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Review

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TRPV1: from structure to function—a multidimensional target for therapeutic advances

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Abstract: Transient receptor potential vanilloid subtype 1 (TRPV1), a polymodally activated, calcium-permeable non-selective cation channel, is broadly present in all parts of the body, with notable expression in nociceptive neurons. Both physiological and pathological functions rely heavily on this ion channel. mediating responses to a variety of stimuli and contributing to the maintenance of bodily homeostasis. Its unique ability to respond to temperature changes, chemical ligands, and voltage fluctuations positions TRPV1 as a key target in understanding and modulating normal bodily functions, in addition to diagnosing and treating diseases. This review synthesizes current knowledge on the structure, gating mechanisms, and physiological and pathological roles of TRPV1, highlighting its potential as a therapeutic target across multiple disease states. By providing a comprehensive overview of the multifaceted functions of TRPV1, this review aims to inform and inspire future research, finally contributing to the advancement of new therapeutic techniques focusing on TRPV1 to enhance human health.

Key words: Transient receptor potential vanilloid subtype 1 (TRPV1); Structure; Gating Mechanism; Therapeutic Target

1 Introduction

TRPV1 is a non-selective cation channel that facilitates the movement of ions such as calcium, sodium, and potassium, comprising six transmembrane domains and a central pore-forming region (Fig.1). TRPV1 is stimulated by a range of factors, including capsaicin from chili peppers, high

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temperatures, and acidic pH, leading to the opening of the channel and subsequent ion flux. Expression of TRPV1 mRNA and protein occurs in optic(Sappington et al., 2009), pulmonary(Zhao et al., 2013), nervous(Shirakawa et al., 2008), cardiac(Sun et al., 2014), skeletal(Hu et al., 2008), circulatory(Hofmann et al., 2014), and skin cells(Denda et al., 2010), and in several cancer cell lines(Jambrina et al., 2003; Sanchez et al., 2005; Stock et al., 2012; Vercelli et al., 2015; Liu et al., 2016). Functionally, TRPV1 serves as a critical sensor for nociception, detecting painful stimuli. It is vital for thermoregulation(Yoshida et al., 2016), contributing to the perception of heat and the inflammatory response. Beyond these physiological functions, TRPV1 is implicated in numerous biological processes, including neuroprotection(Kitahara et al., 2005; Sakamoto et al., 2014; Kang et al., 2020; Medicine, 2021), gastrointestinal motility(Matsumoto et al., 2009; Lu et al., 2014; Deng et al., 2021), and taste perception(Lyall et al., 2004; Arai et al., 2010). Therapeutically, TRPV1 holds immense potential. Its modulation offers avenues for the development of novel analgesics to treat chronic pain conditions without the addictive liabilities of traditional opioids(Premkumar, 2010). While current evidence suggests a reduced risk of addiction with TRPV1-targeted analgesics due to their peripheral action and distinct mechanism of pain relief, definitive conclusions await further clinical investigation. Additionally, TRPV1 antagonists are being explored for their potential in managing inflammatory diseases and disorders related to excessive heat sensitivity. Conversely, agonists can be used to enhance thermoregulation or stimulate appetite in certain therapeutic contexts. Thus, TRPV1 is a compelling target for advancing medical interventions across a spectrum of diseases.

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2 Structural features of TRPV1

TRPV1 was cloned in 1997, marking a significant milestone in its study(Michael J. Caterina, 1997). The structural features of TRPV1 have been extensively studied through various structural and experimental approaches(Tamara Rosenbaum, 2002; Cao et al., 2013a). These studies have focused on elucidating the three-dimensional configuration of TRPV1, including its transmembrane domains, ion permeation pathways, and interaction sites for ligands and modulators. Moiseenkova-Bell et al. obtained a 19 Å resolution structure of the TRPV1 channel using cryo-electron microscopy, providing a basis for structural research on TRPV1(Vera Y. Moiseenkova-Bell*, 2008).

The more precise and higher-resolution full-length rat TRPV1 channel structure was first revealed by Julius and Cheng in 2013(Liao et al., 2013). They resolved the structure of TRPV1 at a resolution of 3.4Å, providing a high-resolution structural blueprint for TRPV1 studies and advancing our understanding of its function. This structural information has been pivotal in understanding how TRPV1 is activated by various stimuli, including capsaicin, heat, and protons.

TRPV1 is a homotetramer, composed of four identical subunits (Figs.1 a-c). Each subunit has six transmembrane helices (S1-S6) arranged in a way that forms the ion-conducting pore of the channel (Figs.1d and e). The S5 and S6 helices are crucial for the formation of the pore. The N-terminal domain of TRPV1 is located on the inside of the cell membrane and contains functional regions like ankyrin repeat domain (ARD) and linker domain (Fig.2). The C-terminal domain also resides on the inside cell membrane and contains important functional regions such as the TRP domain (Fig.2). The S1-S4 domains are present in TRPV1 but contribute differently to channel gating. These domains contain

aromatic residues that create a hydrophobic interior, distinct from the charged environment in classical voltage-gated channels.

The S4-S5 linker, an amphipathic helix, connects the S1-S4 and S5-P-S6 domains and plays a crucial role in channel gating by facilitating conformational changes(Liao, et al., 2013). The pore region is wide open compared to Kv channels, with a broad funnel-like structure that enhances accessibility to pharmacophores. A short selectivity filter (GMGD) is present, with backbone carbonyls or side chains pointing into the central pathway, determining ion selectivity. The ARD repeats interact with cytoplasmic domains of adjacent subunits, facilitating channel assembly and stability. The TRP domain is unique to TRP channels and plays a pivotal role in allosteric modulation and subunit assembly (Figs.1e and 2). It interacts with both the S4-S5 linker and the pre-S1 helix, facilitating conformational changes during channel activation(Liao, et al., 2013).

The domain-swapped arrangement of TRPV1 is a structural feature that has attracted significant attention due to its implications in channel function and regulation (Fig.2). The N-terminal ankyrin repeat domain (ARD) of one subunit of TRPV1 extends its β-hairpin motif (residues L238-D245) to intercalate into the ankyrin-transmembrane domain (ARD-TMD) interface of an adjacent subunit, forming a stable inter-subunit bridge(Cao et al., 2013b). This swapped interaction positions the ARD close to the transmembrane domain (TMD), enabling allosteric coupling between distal regulatory sites and the central pore. Specifically, the domain-swapped architecture positions the capsaicin-binding pocket—located at the S3-S4 helix interface within the TMD—within nanometer proximity to the ARD's R2 repeat (K240/E243), which forms salt bridges with TMD residues(Liao, et al., 2013).

Subsequent studies have further explored the structural dynamics of TRPV1, particularly in the context of its interactions with lipids and ligands (Fig.2). For instance, the use of cryo-EM has allowed researchers to capture the channel in different conformational states, providing a detailed view of the molecular mechanisms underlying its activation and inhibition(Cao, et al., 2013b; Liao, et al., 2013; Gao et al., 2016; Kwon et al., 2021; Nadezhdin et al., 2021; Zhang et al., 2021a; Kwon et al., 2022; Arnold et al., 2024; Fan et al., 2024). These studies have highlighted the role of specific lipid interactions in modulating TRPV1 activity, suggesting that lipids can enhance the binding of toxins and other ligands to the channel(Gao, et al., 2016).

Moreover, the structural basis of TRPV1 modulation by endogenous bioactive lipids has been investigated, revealing a regulatory pocket within the transmembrane core that accommodates diverse lipid species. This pocket plays a crucial role in the channel's response to inflammatory lipids, which can enhance its activity in the context of pain(Arnold, et al., 2024). The identification of this pocket has provided a framework for understanding how lipid modulation can influence TRPV1 function and has opened new avenues for therapeutic intervention.

In addition to lipid interactions, the structural analysis of TRPV1 has focused on its inhibition by specific antagonists. For example, study of the cryo-EM structure of human TRPV1 in complex with the analgesic SB-366791 have elucidated the mechanism by which this antagonist binds to the vanilloid site and inhibits channel activity(Neuberger et al., 2023)(Fig.2). SB-366791 binds to the vanilloid site on the TRPV1 ion channel. The binding site, situated within the TMD region and oriented towards the cytoplasmic leaflet of the membrane, is found in the cleft between the S1-S4 domains and the pore domain. This site is also known to bind other ligands such as capsaicin (an agonist), resiniferatoxin (RTX),

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a diterpene agonist found in the latex of different cactus species of the Euphorbia genus(Seabrook et al., 2002),and the competitive antagonist capsazepine. Four identical densities corresponding to the shape of an SB-366791 molecule were observed, one per subunit of the hTRPV1 tetramer. These densities allowed for unambiguous modeling of the ligand's position and orientation within the vanilloid site. This structural insight is crucial for the development of new pain therapies targeting TRPV1. Furthermore, the structural basis of TRPV1 inhibition by SAF312 and cholesterol has been explored, revealing how these molecules interact with the channel to prevent its activation. SAF312 binds to the vanilloid binding pocket (VBP) of the TRPV1 channel (Fig.2), where it forms specific interactions with key residues including Y511, S512, L515, L553, A566, N551, and R557 through hydrophobic forces, hydrogen bonds, and electrostatic interactions. The benzonitrile group of SAF312 is positioned atop the TRP-helix, while its quinazolinone group points upwards. The binding site also accommodates a cholesterol molecule, which contributes to the stability of the SAF312-TRPV1 complex through hydrophobic interactions. Mutagenesis and molecular dynamics simulations confirmed the importance of these interactions, with specific mutations significantly reducing the potency of SAF312. These structural and functional analyses provide significant insights into the molecular basis of TRPV1 inhibition by SAF312, facilitating the development of more effective TRPV1-targeted drug candidates. The interplay between SAF312 and cholesterol in modulating TRPV1 function underscores the complexity of its regulation and highlights potential targets for drug development(Fan, et al., 2024).

