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Yizheng Wang *Editor*

Transient Receptor Potential Canonical Channels and Brain Diseases

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TRP Channel Classification

1

Hongyu Li

Abstract

The transient receptor potential (TRP) ion channels are named after the discovery of the photo-transducted channels in *Drosophila*. TRPs, activated by various extracellular and intracellular stimuli, play a plethora of physiological and pathological roles. There are seven families of TRPs including TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPA (ankyrin), TRPP (polycystin), TRPML (mucolipin), and TRPN (*Drosophila* NOMPC) in mammals. In yeast, the eighth TRP family was recently identified and named as TRPY. We here briefly summarize the classification and function of TRP cation channel superfamily.

Keywords

Transient receptor potential (TRP) protein • *trp* gene • Ion channel

Transient receptor potential (TRP) channels are wildly expressed on the plasma membrane in numerous types of cells, including neurons. The *trp* gene was initially identified in *Drosophila melanogaster* in the late 1960s. The first human homolog was reported in 1995. Since then about 30 *trp* genes and more than 100 TRP channels have been identified. There are seven families of TRP (a phylogenetic tree of human TRP channels is shown in Fig. 1.1): TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPA (ankyrin), TRPP (polycystin), TRPML (mucolipin), and TRPN (*Drosophila* NOMPC). In yeast, the eighth TRP family was recently identified and named as TRPY in which Y stands for yeast. TRPC, TRPV, TRPM, and TRPA are classified as Group1 TRP channels which have the strongest similarity with the *Drosophila* TRP. The Group2 TRP channels, including TRPP and TRPML, have distal relevance to *Drosophila* TRP. The classification of TRP superfamily is based on the differences in their amino acid sequences and topological structures, while it is difficult to differentiate the function of individual family and member simply according to the classification. Actually, TRPs play a plethora of physiological and pathological roles in response to various extracellular and

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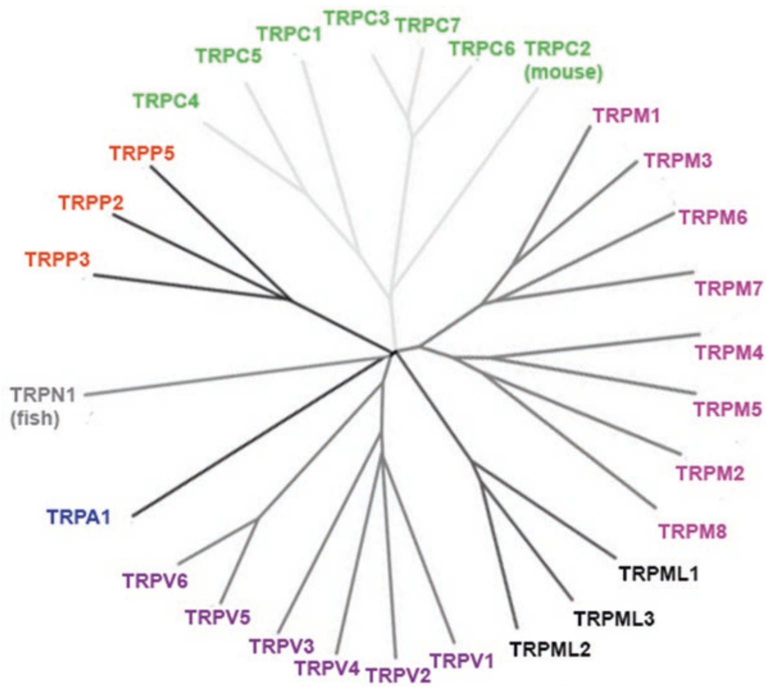

Fig. 1.1 A phylogenetic tree of human TRP channels (Modified from [40]). TRP channels fall into seven families, based on full-length sequence comparisons of human TRP channel proteins. TRPNs are not present in mammals and trpc2 is a pseudogene in human.

intracellular stimuli, such as changes of temperature, pH, or osmolarity, injury, depletion of calcium stores, as well as volatile chemicals and cytokines. Once activated, TRP channels, with homo- or hetero- tetrameric configurations, function as an integrator of several signaling pathways to elicit a serial of responses. TRPs share common structure features, including six putative transmembrane spanning domains with intracellular C and N termini and a pore lining between the fifth and sixth transmembrane domains [17, 39, 43, 51].

1.1 TRPC Channels

The TRPC family is the closest homolog to *Drosophila* TRP channels. The TRPC family consists of seven members (TRPC1–7) with trpc2 being a pseudogene in human beings [38]. The seven mammalian homologs share ≥30% amino acid identity within the N-terminal 750–900 amino acids. Based on sequence alignments and functional comparisons, the mammalian TRPCs fall into four subsets: TRPC1, TRPC2, TRPC3/6/7, and TRPC4/5.

