20.4.379

[127] Bruner JK, Zou BY, Zhang HK, et al. Identification of novel small molecule modulators of K2P18.1 two-pore potassium channel. Eur J Pharmacol. 2014;740:603–610. doi: 10.1016/j.ejphar.2014.06.021

[128] Park H, Kim EJ, Ryu JH, et al. Verapamil inhibits TRESK (K2P18.1) current in trigeminal ganglion neurons independently of the blockade of Ca2+ influx. Int J Mol Sci. 2018;19(7):1961. doi: 10.3390/ijms19071961

[129] Czirják B, Tóth ZE, Enyedi P. The two-pore domain K+ channel, TRESK, is activated by the cytoplasmic calcium signal through calcineurin. J Biol Chem. 2004;279 (18):18550–18558. doi: 10.1074/jbc.M312229200

[130] Andres-Bilbe A, Castellanos A, Pujol-Coma A, et al. The background K+ channel TRESK in sensory physiology and pain. Int J Mol Sci. 2020;21(15):5206. doi: 10.3390/ijms21155206

[131] Czirják G, Enyedi P. TRESK background K(+) channel is inhibited by phosphorylation via two distinct pathways. J Biol Chem. 2010;285(19):14549–14557. doi: 10.1074/jbc.M110.102020

[132] Weir GA, Pettingill P, Wu Y, et al. The role of TRESK in discrete sensory neuron populations and somatosensory processing. Front Mol Neurosci. 2019;12:170. doi: 10.3389/fnmol.2019.00170

[133] Tulleuda A, Cokic B, Callejo G, et al. TRESK channel contribution to nociceptive sensory neurons excitability: modulation by nerve injury. Mol Pain. 2011;7:30. doi: 10.1186/1744-8069-7-30

[134] Guo ZH, Qiu CS, Jiang XH, et al. TRESK K+ channel activity regulates trigeminal nociception and headache. eNeuro. 2019;6(4):UNSP ENEURO.0236–0219.2019. doi: 10.1523/ENEURO.0236-19.2019

[135] Dilek M, Kilinc YB, Kilinc E, et al. Activation of TRESK background potassium channels by cloxyquin exerts protective effects against excitotoxic-induced brain injury and neuroinflammation in neonatal rats. J Neuroimmunol. 2022;368:577894. doi: 10.1016/j.jneuroim.2022.577894

[136] Liu P, Cheng Y, Xu HL, et al. TRESK regulates Gm11874 to induce apoptosis of spinal cord neurons via ATP5i mediated oxidative stress and DNA damage. Neurochem Res. 2021;46(8):1970–1980. doi: 10.1007/s11064-021-03318-w

[137] Kollert S, Dombert B, Döring F, et al. Activation of TRESK channels by the inflammatory mediator lysophosphatidic acid balances nociceptive signalling. Sci Rep. 2015;5(1):12548. doi: 10.1038/srep12548

[138] Zhu YF, Linher-Melville K, Wu JH, et al. Bone cancer-induced pain is associated with glutamate signalling in peripheral sensory neurons. Mol Pain. 2020;16:1744806920911536. doi: 10.1177/1744806920911536

[139] Khasabova IA, Khasabov SG, Johns M, et al. Exosome-associated lysophosphatidic acid signaling contributes to cancer pain. Pain. 2023;164(12):2684–2695. doi: 10.1097/j.pain.0000000000002967

[140] Gavioli E, Abrams M. Prevention of granulocyte-colony stimulating factor (G-CSF) induced bone pain using double histamine blockade. Support Care Cancer. 2017;25(3):817–822. doi: 10.1007/s00520-016-3465-y

[141] Kim GT, Siregar AS, Kim EJ, et al. Upregulation of TRESK channels contributes to motor and sensory recovery after spinal cord injury. Int J Mol Sci. 2020;21(23):8997. doi: 10.3390/ijms21238997

[142] Yang Y, Li S, Jin ZR, et al. Decreased abundance of TRESK two-pore domain potassium channels in sensory neurons underlies the pain associated with bone metastasis. Sci Signal. 2018;11(552):eaao5150. doi: 10.1126/scisignal.aao5150

[143] Yang T, Zhou YQ, Zhang W, et al. The spinal α7-nicotinic acetylcholine receptor contributes to the maintenance of cancer-induced bone pain. J Pain Res. 2021;14:441–452. doi: 10.2147/JPR.S286321

[144] Zhang DW, Wu HB, Zhang CH, et al. Expression of TRESK in spinal dorsal horn of rats with bone cancer pain. Acta Med Univ Sci Technol Huazhong. 2013;42(02):-127–129+142. doi: 10.3870/j.issn.1672-0741.2013.02.001

[145] Ho IHT, Zou Y, Luo K, et al. Sodium butyrate restored TRESK current controlling neuronal hyperexcitability in a mouse model of oxaliplatin-induced peripheral neuropathic pain. Neurotherapeutics. 2024;22(1):e00481. doi: 10.1016/j.neurot.2024.e00481

[146] Lee PR, Ha T, Choi H-S, et al. Piezo1 mediates mechanical signals in TRPV1-positive nociceptors in mice. Acta Physiol (oxf). 2024;240(11):e14236. doi: 10.1111/apha.14236

[147] Ying YJ, Huang Y, Zheng YY. Research progress of ultrasonic neuroregulation of potassium channels in the treatment of pain. J Clin Ultrasound Med. 2021;23:145–148. doi: 10.16245/j.cnki.issn1008-6978.2021.02.024

[148] Li C, Rezania S, Kammerer S, et al. Piezo1 forms mechanosensitive ion channels in the human MCF-7 breast cancer cell line. Sci Rep. 2015;5(1):8364. doi: 10.1038/srep08364

[149] Xu Y, Wang Y, Mei S, et al. The mechanism and potential therapeutic target of piezo channels in pain. Front Pain Res (Lausanne). 2024;5:1452389–1452389. doi: 10.3389/fpain.2024.1452389