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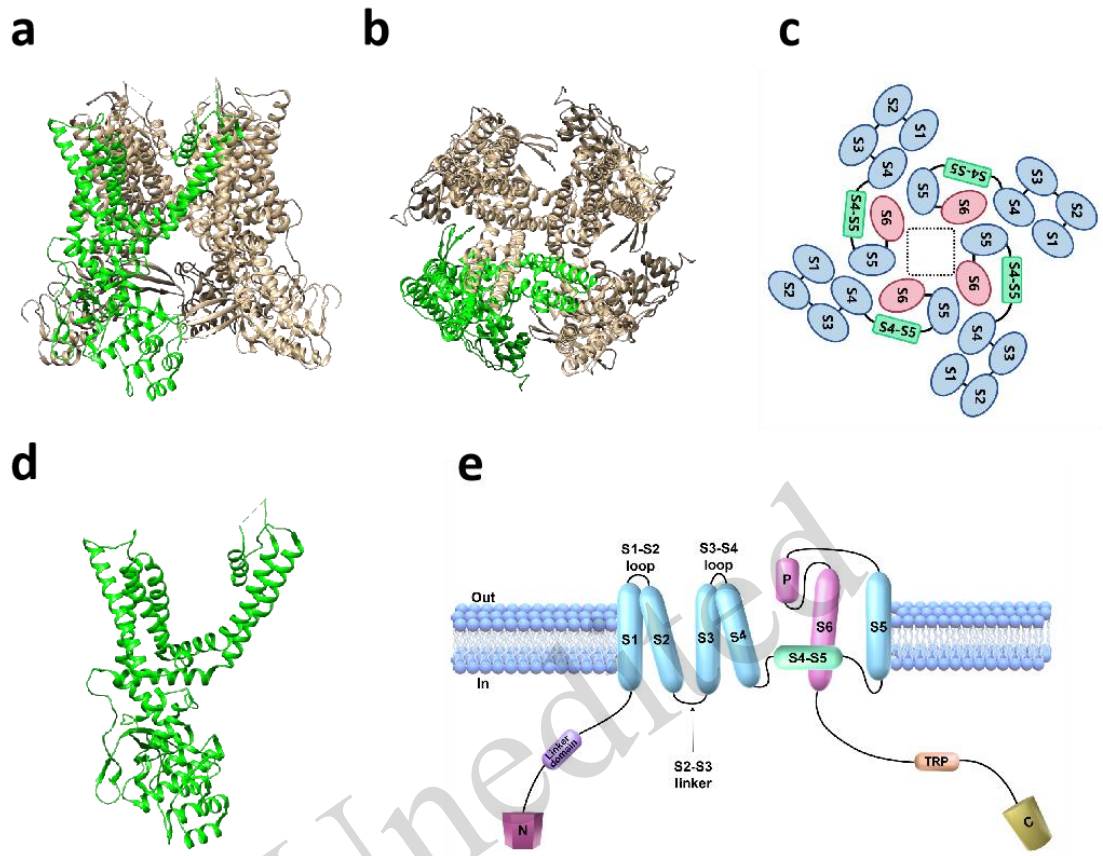

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Fig.1: Structure of Rat TRPV1. (a) The tetrameric structure of the TRPV1 channel with one subunit highlighted from a side perspective. (b) The top view displays the fourfold symmetry architecture of TRPV1, showing the domain-swap interaction between S1-S4 and PD. (c) The simplified schema of fourfold symmetry architecture of TRPV1, showing the domain-swap interaction between S1-S4 and PD. (d)The six-transmembrane structure of TRPV1(in green) (PDB code: 7l2h). (e) The simplified schema of six-transmembrane structure of TRPV1 within the plasma membrane. The structure of TRPV1consists of six transmembrane helices (S1 to S6), a pore loop between S5 and S6, the N-terminal domain and the C-terminal domain. This was Created with figdraw.com. Figs. 1c and e were generated using figdraw (figdraw.com) and adapted with permission.

Overall, the structural study of TRPV1 has significantly advanced our understanding of its role in sensory perception and other theoretical aspects. High-resolution cryo-EM has provided detailed snapshots of TRPV1 in various states(Cao, et al., 2013b; Gao, et al., 2016; Zhang, et al., 2021a; Arnold, et al., 2024), revealing how ligand binding and membrane voltage modulate its conformation. These insights have highlighted the channel's dynamic architecture, particularly the interactions between the ankyrin repeat domains (ARDs), transmembrane helices (TMDs), and the C-terminal domain (CTD), which collectively govern its gating and sensitivity to stimuli like capsaicin and heat. Despite these advances, TRPV1 exhibits a broad range of conformations—particularly those induced by temperature activation, novel ligand interactions, and its behavior in the native membrane environment—that remain incompletely characterized by existing static structures, warranting further exploration. Furthermore, the role of ARD-TMD and TMD-CTD interfaces in allosteric regulation is not fully understood. These

interactions likely underpin the channel's sensitivity to diverse stimuli, but their structural dynamics remain elusive. Finally, the structural consequences of TRPV1 variants linked to diseases are largely unexplored. Identifying how these mutations alter channel function could inform therapeutic strategies.

3 Gating mechanisms of TRPV1

3.1 Temperature sensitivity

TRPV1 was identified as the first heat-activated ion channel(Michael J. Caterina, 1997)(Fig.3). Its activation by high temperature(Michael J. Caterina, 1997; Makoto Tominaga and Brigitte E. Raumann, 1998a; Cao, et al., 2013a), which was demonstrated as early as 1997 by Julius et al. Their research indicated that vanilloid-induced pain shares a common pathway with heat-evoked responses. They studied the effects of elevated temperature on TRPV1 activity through electrophysiological and calcium Imaging methods and found that high temperature(above 43℃)activates TRPV1 at the cell level(Michael J. Caterina, 1997). Furthermore, sensory neurons from mice lacking TRPV1(TRPV1$^{-/-}$mice) are severely deficient in their responses to the noxious stimuli of heat(M. J. Caterina, 2000). Thus, TRPV1 is essential for thermal sensation (Fig.3). However, the gating mechanism of thermal sensation of TRPV1 remains elusive. The heat-induced activation of TRPV1 is the result of a drastic leftward shift of the voltage dependence of activation(Thomas Voets, 2004). Therefore, the temperature-gating of TRPV1 is closely related to voltage-gating or ligand gating of TRPV1(Thomas Voets, 2004; Matta and Ahern, 2007; Yao et al., 2010). TRPV1 is activated by temperature in a single exponential time course, occurring in mere milliseconds(Yao, et al., 2010). Miller et al,shared a thermodynamic framework to explain how TRPV1 senses high temperature(Clapham and Miller, 2011).High temperature sensitivity is due to the disparity in heat capacity between the channel's open and closed conformations. Q10 is a vital parameter in ion channel research, used to evaluate the sensitivity of ion channel activity to temperature changes, focusing on the rate of activation or opening. It refers to the ratio of the channel's activity, for instance, open probability or activation rate, at two temperatures that are 10°C apart, generally measured at physiological or experimentally important temperature ranges, like 20℃ and 30°C. Q10 is empirically related to the standard enthalpy change (ΔH^{o}) of channel gating through a quantitative relationship derived from the principles of chemical thermodynamics. The enthalpy change (ΔH^{o}) of TRPV1 is 75-100 kcal mol^{-1}and Q10 value is 40(Beiying Liu, 2003). The relatively high $Q1_{0}$ highlights the high temperature sensitivity of TRPV1(Yao, et al., 2010), and the substantial enthalpy change associated with its gating process. The temperature sensitivity of TRPV1 is affected by the transmembrane voltage, with ambient temperature changes leading to gradual shifts in the voltage dependence of channel activation(Thomas Voets, 2004). The C-terminal tail inside the cell is crucial for the thermal activation of TRPV1(Viktorie Vlachova´, 2003; Brauchi et al., 2006). Removing 31 residues from the C-terminal tail was enough to alter the functional properties of TRPV1. Furthermore, more significant effects were observed in truncations missing the last 72 amino acids of C-terminal tail, which led to reduced heat sensitivity(Viktorie Vlachova´, 2003). Furthermore, chimeric TRPV1/TRPM8 constructs have shown that the C-terminal structure following the S6 inner helix influences how temperature modulates TRPV1 channel gating behavior(Brauchi, et al., 2006). TRPV1 shares the same structural characteristics with the

