Introduction to TRP Channels: Structure, Function, and Regulation

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Abstract Transient receptor potential or TRP families of ion channels demonstrate great diversity in activation and inhibition, and they are diverse in selectivity of ion conductance. TRP ion channels function as signal integrators through their ion conductance properties, and in some cases kinase activity. They mediate processes such as vision, taste, olfaction, hearing, touch, and thermo- and osmosensation. TRP cation channels function by mediating the flux of Na^+ and Ca^{2+} across the plasma membrane and into the cytoplasm. The influx of cations into the cytoplasm depolarizes cells and is necessary for action potentials in excitable cells such as neurons. In non-excitable cells, membrane depolarization by TRP) and-channels stimulates voltage- dependent channels (Ca^{2+}, K^+, Cl^- influences many cellular events, such as transcription, translation, contraction, and migration. TRP channels are important in human physiology, and mutations in TRP genes are associated with at least four diseases. Furthermore, altered expression, function, and/or regulation of TRP channels have been implicated in diseases such as pulmonary hypertension.

Keywords Canonical • Vanilliod • Melastatin • Ankyrin • Trpn=No mechanoreceptor potential • Trpp=Polycystin • Trpml=Mucolipin

1 Introduction

Transient receptor potential (TRP) cation channels mediate the flux of Na^+ and Ca^{2+} across the plasma membrane and into the cytoplasm.[1] TRP channels were first discovered due to a mutation in the *Drosophila* photoreceptor, which resulted in inhibited Ca^{2+} permeability and sensitivity to light.[2] The influx of cations into the cytoplasm depolarizes cells and is necessary for action potentials in excitable cells

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such as neurons.[3] In nonexcitable cells, membrane depolarization by TRP channels stimulates voltage-dependent channels (Ca^{2+}, K^+, Cl^-) and influences many cellular events, such as transcription, translation, contraction, and migration.[4] TRP channels and their regulation are fundamentally important in cellular function and disease.[1]

2 TRP Gene Expression

TRP genes are expressed in organisms from archaea to plants to animals.[5] In animals, TRP is expressed in brain, heart, lung, and other tissues.[5] Mammalian TRP channels possess a high degree of sequence homology, particularly in the putative functional regions.[6] The TRP superfamily of genes is categorized into two groups based on sequence and topological similarities.[6] Group 1 includes TRPC, TRPV, TRPM, TRPA, and TRPN. Group 2 includes TRPP and TRPML.

3 TRP Protein and Channel Function

TRP proteins form cation channels with varying selectivity to different cations.[7] TRP proteins are transmembrane proteins with six transmembrane domains with a pore domain wedged between the fifth and sixth transmembrane domains. The N- and C-terminal domains are intracellular and believed to be involved in regulation of TRP channel function and in channel assembly. It is believed that TRP channels are homo- or heterotetramers of TRP proteins, with each subunit contributing to selectivity of the ion-conducting pore.[8] Allosteric interactions between subunits are thought to contribute to gating of TRP channels; however, the location and structure of these gates are unknown. Amino acid sequences flanking the pore-forming regions of TRP proteins are strongly conserved across the various TRP channel families, highlighting their importance in pore formation or pore gating.[9]

4 TRP Channel Regulation

TRP channel function is regulated by (1) plasma membrane receptor activation, (2) ligand activation, (3) direct activation, and (4) indirect activation.[10] G protein-coupled receptors (GPCRs) and receptor tyrosine kinase act through diacylglycerol (DAG) to activate TRP channels on the plasma membrane.[11,12] These channels are termed *receptor-operated channels*. Furthermore, stimulation of these receptors depletes intracellular endoplasmic reticulum/sarcoplasmic reticulum (ER/SR) Ca^{2+} stores and leads to store-operated Ca^{2+} entry through TRP channels on the PM.[13] Various ligands can activate TRP channels. Ligand activation includes

activation by exogenous small molecules such as capsaicin, icilin, 2-Aminoethoxydiphenyl Borate, endogenous lipids such as DAG, phosphoinosidides, eicosanoids, purine nucleotides, ions such as Ca^{2+}, and Mg^{2+}, and the Ca^{2+}/Calmodulin complex.[14–16] TRP channel activity can be stimulated through direct activation. Examples of direct activation of TRP channels include temperature change,[17] mechanical stimulation,[18] and conformational coupling with other proteins such as STIM1 (stromal interacting molecule 1) or IP_3R (inositol 1,4,5-trisphosphate receptor). Indirect activation refers to transcriptional control or insertion of vesicles containing TRP proteins into the plasma membrane.