TRPC1 protein shows a broad expression across different cell types [9]. It can interact with all other human TRPC proteins (TRPC3–7) to form a heterotetrameric channel [16, 23, 35, 55–57, 68]. TRPC1 is also able to interact with members in other families of TRP channel, such as TRPP2 [65] and TRPV4/6 [36, 54]. It is reported that TRPC1 and other TRP channels form a receptor-activated channel. For example, TRPC1/TRPP2 channel is activated by G-protein-coupled receptors (GPCRs). TRPC1 is also activated by hormone, orexin A, which is associated with the regulation of sleep/wake-up states, alertness, and appetite [27]. As expressed broadly, TRPC1 channel is related with many physiological functions.

The *trpc2* is a pseudogene in humans; however, in rodents it plays an important role in pheromone detection via the vomeronasal sensory neurons (VSN) [66]. In these cells, TRPC2 protein is mainly localized to the sensory microvilli, which are specialized for chemical signal detection.

Outside the vomeronasal organ, TRPC2 has been detected in the main olfactory epithelium [34], testes, heart, brain, liver, spleen, and erythrocytes [21, 22]. In the acrosome region of sperm, TRPC2 was also detected, which indicated its possible role in fertilization [25].

TRPC3 is most prominently expressed in specific regions of the brain, in the heart, and lungs [7, 50]. Its proteins could assemble homotetrameric and heterotetrameric channels with some other TRPC proteins. In brain synaptosomes, TRPC3 has been shown to interact with TRPC6 and 7 but not with other members of the TRPC family [16]. Many evidences show that TRPC3 is a constitutively active receptor-operated channel that can be further stimulated by DAG [29]. TRPC3 is a multifunctional cellular sensor with a wide range of physiological/pathological functions.

TRPC4 exists in many brain regions [69], endothelium and smooth muscle cells [2, 59], intestinal pacemaker cells (ICC) [26], adrenal glands [46], and kidneys [14]. Multiple signalings downstream of receptors mediate activity of TRPC4 homo-/heterotrimeric channels. TRPC4 can interact with TRPC1 and TRPC5 but not with TRPC3, TRPC6, or TRPC7 [16, 23]. TRPC4 has been shown to be involved in response to neural injury, the regulation of neurite outgrowth and neuronal exocytosis [41]. In human kidney epithelial cells, silencing TRPC4 impairs secretion of thrombopsondin-1 (TSP1) [61].

TRPC5 is mainly expressed in brain tissue [22], especially in fetal brain, indicating that TRPC5 may play an important role during brain development [56, 57]. TRPC5 participates in the formation of transient working memory in the entorhinal cortex [71]. TRPC5 is important for amygdala function and fear-related behavior [48]. In the central nervous system (CNS), TRPC5 can form heteromeric cation channels with TRPC1, and these heteromultimers are involved in store-operated Ca^{2+} entry (SOCE). The homotetrameric TRPC5 channel functions as a receptor-activated channel. Some studies report that TRPC5 is also activated by nitric oxide (NO) [67].

TRPC6 expression is the lowest in the brain compared to other TRPCs while still widely expressed in the cardiac neurons [4], retinal ganglion cells [64], olfactory epithelium neurons [12], and some areas of the brain, such as the cortex, substantia nigra, hippocampus, and cerebellum [6, 15]. TRPC6 has been reported to play important roles in brain development and diseases. Its physiological function is involved with excitatory synapse formation [72], dendritic outgrowth [58], and BDNF-mediated survival of granule cells in the cerebellum [24]. TRPC6 also participates in many pathological processes, including neuronal damage in stroke [11, 31], Aβ-production in Alzheimer's Disease (AD) [63], and human glioma cell proliferation [10, 32].

TRPC7 is mainly expressed in the kidney and pituitary gland [22, 37, 49] and closely related with TRPC6. TRPC7 has high sequence homology with TRPC3 and TRPC6 and always forms heteromultimers with TRPC3 and TRPC6. The functions of the heterotetrameric TRPC7 channel with TRPC3 and TRPC6 in kidney and heart disease were reported previously [1, 53]. TRPC7 is a receptor-activated channel activated by PLC-mediated metabolism of PIP2 and production of DAG [42, 60].