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other thermosensitive TRP channels of TRPV2-TRPV4, with four subunits surrounding a central ion permeation pore. Each subunit contains six transmembrane helices (S1–S6) and intracellular N and C termini. The pore turret seems important to the thermosensation of TRPV1. Thermodynamic, functional, and structural experiments suggest that the pore turret is integral to the heat activation mechanism(Yang et al., 2010). Double-mutant cycle analysis has been used to identify more exact gating mechanism of TRPV1 temperature sensation. Ardem Patapoutian et al. have mapped TRPV1 residues that are uniquely important for temperature gating(Grandl et al., 2010). The double-mutant cycle analysis pinpointed a single residue, Y653, that exhibits a temperature-specific phenotype(Grandl, et al., 2010). Grandl et al. used the cysteine accessibility technique to investigate how single amino acids in TRPV1 change conformation with temperature(Grandl, et al., 2010). By using cysteine-accessibility experiments alongside a high-throughput functional assay, they effectively screened 52 candidate residues at two different temperatures and found that Y653 was the only residue specific to the temperature sensation of TRPV1. However, it remains unclear if the pore-loops of TRPV1 exhibit distinct structural changes upon activation by temperature or if they are structurally identical to the inactivated state. An approach involving combining high-throughput mutagenesis, functional screening, and deep sequencing to detect mutations from a pool of about 7,300 TRPV1 random mutant clones indicated that a significant reduction in amino acid hydrophobicity is negatively related to the probability of temperature-induced ion channel activation(Sosa-Pagan et al., 2017). Swartz et al. investigated the molecular mechanism of heat activation of TRPV1. They created chimeras by transplanting the pore domain of TRPV1 into the Shaker K^+ channel and tested them for their ability to sense high temperatures(Zhang et al., 2018). They showed that the pore domain of TRPV1 is a transportable domain that contains the structural elements sufficient for activation by noxious heat. The pore domain of TRPV1 plays a critical role in the temperature-sensing mechanism of the channel(Zhang, et al., 2018). Islas et al. used a multifaceted approach to investigate the role of the ARD of TRPV1 as a thermal module. The ARD of TRPV1 undergoes significant conformational changes with increasing temperature, indicating its crucial involvement in temperature-dependent structural alterations that ultimately lead to channel activation and its pivotal role in thermal sensation.(Ladron-De-Guevara et al., 2020). Lee et al. used advanced cryo-EM techniques to elucidate the gating mechanism of TRPV1, reconstituting full-length rat TRPV1 into lipid nanodiscs and capturing its structure at various temperatures in the presence of capsaicin. While capsaicin is often used to stabilize TRPV1 for structural studies, functional and mutational analyses suggest that heat and capsaicin activate the channel through different mechanisms. Alanine substitutions and mutagenesis studies further highlighted the residues critical for heat-dependent gating, including M572 and M677(Kwon, et al., 2021). Recently, Qin et al. used differential scanning calorimetry to directly measure the heat absorption of TRPV1 in reconstituted channels within vesicles. They concluded that energy changes from heat activation do affect protein stability, in which a significant number of nonpolar residues need to be transferred into the aqueous surroundings, but the partial unfolding of TRPV1 upon heat-dependent activation is essential to thermal transduction(Tuomas Haltia, 1995; Otzen, 2014; Mugo et al., 2023). Intensive structure–function studies have also been undertaken to identify functionally important molecular sites significant for TRPV1 sensing temperature. These investigations have yet to align on a consensus model or a reliable heat-sensor domain. A variety of molecular sites have been identified, but they are scattered within

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channels and lack distinct endothermic traits needed for pronounced temperature dependence. Therefore, more solid proof and experimental verification are needed to achieve a deeper understanding of the molecular mechanism of temperature sensing of TRPV1.

Because of temperature sensitivity, TRPV1 normally acts as a "thermal sensor" in the preoptic area of the hypothalamus and peripheral vasculature [13]. Its blockade disrupts homeostatic heat-dissipation pathways, leading to elevated core body temperature (hyperthermia)(Devin M. Swanson Et Al., 2005; Rowbotham Mc, 2011; Garami et al., 2020) . TRPV1 is a pivotal component of the body's thermal sensing and regulatory systems, with its temperature sensitivity being a key feature of its physiological and pathological roles.

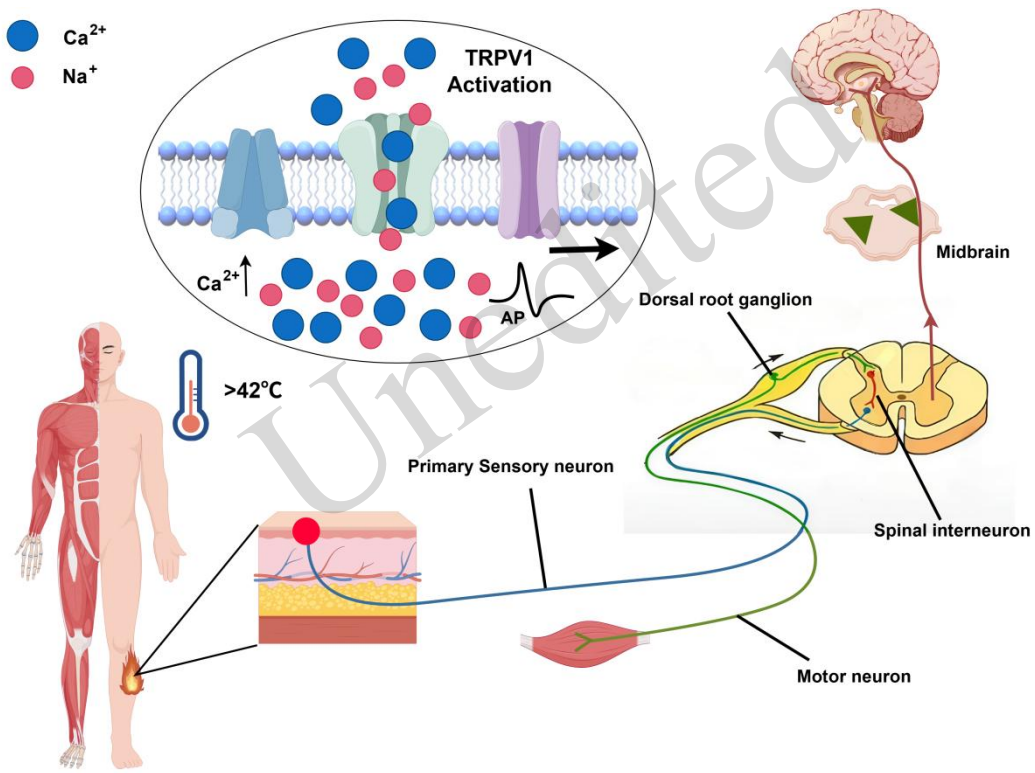

Fig.2: Heat sensation mechanism of TRPV1. TRPV1 is expressed on the terminal membranes of primary afferent neurons. When exposed to temperatures of 42°C or higher, TRPV1 undergoes a conformational shift, transitioning from an inactive to an active state. This activation triggers permitting the influx of calcium (Ca^{2+}) and sodium (Na^{+}) ions into the neuron. The resulting depolarization generates an action potential, which propagates along the nerve fiber. This electrical signal is then transmitted to the central nervous system, where it is interpreted as thermal sensation, thus completing the sensory feedback loop for high-temperature detection. Fig.2 was generated using figdraw (figdraw.com) and adapted with permission.

3.2 Ligand gating characteristics

TRPV1 is modulated by various chemical stimuli, including capsaicin(Michael J. Caterina, 1997), low pH(Makoto Tominaga and Brigitte E. Raumann, 1998b; Aneiros et al., 2011; De La Roche et al., 2016; E.A. Tsvetkov1, 2016), phosphatidylinositol 4,5-bisphosphate (PIP2)(Arnold, et al., 2024), divalent cations

such as $Mg2^{+}$ and $Ba2^{+}$(Ahern et al., 2005; Cao et al., 2014; Yang et al., 2014) and some animal toxins(Siemens et al., 2006; Bohlen et al., 2010; Yang et al., 2015b).