5 Summary of Mammalian TRPs (Fig. 6.1)

5.1 TRPC

TRPC1–7 are categorized into three categories based on sequence and functional characteristics.[5] TRPC1, 4, and 5 form one group. TRPC1 was the first mammalian TRP protein discovered. It is widely expressed in many tissues and thought to form heteromeric channels with TRPC4 and TRPC5.[19] TRPC4 and TRPC5 are believed to form homomeric channels. When expressed together, TRPC1, 4, and 5 form nonselective cation channels that are activated by G_q signaling through a phospholipase Cβ1 (PLCβ1) pathway.[20] Growth factor stimulates rapid translocation of TRPC5 into the plasma membrane from vesicles located near the plasma membrane.[21]

TRPC3, 6, and 7 have roughly 75% sequence homology and when coexpressed reconstitute nonselective, inward and outward rectifying cation channels.[10] These channels are activated by a receptor-mediated pathway involving DAG and are believed to be important in vascular and airway smooth muscle.[22] Channels formed by TRPC3 or TRPC6 are also regulated by N-linked glycosylation and Ca/CaM.[23] TRPC3 is activated by phosphorylation by PKG.[24] TRPC6 is phosphorylated by the Src family of tyrosine kinases.[25]

TRPC2 shares roughly 30% sequence homology with TRPC3/6/7.[26] TRPC2 full-length messenger RNA (mRNA) is expressed in mouse and rat tissues.[27] However, TRPC2 is a pseudogene in humans.[10]

5.2 TRPV

TRPV is subdivided into two groups composed of TRPV1–4 and TRPV5 and 6.[28] TRPV1 forms vanilloid receptor and noxious thermosensor cation channels that are outwardly rectifying in humans and mice.[29] Capsaicin-activated TRPV1 channels have roughly a 10:1 selectivity of Ca^{2+} over Na^+, with selectivity of $Ca^{2+} > Mg^{2+} > Na^+ = K^+ = Cs^+$.[30] Heat-activated TRPV1 channels have a 4:1 selectivity of Ca^{2+}