1.2 TRPV Channels

TRPVs, activated by vanillin, vanillic acid, and capsaicin in the plants, are thermo-TRP channels, as TRPV1, TRPV2, TRPV3, and TRPV4 can be activated by heat. There are six different members (TRPV1–6) in this family. Compared to TRPV1–4 which are referred to as nocireceptor that sense the damaging signals, TRPV5 and TRPV6 are epithelial calcium ion channels [52]. TRPV1 was first identified and cloned in the late 1990s. It can be activated by multiple stimuli, such as moderate heat (≥43 °C), low pH, capsaicin, ethanol, endogenous lipids, black pepper, and garlic as well as inflammatory mediators. TRPV1 is expressed in most neurons and widely investigated. In nerve injury associated with neuropathic pain and chronic pain, TRPV1 plays a central role. TRPV2 shares 50% of sequence homology with TRPV1 and is activated by higher temperature (52 °C). Other stimuli responsible for TRPV2 activation include osmotic stress and mechanical stretch. TRPV2 is expressed both in neuronal and nonneuronal cells. However, the exact physiological function of this TRPV member remains to be clarified. TRPV3 is expressed in the brain, spinal cord, trigeminal ganglia, and DRG neurons. It acts as a thermo-sensor in the skin and is activated by temperature higher than 34 °C. Other activators of TRPV3 include endogenous ligands such as PGE2, ATP, bradykinin, and histamine. TRPV4 is a nonselective cation channel and activated by temperature higher than 27 °C, mechanical stimuli, hypotonicity, and metabolites of arachidonic acid. It serves as a sensor of osmolality and mechanical stretch. TRPV5 is mainly expressed in kidney epithelial cells and plays an important role in the reabsorption of Ca^{2+}. It can be regulated by various factors, including 1,25-dihydroxyvitamin D3, parathyroid hormone, dietary Ca^{2+}, and acid-base status change of pH [30]. TRPV6 share some common features with TRPV5. They are co-expressed in several tissues, such as intestine, kidney, prostate, and testis. Unlike TRPV1–4, they are selective channels for Ca^{2+}. The gene expression of TRPV6 is upregulated in most common cancers, including prostate and breast cancers. TRPV6 is also an important channel for male fertility [13, 19].

1.3 TRPM Channels

There are eight members (TRPM1–8) of TRPM family in mammals. Based on sequence homology, TRPMs fall into three subgroups: TRPM1–3, TRPM4–5, and TRPM6–7. Some of TRPMs are located on intracellular membranes. TRPM1 is a prognostic marker for metastasis of melanoma [44]. TRPM2 is widely expressed in various tissues, including brain, heart, hematopoietic, vascular smooth muscle, and endothelial cells. It functions as a Ca^{2+} permeable channel in plasma membrane and a lysosomal calcium release channel in pancreatic beta-cell and dendritic cells [70]. TRPM3 is activated by moderate heat and steroid pregnenolone sulfate. It is expressed in islet cells of the pancreas, regulating insulin secretion, and in the brain, both in neurons and oligodendrocytes, as well as in the peripheral nervous system [3]. TRPM4 channels are Ca^{2+}-activated nonselective cation channels permeable only to monovalent ions (K^+ and Na^+). TRPM4 forms a functional channel as a tetramer which is expressed in a wide range of human tissues and involved in various physiological processes such as T cell activation, myogenic vasoconstriction, allergic reactions, and neurotoxicity [5]. TRPM5 shows 40% identity of the amino acid sequence with TRPM4 and is a Ca^{2+}-activated cation channel that mediates signaling in taste and other chemosensory cells. TRPM6 is a bifunctional protein comprising a TRP cation channel segment covalently linked to α-type serine/threonine protein kinase. TRPM6 is expressed in the intestinal and renal epithelial cells. TRPM7 has been found in mammalian tissues and plays important roles in cellular and systemic magnesium homeostasis. TRPM8 plays a critical role in the detection of environmental cold temperatures [33].

1.4 TRPA Channels

TRPA was firstly named as ANKTM1, because it has many N-terminal ankyrin repeats. TRPA1 is the only member of TRPA family in mammals, while there are two and four TRPA members in *C. elegans* and *Drosophila*, respectively [62]. TRPA1 is activated by painful cold with the temperature that is lower than 17 °C. TRPA1 is found in the plasma membrane of pain-detecting sensory nerves and activates pain pathways that trigger avoidance behaviors and pathways that promote long-lasting responses, such as inflammation. Blocking TRPA1 function is therefore a promising strategy to reduce pain. Pungent agents from wasabi and other TRPA1 triggers, known to be electrophiles, activate TRPA1 by forming covalent bonds with specific cysteine or lysine amino-acid residues [8]. TRPA1 antagonists, such as mustard oil and garlic, have potential for improving neurogenic inflammatory conditions provoked or exacerbated by irritant exposure [45].

1.5 TRPN Channels

Mammals do not encode any TRPN members. They are found in worms, flies, and zebrafish. The TRPN proteins are strong candidates for mechano-transducing channel subunits in both vertebrates and invertebrates. TRPN homologs are present in insects, nematodes, fish, and amphibians and required for tactile and proprioceptive behavior in insects and nematodes and for transduction of vibratory stimuli in zebrafish hair cells [28].