Upon capsaicin activation of TRPV1, sodium and calcium ions influx through TRPV1, depolarizing nociceptive neurons, which triggers action potential firing and ultimately elicits the sensation of spiciness(Michael J. Caterina, 1997). The existence of a capsaicin receptor was suggested as early as 1975 by Szolcsányi and Jancsó-Gábor (Szolcsanyi and Jancso-Gabor, 1975). The receptor was subsequently cloned from rat dorsal root ganglia in 1997 by Caterina et al.[24] and identified as TRPV1(Craig Montell, 2002). The EC_{50} value for capsaicin-induced activation of TRPV1 has been consistently reported in the range of 0.04–0.29 μM across multiple studies(J N Wood 1, 1988; Caterina et al., 1997; Jordt and Julius, 2002), with specific measurements including 0.29 μM in HEK293 cell models(Caterina, et al., 1997) , reflecting variation in experimental conditions such as cell type and assay sensitivity. The activation of TRPV1 by capsaicin has been extensively studied, revealing that capsaicin binds to a specific pocket within the transmembrane domain of TRPV1, stabilizing the open state of the channel and allowing cation influx, which is crucial for its role in nociception(O'neill et al., 2012). Zheng et al. used an iterative approach combining structural computation, functional analyses, and cryo-EM information to investigate how the capsaicin binds to TRPV1(Yang et al., 2015a). Jiezheng et al. and Julius et al. found that capsaicin activates TRPV1 by binding to a specific pocket within the channel(Liao, et al., 2013; Yang, et al., 2015a).The location of the capsaicin-binding pocket, formed by S3, S4 and the S4-S5 linker within the membrane, was previously determined by cryo-EM structures(Liao, et al., 2013). However, crucial details for understanding the mechanism are missing. Then, it was confirmed that the vanillyl group and amide neck of capsaicin form crucial hydrogen bonds with residues in the channel, while the aliphatic tail interacts non-specifically through van der Waals forces. Capsaicin stabilizes the open state by "pull-and-contact" interactions between the vanillyl group and the S4-S5 linker, allowing sodium and calcium ions to influx and depolarize nociceptive neurons(Yang, et al., 2015a).

Low pH is another significant activator of TRPV1(Makoto Tominaga and Brigitte E. Raumann, 1998b), as protons can directly gate the channel(Fig.2). Protons were shown to activate TRPV1 when the extracellular pH was lowered to about 6(Aneiros, et al., 2011; De La Roche, et al., 2016). Grimm et al. used the whole-cell patch-clamp technique to investigate the proton gating of TRPV1 channels and concluded that protons activate and potentiate TRPV1 by shifting the voltage dependence of the activation curves towards more physiological membrane potentials. A key residue, F660 in S6, was identified as critical for both proton activation and potentiation. Mutations at this position abolished proton-mediated gating while preserving capsaicin and heat responsiveness(Aneiros, et al., 2011). TRPV1 proton sensing is tightly linked to voltage-dependent gating and suggest that F660 serves as the key integrator of proton-mediated activation and potentiation. The proton-mediated activation of TRPV1 is crucial for the channel's role in detecting acidic environments, which often occur during tissue injury or inflammation. Furthermore, studies have identified E600 and E648, two negatively charged residues, as essential for the response of TRPV1 to extracellular protons(Jordt et al., 2000; Ahern, et al., 2005). E600 is located in an extracellular loop that moves significantly when the TRPV1 channel opens(Cao, et al., 2013b), indicating that protonation of E600 interferes with hydrogen bonds that maintain the apo state. Further research showed that when E600 undergoes protonation, it disrupts a salt bridge with R455 in the neighboring subunit's voltage-sensor-like domain (VSLD), leading to the

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destabilization of the apo conformation(Zhang, et al., 2021a). Meanwhile, when E648 in the pore helix is protonated, its interactions with K639 are weakened, further setting the channel up for activation(Zhang, et al., 2021a).

Phosphoinositides (phosphoinositol lipids) play a critical role in modulating TRPV1 activity. They include mainly phosphatidylinositol (PI) and its various phosphorylated derivatives, such as phosphatidylinositol-4-phosphate (PIP), and phosphatidylinositol-4, 5-diphosphate (PIP2 or PI(4,5)P2), etc. They have been investigated widely through a multifaceted approach including cryogenic electron microscopy (cryo-EM) and patch clamp recordings (Klein et al., 2008; Cao, et al., 2013a; Senning et al., 2014; Arnold, et al., 2024). Research has showed that PIP2 has a dual role in TRPV1 regulation, where its influence is determined by the membrane leaflet in which it is located(Senning, et al., 2014). When PIP2 is on the intracellular leaflet, it potentiates TRPV1 activity, while when on the extracellular leaflet, it inhibits the activity but only at higher concentrations. Another study showed that TRPV1 channels are intrinsically heat-sensitive and that phosphoinositide lipids, including PIP2, negatively regulate this sensitivity. The study reconstituted TRPV1 in artificial liposomes and found that the introduction of various phosphoinositides inhibited TRPV1 activity, supporting a model in which the turnover of phosphoinositide contributes to thermal hyperalgesia by disinhibiting the channel(Cao, et al., 2013a). Additionally, research has shown that PIP2 is the endogenous lipid regulating TRPV1, as opposed to other phosphoinositides like PI(4)P or PI(3,4,5)P3. This specificity was highlighted using recombinant pleckstrin homology domains, which showed that depletion of PIP2 inhibits capsaicin-activated TRPV1 currents, whereas other phosphoinositides do not support TRPV1 function(Klein, et al., 2008). This specificity underscores the critical role of PIP2 in TRPV1 regulation and highlights the importance of precise lipid-protein interactions in cellular signaling pathways. Recent studies have provided a deeper understanding of the structural and functional nuances of the interactions between phosphoinositides and TRPV1. They show that the vanilloid binding pocket (VBP) of TRPV1 can accommodate a variety of lipid species, including phosphoinositides and the inflammatory lipid lysophosphatidic acid (LPA). The presence of PI or PIP2 in the VBP stabilized the closed state of the channel, while their removal or displacement by agonists like LPA promoted channel opening(Arnold, et al., 2024). The authors used diC8-PIP2, a soluble analog of PIP2 with shortened acyl tails, for further experiments. They found that diC8-PIP2(short-chain PIP2) was a potentiator, and full-length PIP2 was an inhibitor of rat TRPV1, similarly to PI(Arnold, et al., 2024). A single ligand can attach to the same pocket, but its inositol headgroup can occupy two different positions linked to either closed or open pore states. This comprehensive structural understanding clarifies a previous puzzle by showing how diC8-PIP2 and full-length PIP2 can influence TRPV1 function differently. Furthermore, the presence of the resident PI lipid keeps TRPV1 closed, whereas its removal leads to the open state(Arnold, et al., 2024). Then, Szőke et al. investigated the effects of lipid raft disruption by methyl-beta-cyclodextrin (MCD) and sphingomyelinase (SMase) on TRPV1(Payrits et al., 2024). They found that MCD and SMase treatment inhibited capsaicin-induced TRPV1 ion channel activation, which indicates that lipid raft disruption inhibits the activation of TRPV1.

Divalent cations, including $Mg2^{+}$ and $Ba2^{+}$, also can activate TRPV1. Zheng et al. used mutagenesis to systematically alter sequences in various regions of the TRPV1 channel, followed by functional assessments using electrophysiological recordings and concluded that divalent cations activate

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TRPV1(Yang, et al., 2014). According to another study by Zheng et al. $Mg2^{+}$ and $Ba2^{+}$ were found to potentiate TRPV1 activation mainly by lowering the heat activation threshold(Cao, et al., 2014). $Mg2^{+}$ activates TRPV1 by promoting conformational changes in the extracellular regions of the channel. Furthermore, mutations in the extracellular S1–S2 linker and pore turret significantly diminished divalent cation-induced activation, thus, the extracellular S1–S2 linker and pore turret are essential for divalent cation activation of TRPV1. Mg^{2+}binds to negatively charged residues in the extracellular loops of TRPV1, triggering a cascade of conformational changes. These alterations stabilize the channel in an "open" state by repositioning the S1-S2 and S3-S4 linkers, that connect transmembrane helices (S1-S4) to the pore domain (S5-S6). Mg^{2+} binding induces outward movement of S1-S2 linkers, disrupting interactions that stabilize the closed state. This repositioning widens the lower gate (S6 helix bundle crossing), facilitating cation influx. Mg^{2+} binding the S3-S4 linker causes inward tilting of the linker, which couples to the S1-S2 movement via allosteric networks. This dual action ensures coordinated opening of the pore.

Oleic acid, a monounsaturated fatty acid, has been proposed to have potential in modulating TRPV1 activity and influencing pain pathways. Oleic acid is released by sensory neurons and has been shown to inhibit TRPV1-mediated thermal hypersensitivity via the GPR40 receptor, also known as FFAR1. This interaction suggests a protective mechanism in which oleic acid acts as a feedback inhibitor, preventing excessive nociceptive signaling through the TRPV1 channel. The inhibition of TRPV1 by oleic acid involves a calcineurin (CaN) and GPR40-dependent pathway, highlighting the complex interplay between lipid mediators and ion channels in sensory neurons(Sendetski et al., 2024).