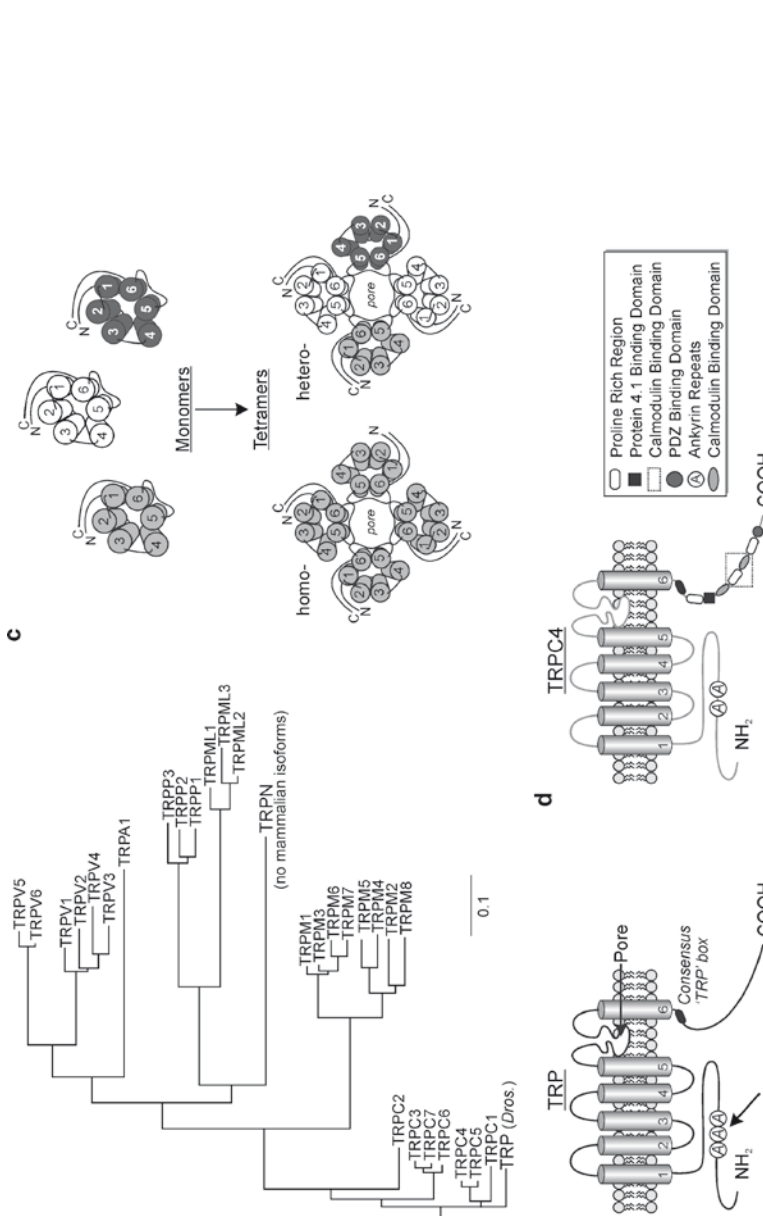

Fig. 6.1 Classification and structure of TRP channels. (**a**) Phylogenic tree of the seven known families of TRP proteins. The original TRP protein identified in *Drosophila melanogaster* is most closely related to TRP channels. (**b**) Two-dimensional representation of TRP channel structure. Six transmembrane domains (TM1-TM6), ankyrin repeats, pore region, and TRP box are shown and described further in the text. (**c**) Subunit arrangement of TRP monomers into functional homo- or heterotetrameric channels with a central ion-conducting pore. (**d**) Schematic representation of key regulatory sites for the TRPC4 protein. Regions and domains are described in the text

over Na^+.[31] TRPV1 is inactivated by phosphorylation by cyclic adenosine monophosphate (cAMP)-dependant protein kinase and pharmacologically by capsazepine, ruthenium red, iodoresiniferatoxin, (N-(4-tertiarybutylphenyl)-4-(3-cholorphyridin-2-yl)tetrahydropryazine-1(2H)-carbox-amide) (BCTC), and Phosphatidylinositol 4, 5-Bisphosphate (PIP_2). TRPV1 channels are activated by capsaicin (EC_{50} = 0.7 μ*M*), resiniferatoxin (EC_{50} = 40 n*M*), anandamide, heat (threshold of 43°C), extracellular protons, and ethanol.[32] TRPV1 is expressed in trigeminal and dorsal root ganglia, brain, and spinal cord.[10] TRPV1 channels function physiologically in nociception, inflammation, temperature sensation, and capsaicin detection.[33]

RPV2 possesses roughly 50% sequence homology to TRPV1 and is thought to function as a noxious heat thermosensor channel.[34] TRPV2 channels constitute an outwardly rectifying nonselective cation current with roughly 3:1 selectivity for Ca^{2+} over Na^+. TRPV2 channels are insensitive to capsaicin and activated by heat, with a threshold of 52°C. TRPV2 channels can be inhibited by ruthenium red, La^{3+}, and SKF-96365. TRPV2 is expressed in dorsal root ganglion neurons, brain, spinal cord, spleen, lung, vascular myocytes, and vascular smooth muscle.[31,34]

TRPV3 forms outwardly rectifying cation channels with roughly 10:1 selectivity of Ca^{2+} over Na^+. TRPV3 channels are activated by temperature at roughly 35°C and are believed to mediate sensation of warmth in skin. TRPV3 is inactivated by cooling and blocked by ruthenium red.[35]

TRPV4 forms outwardly rectifying cation channels with roughly 6:1 selectivity of Ca^{2+} over Na^+.[36] TRPV4 channels function as osmosensor channels, which mediate sensitivity to pressure and acidic nociception in nerve cells.[33] TRPV4 is activated by reduction in osmolarity, phorbol esters, arachidonic acid, and stretch.[37] TRPV4 is inactivated by the Ca/CaM complex and blocked by ruthenium red, gadolinium, and lanthanum. TRPV4 is expressed in brain, liver, kidney, fat, heart, testis, salivary gland, and trachea.[38]

TRPV5 forms constitutively active inwardly rectifying Ca^{2+} selective cation channels with 107:1 selectivity of Ca^{2+} over Na^+.[39] TRPV5 is expressed in intestine, kidney, and placenta.[40] However, its mechanisms of activation and inactivation are unclear. TRPV5 channels can be inhibited with ruthenium red and La^{3+}.[41]

TRPV6 also forms constitutively active inwardly rectifying Ca^{2+} selective cation channels with 130:1 selectivity of Ca^{2+} over Na^+.[42] TRPV6 is expressed in the intestine and in the kidneys.[40] However, its physiological function as well as mechanisms of activation and inactivation are unclear.[43] TRPV6 channels can be blocked by ruthenium red and La^{3+}.[43]

5.3 TRPM

TRPM is categorized into four groups: TRPM1/3, TRPM7/6, TRPM2/8, and TRPM4/5.[10] TRPM1, the first member of the TRPM family discovered, is a Ca^{2+}-permeable channel in the eye and melanocytes.[44] Downregulation of TRPM1 is a marker for metastasis in patients with melanoma.[45] TRPM1 is regulated by an

alternatively spliced form of TRPM1 and the transcription factor Microphthalmia-associated transcription factor (MITF).[45]