1.6 TRPP Channels

As mentioned above, TRPP and TRPML belong to Group2 of TRP channels and have limited similarity to the Group1 in homology. Furthermore, they have a large loop between transmembrane domain one and two, which discriminates them from Group1 [62]. The three human genes encoding for TRPP protein family are polycystic kidney disease 2 (PKD2, TRPP2), PKD2-like 1 (PKD2L1, TRPP3), and PKD2-like2 (PKD2L2, TRPP5). TRPP2 is a 110 kDa protein and involved in autosomal dominant polycystic kidney disease (ADPKD). TRPP2 functions as a Ca^{2+}-permeable nonselective cation channel. The highest sequence similarity between TRPP channels is in transmembrane segments S1–S6, with rather little sequence homology in their predicted amino and carboxyl terminals. All mammalian TRPP orthologues are highly conserved, with ~90% identities for TRPP2 and TRPP3 and ~80% for TRPP5. TRPP ion channels are regulated by and assemble with Polycystin-1 family proteins into receptor-channel complexes to form the core of a signaling pathway where Ca^{2+} is a second messenger [20].

1.7 TRPML Channels

TRPML includes three members TRPML1, TRPML2, and TRPML3, among which they share about 75% amino acid similarity. TRPML1 has 580 amino acids and a molecular weight of 65 kDa. It is also referred to as mucolipin-1 or MCOLN1. Mutations in this protein are responsible for lysosomal storage disorder mucolipidosis IV. TRPML1 is responsible for iron ions across the endosome/lysosome membrane into the cell [18, 47]. TRPML2 is a 566-amino acid protein with a predicted weight of 65 kDa. No evidence suggests that its mutations associated with any disorder in either human or animal models to date. TRPML3 has 533 amino acids and predicted weight of about 64 kDa. It is mainly expressed intracellularly in the inner ear. Previous reports suggested that TRPML3 is an inwardly rectifying monovalent cation channel that is permeable to Ca^{2+} and suppressed by H^+ [47].

1.8 Conclusion and Perspectives

Now there are at least 28 genes encoding mammalian TRP channel subunit proteins. Seven families of TRP are grouped, including TRPC (1–7), TRPV (1–6), TRPM (1–8), TRPA (1), TRPP (2/3/5), TRPML (1–3), and TRPN (1), respectively. Based on the similarity to *Drosophila* TRP, TRPC, TRPV, TRPM, and TRPA are classified as Group1 TRP channels, which have the strongest similarity. The Group2 TRP channels, including TRPP and TRPML, have distal relevance to *Drosophila* TRP. It has been demonstrated that these TRP family members are involved in cell physiological functions and also in many hereditary and acquired diseases. Some TRPs are involved in sensory functions such as smell, taste, pain, and pheromone sensing. Some are responsive to temperature and may help to avoid tissue-damaging noxious temperatures. Some TRPs are sensitive to natural compounds or their ingredients that have been used in medical practice.

Abnormalities in TRP channel function, as the result of alteration of protein expression levels, changes in channel properties, or changes in their myriad regulators, have been associated with numerous diseases ranging from chronic pain to cardiovascular disease, skeletal abnormalities, kidney diseases, brain diseases, and cancer, which provides numerous opportunities for therapeutic intervention.

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TRPC Channel Structure and Properties

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Abstract

TRPC channels are the first identified members in the TRP family. They function as either homo- or heterotetramers regulating intracellular Ca^{2+} concentration in response to numerous physiological or pathological stimuli. TRPC channels are nonselective cation channels permeable to Ca^{2+}. The properties and the functional domains of TRPC channels have been identified by electrophysiological and biochemical methods. However, due to the large size, instability, and flexibility of their complexes, the structures of the members in TRPC family remain unrevealed. More efforts should be made on structure analysis and generating good tools, including specific antibodies, agonist, and antagonist.

Keywords

TRPC • Structure • Property

TRP channel subunits are rather large, ranging from 70 kD to more than 200 kD [40]. Transmembrane (TM) segment prediction suggests TRP channels resemble voltage-gated K^{+} or Ca^{2+} channels [74]. A consensus has been reached by researchers that putative organization of TRP channels consists of six transmembrane (TM) domains with the carboxyl (C-) and amino (N-) terminals facing the intracellular side of the membrane [20, 73, 74]. The features of TRP channels change from family to family. However, no matter how diverse these subunits are, they are conserved in their pore region, a hydrophobic region between fifth and sixth segment and their TRP domain on the proximal C-terminal region [40, 67]. The results obtained by biochemical and optical methods strongly suggest that TRP channels are formed by four subunits [2, 29, 35],

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