TRPV1 can be modulated by various animal toxins, including DkTx, RhTx, and RhTx2. These toxins have been extensively studied to understand their molecular mechanisms of binding and modulation of TRPV1 activity. DkTx, a tarantula toxin, identified by Julius et al. is known for its unique bivalent structure, which allows it to lock TRPV1 in its open state, leading to irreversible channel activation. This toxin binds to the outer edge of the TRPV1 external pore in a counterclockwise configuration, using a limited protein-protein interface and inserting hydrophobic residues into the bilayer. This binding disrupts a cluster of hydrophobic residues behind the selectivity filter, which is critical for channel activation(Bohlen, et al., 2010; Bae et al., 2016). Lai et al. found that a series of animal toxin peptides extracted from red headed centipedes potently activate TRPV1. The toxin targets the outer pore region of TRPV1, causing heat activation and eliciting pain behavior in mice(Yang, et al., 2015b). Zeng et al. isolated and identified two novel peptide neurotoxins, Hainan toxin-XXI (HNTX-XXI) and Hainan toxin-XXII (HNTX-XXII), from the venom of the Chinese spider Ornithoctonus hainana, which activate the TRPV1 channel with high specificity. Then, key amino acid residues in TRPV1 were identified that mediate the interaction with HNTX-XXI and HNTX-XXII. Specifically, L465, V469, and D471 are crucial for the activation of TRPV1 by HNTX-XXI, while A657, F659, E600, and R601 play a pivotal role in activation by HNTX-XXII(Chen et al., 2024). Overall, these studies highlight the diverse mechanisms by which animal toxins and other modulators interact with TRPV1, providing valuable insights into the channel's structure and function.

RTX, a potent ultrahot capsaicin analog derived from the latex of different Euphorbia cactus species exerts its biological effects mainly through selective modulation of TRPV1(Seabrook, et al., 2002; Elokely et al., 2016). Middleton et al. investigated the interaction between RTX and TRPV1 by molecular biology techniques and radioligand binding studies(Margaret Z. Chou, 2004). RTX binds with high affinity to the

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capsaicin receptor TRPV1, specifically at the pore-facing side of the S4 helix. This binding was shown to be specific and saturable, with RTX competing for the same binding site as capsaicin and capsazepine. Furthermore, mutations in the S4 domain affected RTX binding affinity, suggesting that this region is critical for RTX-TRPV1 interaction. Carnevale et al. then used cryo-electron microscopy (cryoEM) to obtain structural insights into the TRPV1 channel in its apo form and in complex with capsaicin and RTX, characterizing the protein-ligand contacts and the role of individual water molecules in the binding process(Elokely et al., 2015).

3.3 Voltage-gated characteristics

One of the intriguing aspects of TRPV1 is its sensitivity to membrane potential, which plays a significant role in modulating its activity. Unlike classic voltage-gated ion channels, TRPV1 does not derive its voltage sensitivity from the S4 segment. Instead, outer pore acidic residues are directly involved in voltage-sensitive activation, with their negative charges collectively constituting the observed gating charges. This unorthodox voltage-gating process provides a mechanistic foundation for understanding polymodal gating of TRPV1 and opens the door to novel approaches for regulating channel activity, particularly in pain management(Yang et al., 2020).

Bolshakov et al. investigated the impact of two structurally related non-toxic gating modulators, NH17 and NH29, on the voltage sensor (VSD) sensitivity of different voltage-gated cation channels (VGCCs). NH17 acts as an activator of TRPV1 current, whereas NH29 functions as a blocker, with EC_{50} and IC_{50} values ranging between 4 and 40 μM. Both NH17 and NH29 target the VSD of TRPV1 channels and engage in π-π stacking, hydrogen bonding, and hydrophobic interactions, similar to vanilloid analogs. Subtle differences in the VSD-ligand interface determine whether the gating modulator stabilizes the channel in the closed or open state, indicating that the voltage-gating mechanism of TRPV1 is crucial for its proper functioning(E.A. Tsvetkov1, 2016). Recent studies have further elucidated the structural basis of voltage sensitivity of TRPV1. They have shown that the outer pore is not only important for temperature sensitivity but also plays a role in the channel's voltage sensitivity, as it is involved in the gating mechanism that responds to changes in membrane potential(Yang, et al., 2020).

The response of TRPV1 to voltage is predicted to be key in modulating pain reactions. The channel's responses to each of its stimuli are profoundly regulated by membrane potential, which can dampen or even prohibit its response at negative voltages while amplifying its response at positive voltages. This voltage-dependent modulation is crucial for the channel's function as a nociceptor, as it allows TRPV1 to integrate multiple signals and respond appropriately to different physiological conditions(Grandl, et al., 2010; Yang, et al., 2020).The voltage sensitivity of TRPV1 is not unique among ion channels. Mechanosensitive PIEZO channels, which are critical for normal physiology, are also modulated by voltage and can switch to a purely voltage-gated mode. This suggests that voltage sensitivity is a deep property that can be co-opted to add a regulatory mechanism for channel activation in different cellular contexts(Moroni et al., 2018).

The voltage-gated properties of TRPV1 are crucial for its role as a polymodal nociceptor, enabling it to integrate various signals and react suitably to diverse physiological states, making it an important target for pain management and other therapeutic interventions. Despite progress, the precise molecular interactions and conformational changes in VSD of TRPV1 during gating remain incompletely

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understood. The role of specific residues and domains in voltage sensing and channel opening needs further elucidation.

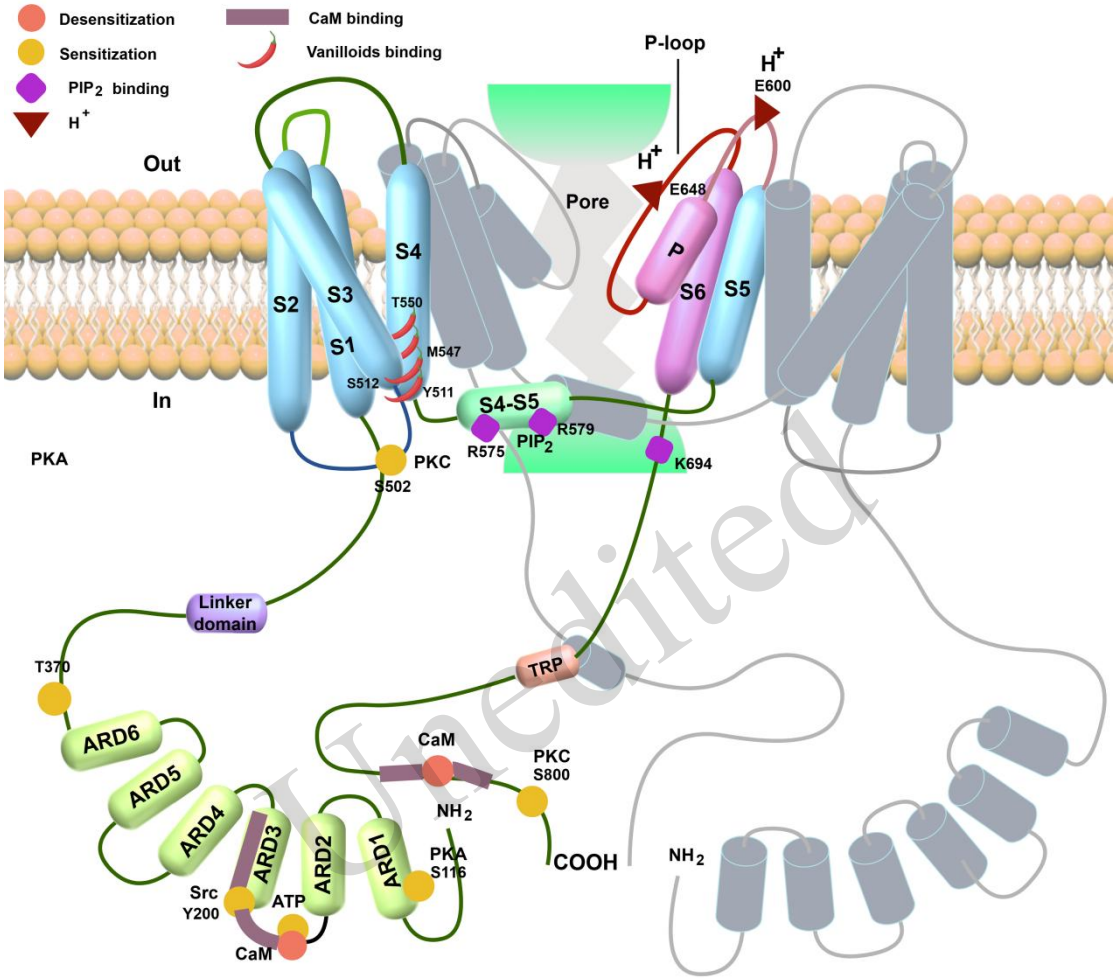

Fig.3: Diagrammatic representation of the TRPV1 channel's membrane structure highlighting key functional areas. Comprising four TRPV1 subunits (one of them in cyan), the TRPV1 channel forms a tetramer. Between the S5 and S6 helices lies the pore loop, and both the N and C termini are located inside the cell. Amino acid residues or binding pockets specific for capsaicin and proton activation, as well as residues important for toxins binding, phosphorylation by protein kinases A and C (PKA, PKC) and Ca^{2+} - calmodulin - dependent kinase II (CaMKII) kinases are highlighted. Fig.3 was generated using figdraw (figdraw.com) and adapted with permission.