TRPM2 is a weakly voltage-sensing nonselective cation channel, which is expressed in the brain, placenta, lung, spinal cord, spleen, and lymphocytes.[46] TRPM2 is activated by increased cytoplasmic Ca^{2+} concentration, Nicotinamide adenine dinucleotide (β-NAD^+), and adenosine diphosphate (ADP)-ribose. TRPM2 is also activated by H_2O_2 and tumor necrosis factor α (TNF-α), suggesting that it may function as a redox sensor.[47] TRPM2 can be inactivated by flufenamic acid, clotrimazole, econazole, and Poly (ADP-Ribose) polymerase (PARP) inhibitors.[48]

TRPM3 is a constitutively active (enhanced by hypoosmolarity and sphingolipids) nonselective cation channel widely expressed in kidney and brain.[49] TRPM3 can be blocked by Gd^{3+} but is insensitive to ruthenium red.[7] Physiologically, TRPM3 is involved in Ca^{2+} absorption in renal collecting tubules.[49]

TRPM4 is a Ca^{2+}-activated Na^+ channel with roughly 100:1 greater selectivity to Na^+.[50] There are two splice variants of TRPM4: TRPM4a and TRPM4b. TRPM4a is inhibited by La^{3+} and Gd^{3+}, and TRPM4b is inhibited by free intracellular adenosine triphosphate (ATP), ADP, and spermine.[51] TRPM4 is regulated by calcium oscillations in activated T lymphocytes and causes myogenic cerebral artery vasoconstriction.[52]

TRPM5 forms outwardly rectifying nonselective, monovalent cation channels in eye, liver, lung stomach, and tongue.[53] TRPM5 is activated by cytoplasmic Ca^{2+}, GPCRs, and PLCβ2.[54] TRPM5 is believed to mediate tastes of sweet, bitter, and umami.[52]

TRPM6 functions as an outwardly rectifying nonselective cation channel and contains a protein kinase on its C-terminal domain.[55] TRPM6 is widely expressed in kidney and the gastrointestinal tract. Mutation of TRPM6 has been linked to human hypomagnesemia and secondary hypocalcemia.[56] TRPM6 channels can be blocked by ruthenium red.[55]

TRPM7 is similar to TRPM6 in that it forms cation channels and possesses kinase activity that autophosphorylates.[57] Furthermore, TRPM6 and TRPM7 can heteromulterimize into active ion channels.[58] TRPM7 is activated by PIP_2.[59] TRPM7 is also involved in cellular Mg^{2+} homeostasis.[60] TRPM7 can be blocked by Mg^{2+}, La^{3+}, and polyamines.[61]

TRPM8 channels are believed to be involved in cooling and menthol sensation. TRPM8 forms nonselective cation channels in sensory neurons of trigeminal and dorsal root ganglia and prostate epithelium.[62] TRPM8 channels are activated by cooling below about 22°C and menthol.[63] TRPM8 channels are inhibited by BCTC and capsazepine.[64]

5.4 TRPA

The TRPA "family" has only one member. TRPA1 has over a dozen ankyrin repeats near its N terminus. TRPA1 is a nonselective cation channel that is activated by membrane stretch, cytoskeletal perturbation, mustard oils, PLC-coupled GPCRs, and icilin.[65,66] TRPA1 channels are blocked by ruthenium red. TRPA1 is expressed in sensory neurons of trigeminal and dorsal root ganglia and the ear.[67,68] TRPA1 is believed to function as the putative sensor of wasabi.

5.5 TRPP

Mutation in TRPP1 causes autosomal dominant polycystic kidney disease.[69] TRPP1 forms nonselective cation channels in kidney, pancreas, heart, testis, and blood.[10] TRPP1 may be activated by mechanical stress and blocked by amiloride, Gd^{3+}, and La^{3+}. TRPP1 is involved in the development of mouse cardiac, skeletal, and renal cells and is important in kidney and liver cyst formation.[70]

TRPP2 forms nonselective cation channels in kidney, testis, and eye.[71] TRPP2 is activated by increased cytoplasmic calcium concentration.[72] TRPP2 is involved in kidney and retinal development.[73] TRPP3 forms nonselective cation channels.[10]

5.6 TRPML

The TRPML family of ion channels is likely restricted to intracellular vesicles.[74] TRPML1–3 form nonselective cation channels.[75] TRPML1 channels are widely expressed in heart kidney, testis, and blood and blocked by amiloride, Gd^{3+}, La^{3+}, and Ni^{2+}.[10] Not much is known about TRPML2 and TRPML3.

6 Conclusion

TRP families of ion channels demonstrate great diversity in activation and inhibition, and they are diverse in selectivity of ion conductance. TRP ion channels function as signal integrators through their ion conductance properties and in some cases kinase activity. They mediate vision, taste, olfaction, hearing, touch, and thermo- and osmosensation. TRP channels are important in human physiology, and mutations in TRP genes are associated with at least four diseases. Furthermore, altered expression, function, or regulation of TRP channels has been implicated in diseases such as pulmonary hypertension.

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