4 TRPV1 in diseases and therapeutics

TRPV1 serves as a crucial component in various systems, including sensory, metabolic systems and neurological systems. As a nonselective cation channel, TRPV1 is widely expressed in sensory nerve fibers and non-neuronal cells, including vascular endothelial cells, smooth muscle cells, and immune cells. In the context of diseases, TRPV1 plays a significant role in various physiological and pathological processes.

It is particularly noted for its involvement in pain management, inflammation, cancer and metabolic disorders, and neurodegenerative diseases.

4.1 TRPV1 and pain

The distribution of TRPV1 in both peripheral and central terminals of sensory neurons underscores its importance in initiating action potentials(Holzer, 1991) and modulating neurotransmitter release(Holzer, 1988), which are essential processes in pain signaling pathways(Fig.4). TRPV1 is activated by various physical and chemical stimuli, including heat, protons, and capsaicin, making it a critical player in the detection of nociceptive (M. J. Caterina, 2000)and thermal inflammatory pain(Holzer, 1988) . Extensive research has highlighted the significant role of TRPV1 channel in different types of pain, such as neuropathic(Szallasi, 2024), cancer-related pain(Szallasi, 2024), and migraines(Gao et al., 2025). This multifaceted role of TRPV1 in pain perception makes it an attractive target for analgesic interventions.

TRPV1 antagonists have shown potential in treating chronic pain conditions. They can reduce pain by blocking the receptor's activation by noxious stimuli, which are known to trigger pain pathways(O'neill, et al., 2012; Yekkirala et al., 2017). Parsadaniantz et al. have investigated the role of capsazepine on corneal pain syndrome. Capsazepine, a competitive antagonist of TRPV1, effectively inhibited the activation of TRPV1, thereby blocking the transmission of pain signals and reducing pain perception(Fakih et al., 2021).The compound SB-366791, recognized as a potent and selective inhibitor of the TRPV1 channel, holds promising potential in the field of analgesia(Gunthorpe et al., 2004; Mazeto et al., 2020).

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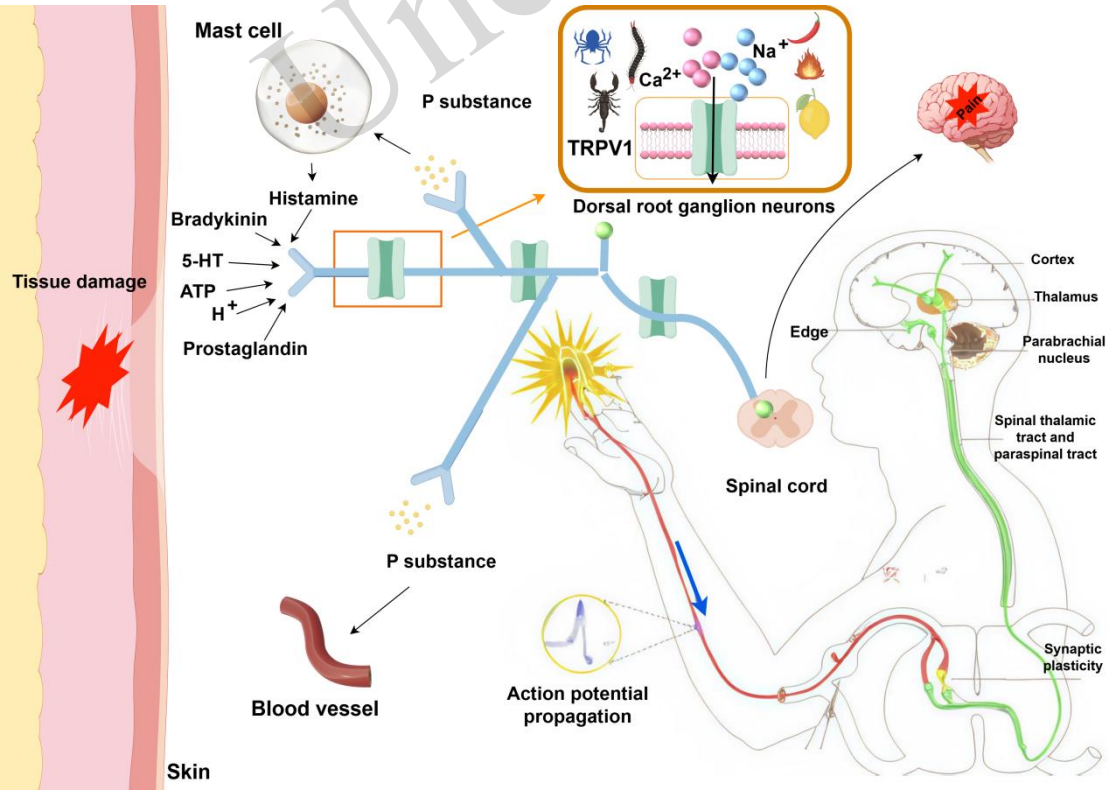

Fig.4: Pain sensation mechanism of TRPV1. The release of pain-inducing substances (such as histamine, substance P, prostaglandins, and 5-HT) in the body, caused by tissue damage or other factors, can to some extent activate TRPV1 receptors expressed on the membranes of primary afferent nerve terminals. This activation mediates the influx of calcium

and sodium ions, leading to depolarization, generation of action potentials, and triggering a series of intracellular signaling pathways. These pathways result in the release of neurotransmitters and the transmission of pain signals. TRPV1 itself can also be activated by capsaicin, high temperatures, acidic environments, and several toxic molecules, thereby mediating pain responses. Fig.4 was generated using figdraw (figdraw.com) and adapted with permission.

TRPV1 agonists, such as capsaicin, have been used topically to treat neuropathic pain and chronic pain conditions. The high-concentration (179mg) capsaicin patch (HC capsaicin patch), referred to as the capsaicin 8% topical system in the USA, offers a topical therapeutic approach for addressing peripheral neuropathic pain (pNeP) in adults. It can be administered either as a standalone treatment or in conjunction with other analgesic medications(Derry et al., 2017; Sendel et al., 2023; Freynhagen et al., 2025). By binding to TRPV1, capsaicin depletes substance P—a neuropeptide critical for transmitting pain signals from sensory nerves to the spinal cord—along with other neurotransmitters from primary afferent terminals, thereby reducing nociceptive input to the central nervous system (CNS). In addition to depleting neuropeptides, capsaicin, such as that in the Qutenza transdermal patch, exerts its analgesic effect by inducing mitochondrial swelling in nociceptor nerve endings This was evidenced by studies showing mitochondrial changes in specific dorsal root ganglion neurons post-capsaicin treatment, potentially linked to long-lasting desensitization of nociceptive neurons(Chiba et al., 1986).This mechanism of action has made capsaicin-based creams and patches a popular choice for the management of pain(Salat et al., 2014). As for low-concentration capsaicin, one study concluded that out of 13 patients treated with low concentration capsaicin, five were classified as having good-to-excellent responses to pain relief, with 8 (62%) showing at least a 50% improvement(Watson and Evans, 1992). The mechanism is considered to involve the release of somatostatin neuropeptide, which provides antinociceptive benefits, from nociceptor nerve endings(Pintér et al., 2022). However, the data were inadequate to determine the effectiveness of low-concentration capsaicin for treating pain(Derry and Moore, 2012).

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Some components extracted from venomous animals or plants are among the exogenous agents that affect TRPV1.By regulating the activation of TRPV1, these molecules can block the transmission of pain signals and reduce pain perception. Research has shown that RTX significantly alleviates TNF-α-induced mechanical allodynia and thermal hyperalgesia. Specifically, RTX administration abolished the TNF-α-induced reduction in paw withdrawal thresholds observed 24 h post-TNF-α injection(Leo et al., 2017). RTX-induced analgesic effect is due to its high affinity for TRPV1,thereby desensitizing TRPV1 and blocking pain(Szallasi, 2023). RTX is being tested in clinical trials as a 'molecular scalpel' to provide lasting pain relief for severe osteoarthritis(Medicine, 2019) and in cancer patients experiencing persistent, severe pain(Medicine, 2008). Another TRPV1 antagonist toxin, named PnTx3-5, was discovered in the venom of the armed spider Phoneutria nigriventer and is used in vivo to relieve neuropathic and cancer-related pain(Oliveira et al., 2016). Moreover, after administering this toxin in the post-operative pain model, no mechanical hyperalgesia was detected, even in mice tolerant to morphine(Oliveira, et al., 2016). In rat trigeminal ganglia, PnTx3-5 reduced CAP-induced glutamate release in a dose-dependent manner, achieving maximum inhibition at a concentration of 100 nM (Oliveira, et al., 2016). The pain-relieving effect is a result of PnTx3-5 blocking the pain signal in sensory neurons. The specific site where the toxin attaches to TRPV1 is yet to be discovered. Understanding its precise binding site and mechanism of action could provide valuable insights into the development of

novel analgesics and neuroprotective agents. The exploration of its interactions with TRPV1 and other potential targets remains an important area of research, with implications for treating pain and preventing excitotoxicity in neurological disorders. Heteractis crispa, a type of sea anemone, generates multiple venomous polypeptides such as APHC1 and APHC3, which target TRPV1(Andreev et al., 2008). APHC1 and APHC3 consist of 56 amino acids and have notable pain-relieving and antinociceptive effects(Andreev et al., 2013). APHC1 injection, whether given intravenously or intramuscularly, reduces acute pain caused by an intraplantar CAP injection or by immersing the tails of the mice in hot water. Injecting these toxins intravenously also inhibited behavior induced by formalin and counteracted hyperalgesia caused by CFA. Significantly, the toxins led to hypothermia instead of hyperthermia in animal tests(Andreev, et al., 2013), suggesting their specific inhibitory effect was applied in vivo to achieve analgesia without the hyperthermia typically induced by most TRPV1 antagonists. HCRG21 is a peptide consisting of 56 amino acids, originating from the same sea anemone species, Heteractis crispa. It has structural similarities with APHC peptides, sharing 89 to 93% sequence homology with APHC1-3. In animal experiments, HCRG21 shown analgesic properties. HCRG21 alleviates local inflammation and both mechanical and thermal hyperalgesia caused by carrageenan injection into the foot of mice(Sintsova et al., 2021), while also lowering the levels of the pro-inflammatory cytokine TNF-α in the bloodstream(Peter M. Blumberg, 2011). In summary, these toxins serve as essential pharmacological tools, offering new pathways to develop treatments for acute and inflammatory pain. However, natural toxins also have some drawbacks, such as the time-consuming and costly screening process, poor specificity, and severe side effects(Knapp et al., 2012).

Recent research has focused on the development of novel TRPV1 modulators with improved selectivity and reduced side effects. These modulators aim to target specific pain pathways while minimizing off-target effects, leading to more effective and safer pain management strategies(Neuberger, et al., 2023). The development of TRPV1 antagonists has faced challenges, particularly due to side effects like hyperthermia, which have limited their clinical use(Szolcsanyi and Sandor, 2012).

4.2 _TRPV1 and inflammation

TRPV1 is a well-known mediator of inflammation, playing a significant role in various physiological and pathological processes. Its activation leads to the influx of calcium ions, which can trigger a cascade of intracellular events resulting in inflammation. In the context of inflammation, TRPV1 has been shown to be upregulated in response to inflammatory mediators, contributing to the sensitization of sensory neurons and the development of hyperalgesia. Tang et al. showed that Angelica dahurica extracts (ADE) significantly attenuate chronic inflammatory pain in mice by targeting TRPV1 ion channels, which play a pivotal role in pain transduction(Zhu et al., 2022). Oral administration of ADE reduced mechanical and thermal hypersensitivity in a CFA-induced pain model, accompanied by decreased TRPV1 activity and protein expression in dorsal root ganglion (DRG) neurons. TRPV1 is found in glial cells like microglia and astrocytes within the CNS, contributing to neuroinflammation. The activation of TRPV1 in these cells can cause the release of inflammatory agents, which may contribute to neurological disorder pathophysiology. TRPV1 has been implicated in the activation of the NLRP3 inflammasome in microglia, a key component of the inflammatory response in multiple sclerosis and other neurodegenerative

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diseases(Zhang et al., 2021b). Another study found that expression of TRPV1 and its downstream molecules (such as pPKA, pPI3K and pPKC) was upregulated in the hippocampus and prefrontal cortex (PFC) of Parkinson's disease dementia (PDD) mice, suggesting the crucial rule of TRPV1 in the modulation of neuroinflammation in PDD mice(Tsai et al., 2021). In the respiratory system, TRPV1 has been shown to mediate airway inflammation and hyperresponsiveness, particularly in response to environmental pollutants like fine particulate matter (PM2.5). Blocking TRPV1 can reduce lung inflammation and improve airway function, highlighting its potential as a therapeutic target in respiratory diseases(Xu et al., 2019). In the gastrointestinal tract, TRPV1 is involved in the inflammatory processes associated with conditions such as colitis and gastroesophageal reflux disease. Studies have shown that TRPV1 expression is increased in the inflamed tissues of these conditions, and its modulation can alleviate symptoms and reduce inflammation(Lapointe et al., 2015; Zhang et al., 2020). Research has shown that the levels of inflammatory factors such as IL-1β, IL-6, TNF-α, and PGE2 in the peritoneal lavage fluid and serum of mice with endometriosis are significantly elevated.This effect is closely associated with the expression of TRPV1/TRPA1 heteromers in ectopic endometrial tissues and the polarization state of macrophages(Hai Zhu 2022). In the skin, TRPV1 is found in keratinocytes, mast cells, and endothelial cells, where it acts as a nociceptive sensor and potentiates the inflammatory response. Studies have shown that TRPV1 activation in these cells can lead to the release of pro-inflammatory cytokines and the promotion of cutaneous neurogenic inflammation(Gouin et al., 2017; Marek-Jozefowicz et al., 2023). A clinical trial investigated the multifaceted contributions of TRPV1 in driving and sustaining inflammation in psoriasis(Medicine, 2021). Furthermore, TRPV1 is closely involved in the corneal wound repair process. Ablation of $TRPV1^+$ sensory nerves with RTX and blockade of TRPV1 with AMG - 517 delayed corneal wound closure and increased the infiltration of neutrophils and γδ T cells to the wounded cornea after epithelial abrasion. This suggests that $TRPV1^+$ sensory nerves play a crucial role in corneal wound healing by modulating the inflammatory response through RAMP1 and SSTR5 signaling(Liu et al., 2022). The crosstalk between $TRPV1^+$ sensory nerves, immune cells, and inflammatory mediators, including the feedback sensitization of $TRPV1^+$ sensory nerve fibers by immune-released factors, requires more in-depth exploration.

Overall, TRPV1 is a critical player in the modulation of inflammatory responses across various tissues and organ systems. Its widespread expression and involvement in both neuronal and non-neuronal inflammation make it a promising target for therapeutic interventions aimed at treating inflammatory diseases. Further research into the specific mechanisms by which TRPV1 contributes to inflammation will be essential for the development of targeted therapies that can effectively modulate its activity and alleviate inflammatory symptoms.

4.3 TRPV1 and cancer

TRPV1 has a diverse role in cancer. It has been implicated in the regulation of tumor microenvironments, where its activation can modulate immune responses and inflammation, potentially affecting tumor growth and metastasis. In glioma, TRPV1 acts as a suppressor of tumor growth. Its activation induces apoptosis and reduces cell migration and proliferation via the Akt signaling pathway. This underscores the potential of TRPV1 as a therapeutic target for glioma, since its inhibition or silencing results in enhanced tumor growth in vivo(Cheng et al., 2024). TRPV1 has been shown to influence the

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immune microenvironment in colorectal cancer, where its gain-of-function can promote tumor initiation and progression by altering macrophage activation and shifting immune responses towards a Th2 phenotype, which is often associated with tumor-promoting environments(Jiang et al., 2022). In gastric cancer, TRPV1 has been identified as a tumor suppressor. Its expression is significantly downregulated in gastric cancer tissues, and its overexpression can inhibit cancer cell proliferation and migration through a novel $Ca2^{+}$/CaMKKβ/AMPK pathway. This suggests that TRPV1 could be a potential target for gastric cancer prevention and therapy(Gao et al., 2020). Additional studies on gastric cancer indicate that the role of TRPV1 is influenced by SUMOylation, a post-translational modification that enhances its tumor-suppressive properties. SUMOylation of TRPV1 increases its membrane expression, leading to elevated intracellular $Ca2^{+}$ influx and activation of the AMP-activated protein kinase (AMPK) pathway, which inhibits GC cell proliferation and migration(Yang et al., 2024). Similarly, in melanoma, TRPV1 expression is reduced, and its activation has been shown to inhibit melanoma growth by inducing apoptosis through the calcineurin-ATF3-p53 pathway(Yang et al., 2018). In non-small cell lung cancer (NSCLC), TRPV1 is associated with tumor advancement. Elevated TRPV1 levels are linked to a negative prognosis, and reducing its expression leads to decreased cell growth and heightened cell death. This effect occurs via the $Ca2^{+}$-IGF 1R signaling pathway, which also impacts the immune response by altering the infiltration of different immune cells, thereby influencing tumor growth and immune evasion(Wang et al., 2024).The involvement of TRPV1 in cancer is not limited to its expression in cancer cells. It also plays a role in the modulation of cancer-related pain, which is a significant concern in cancer management. TRPV1 antagonists have been explored as potential analgesics for cancer pain, although their development has been challenging due to side effects such as hyperthermia(Voight et al., 2014). Research underscores the importance of TRPV1 as a tumor suppressor in colorectal cancer (CRC), with its expression being significantly diminished in cancerous tissues compared to healthy tissues. The activation of TRPV1 by capsaicin, a known agonist, was found to inhibit CRC growth and induce apoptosis through the activation of the p53 signaling pathway. This suggests that TRPV1 could be a potential target for CRC therapy by promoting apoptosis and inhibiting proliferation(Hou et al., 2019). Furthermore, in addition to directly affecting tumor cells, TRPV1 plays a role in the tumor microenvironment and the immune system. A pan-cancer analysis revealed that increased TRPV1 expression was connected to more favorable clinical outcomes and inversely related to markers of tumor proliferation and immunosuppressive signals, suggesting that TRPV1 could enhance the antitumor immune response(Nie et al., 2022).

Overall, TRPV1 represents a promising target in cancer therapy, not only for its direct effects on tumor cells but also for its role in modulating the tumor microenvironment and cancer-associated pain. Future research should focus on developing TRPV1 modulators that can selectively target its cancer-related functions while minimizing adverse effects. This could lead to novel therapeutic strategies that improve cancer treatment outcomes and patient quality of life.

4.4 TRPV1 and metabolic disorders

Recent research has emphasized the role of TRPV1 in metabolic health and diseases. For instance, TRPV1 activation has been shown to improve exercise endurance and energy metabolism through the upregulation of PGC-1α in skeletal muscles. This suggests a potential therapeutic strategy for managing

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metabolic diseases and enhancing exercise performance(Luo et al., 2012). Moreover, TRPV1 pain receptors have been implicated in regulating longevity and metabolism via neuropeptide signaling. Mice lacking TRPV1 receptors exhibit a youthful metabolic profile at an advanced age, indicating that TRPV1 may influence metabolic health and lifespan. The absence of TRPV1 in these mice leads to decreased production of the neuropeptide CGRP, promoting insulin secretion and metabolic health, highlighting the receptor's role in metabolic regulation(Riera et al., 2014). The interaction between TRPV1 and lipids is another area of interest, as TRPV1 is involved in the regulation of lipid metabolism through complex mechanisms that include the modulation of uncoupling proteins and ATP-binding cassette transporters. These interactions suggest that TRPV1 could be targeted to address hyperlipidemia and associated metabolic disorders(Abdalla et al., 2022). It has been reported that TRPV1 regulates ApoE4-disrupted intracellular lipid homeostasis and decreases synaptic phagocytosis by microglia. Activation of TRPV1 with capsaicin can reverse lipid metabolic impairments and improve memory and neuronal autophagy in ApoE4 mice, suggesting a therapeutic potential for TRPV1 in neurodegenerative diseases associated with metabolic dysfunctions(Wang et al., 2023). Recent research found that capsaicin treatment significantly reduced lipid droplet accumulation and improved mitochondrial function in HepG2 cells. In obese mice fed a high-fat, high-sugar diet, capsaicin reduced body weight gain, restored hepatic circadian rhythm, and modulated the expression of lipid-related genes(Cao et al., 2025). Furthermore, TRPV1 channels have been linked to the regulation of thermogenic adipocytes. Vascular smooth muscle-derived $TRPV1^+$ progenitors have been identified as a source of cold-induced thermogenic adipocytes, which play a role in energy expenditure and thermoregulation. This discovery points to TRPV1 as a potential target for obesity treatment by promoting the development of thermogenic adipocytes (Shamsi et al., 2021). The connection between TRPV1 and metabolic disorders extends to its interaction with the endocannabinoid system, which plays a role in energy homeostasis. The endocannabinoid system, including TRPV1, is involved in lipid and glucose metabolism, and its modulation could offer new therapeutic avenues for metabolic syndrome(Silvestri and Di Marzo, 2013). TRPV1 has been associated with metabolic syndrome and osteoarthritis pain(Valdes et al., 2011), where common molecular mechanisms, including the regulation of the endocannabinoid system and gut dysbiosis, are shared. These interlinked mechanisms suggest that targeting TRPV1 could alleviate both metabolic and pain-related symptoms in osteoarthritis.

In summary, TRPV1 is a multifaceted receptor involved in various aspects of metabolic regulation, from energy metabolism and lipid homeostasis to thermogenesis and pain modulation. Its diverse roles make it a promising target for therapeutic interventions in metabolic disorders.

4.5 TRPV1 and neurodegenerative diseases

TRPV1 has attracted significant attention in the context of neurodegenerative diseases due to its involvement in neuroinflammation and neuronal function. TRPV1 is widely expressed in the CNS and plays a crucial role in modulating neuroinflammatory responses(Wang and Sun, 2023), which are a common feature of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis. TRPV1 is activated by various stimuli, including heat, low pH, and capsaicin, and its activation can influence the function of both neuronal and non-neuronal cells, particularly glial cells like microglia and astrocytes(Kong et al., 2017). The role of TRPV1 in neurodegenerative diseases is further

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underscored by its involvement in synaptic transmission and neuronal survival, making it a promising target for therapeutic intervention(Oz-Arslan et al., 2024). Recent studies have highlighted the potential of TRPV1 as a therapeutic target in neurodegenerative diseases. The activation of TRPV1 has been shown to facilitate myelin repair following demyelination by regulating microglial function, which is crucial for clearing myelin debris and promoting remyelination. This suggests that TRPV1 could be a promising target for therapeutic interventions aimed at enhancing myelin repair in diseases such as multiple sclerosis(Sun et al., 2023). Additionally, the involvement of TRPV1 in regulating neuroinflammation. and expression of TRPV1 in glial cells underscores its potential as a molecular switch in the neuro-immune axis, which could be exploited to develop new therapeutic strategies for neurodegenerative diseases(Kong, et al., 2017). The involvement of TRPV1 in neurodegenerative diseases is further supported by its interaction with other molecular pathways implicated in these conditions. For instance, TRPV1 has been associated with oxidative stress responses, which are known to contribute to neuronal damage and disease progression in neurodegenerative disorders(Azlan et al., 2022). The channel's ability to modulate calcium influx and influence cellular signaling pathways highlights its potential impact on neuronal survival and function.

TRPV1 represents a promising therapeutic target in the context of neurodegenerative diseases due to its multifaceted role in modulating neuroinflammation, neuronal function, and glial cell activity. Further research into the specific mechanisms by which TRPV1 influences these processes could pave the way for the development of novel therapeutic strategies aimed at mitigating the impact of neurodegenerative diseases(Kong, et al., 2017; Sun, et al., 2023).

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5 Conclusions

In summary, TRPV channels are a diverse family of ion channels with critical roles in physiological and pathological processes. Their unique gating mechanisms and tissue distributions make them promising targets for therapeutic intervention. With ongoing research, a deeper understanding of their functions and mechanisms will likely lead to the development of new and more effective treatments for various diseases.

Future research directions for TRPV1 are promising and multifaceted. Structurally, advancements in cryo-electron microscopy and molecular dynamics simulations hold the potential to unveil the dynamic conformational changes associated with channel gating and allosteric modulation. This could facilitate the discovery of channel modulators with improved specificity and efficacy. From a functional perspective, deciphering the intricate signaling networks and downstream effectors of TRPV1 will be crucial for understanding its role in health and disease. The development of TRPV1-targeted therapeutics, including agonists, antagonists, and allosteric modulators, could offer novel treatment strategies for pain management, inflammatory disorders, and potentially other conditions where TRPV1 dysregulation plays a pathogenic role.

TRPV1 represents a complex and versatile ion channel with broad implications for sensory biology and human health. Continued exploration of its structural and functional properties, coupled with innovative therapeutic approaches, promise to expand our understanding of TRPV1 biology and unlock

new avenues for clinical intervention.

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Author contributions

Yi LIU: Writing–original draft, Fuqin DUAN: Writing–original draft. Runpeng LIN: Writing – original draft. Subinuer SHABUERJIANG: Writing–original draft. Fan YANG: Writing–review & editing, Conceptualization. Aerziguli AIERKEN: Writing – review & editing, Conceptualization. All authors have read and agreed the final manuscript.

Compliance with ethics guidelines

Yi LIU, Fuqin DUAN, RunPeng LIN, Subinuer SHABUERJIANG, Fan YANG and Aerziguli AIERKEN have declared no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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