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Review

Emerging structural biology of TRPM subfamily channels

Yixiang Chen[a,1], Xu Zhang[b,1], Tingting Yang[c,1], Ruixue Bi[d], Zhanmei Huang[e], Hao Ding[b], Jian Li[f,g,*], Jin Zhang[a,**]

[a] School of Basic Medical Sciences, Nanchang University, Nanchang, 330031, Jiangxi, China
[b] Queen Mary School, Medical Department, Nanchang University, Nanchang, 330031, Jiangxi, China
[c] School of Pharmacy, Nanchang University, Nanchang, 330031, Jiangxi, China
[d] School of Nursing, Nanchang University, Nanchang, 330031, Jiangxi, China
[e] The First Affiliated Hospital of Nanchang University, Nanchang, 330031, Jiangxi, China
[f] College of Pharmaceutical Sciences, Gannan Medical University, Ganzhou, 341000, Jiangxi, China
[g] Key Laboratory of Cerebrovascular Pharmacology of Jiangxi Province, Gannan Medical University, Ganzhou, 341000, Jiangxi, China

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ABSTRACT

TRPM family (Transient receptor potential channels, M for melastatin) is a group of intrinsic plasma membrane ion channels which are widely expressed throughout human body. It has been identified as a potent entry point of working desperate diseases out in a new way with newfangled ideas and safer technological means. In our review, we discussed the common and unique properties of TRPM family with the elaborate narrate in their overall structures, different states and the underlying activation mechanism. Thus, this review can help to consummate the limited work of TRPM family and provide novel therapeutic targets of certain diseases.

1. Introduction

TRPM family is one of the vital subfamilies of transient receptor potential (TRP) channels, which is ubiquitously expressed in almost all the cell types, participating in the physiological and pathophysiological processes in our human body [1–3]. They are intrinsic membrane proteins with six-transmembrane domains and further divided into eight variable types, named as TRPM1-TRPM8 [4]. All of them are cation channels that are permeable to Ca^{2+}, except TRPM4 and TRPM5 [5–7]. TRPM channels express in wide range of organs throughout our body, such as immune system and cardiovascular system, which are essential guarantee for human health [8–13]. Corresponding to their broad expression, TRPM channels play a significant role in cell development and relevant diseases which are urgent to be solved [14]. For instance, TRPM4 and TRPM5 have been found as a modulator in taste cells [15,16], TRPM8 is important in cold sensation [17,18], and TRPM7 is involved in mammalian homeostasis [19]. As a result, TRPM family have aroused the enthusiasm of scientists to conduct many functional and structural studies on them.

There are now over 50 structures of TRP channels from more than 10 unique channels spanning a range of conformational states from closed states, open states, and partially open states (Table 1) [20–35]. Since 2017, a tremendous progress has been made in TRPM subfamily structural biology using cryo-EM. There are four independent TRPM ion channels in which the cryo-EM structures have been solved. The four ion channels are TRPM2 [20–22], TRPM4 [23–26], TRPM7 [27] and TRPM8 (Table 1) [28]. The TRPM2 structures have been solved in open or closed states [21,21,22]. The TRPM4 structures were determined in different species or states from four independent groups, which were complementary with each other [23–26]. In addition, cryo-EM structure of TRPM7 bound to magnesium has been reported [27]. Structure of TRPM8 from the *collared flycatcher* has been solved in the unliganded (apo) state [28]. In this review, we focus on the common and distinct features of TRPM subfamily members and the underlying molecular mechanisms for the activation of TRP channels based on these structures.

2. Overall structures of TRPM ion channels

The overall architecture of TRPM2, TRPM4, TRPM7 and TRPM8 is similar due to the high sequence conservation within the TRPM subfamily [20–28]. All of them share the common 6 T M domains and have an inverted crownlike shape, consisting of a transmembrane domain (TMD) and a large cytosolic domain formed by the N-terminal MHR

* Corresponding author at: College of Pharmaceutical Sciences, Gannan Medical University, Ganzhou, 341000, Jiangxi, China.
** Corresponding author.
E-mail addresses: rmsl_2040@163.com (J. Li), zhangxiaokong@hotmail.com (J. Zhang).
[1] These authors have contributed equally to this work.

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Table 1
Published cryo-EM structures of TRPMs.

Name	Resolution (Å)	Ligand	PDB ID	Organism	Reference
TRPM2	3.07	CLR, NAG, POV, CA, NA	6CO7	*Nematostella vectensis*	[20]
	3.8		6DRK	*Danio rerio*	[21]
	3.3	APR, CA	6DRJ	*Danio rerio*	[21]
	3.6	NA	6MIX	*Homo sapiens*	[22]
TRPM4	2.88	ATP	6BCO	*Mus musculus*	[23]
	3.25	ATP	6BCQ	*Mus musculus*	[23]
	3.54	NA	6BCL	*Mus musculus*	[23]
	3.14	NA	6BCJ	*Mus musculus*	[23]
	3.8	DVT	5WP6	*Homo sapiens*	[24]
	3.2	Y01	6BQR	*Homo sapiens*	[25]
	3.1	CA, Y01	6BQV	*Homo sapiens*	[25]
	3.7		6BWI	*Homo sapiens*	[26]
TRPM7	4.1		6BWF	*Mus musculus*	[27]
	3.7	Y01, MG	6BWD	*Mus musculus*	[27]
	3.28	Y01	5ZX5	*Mus musculus*	[27]
TRPM8	4.1		6BPQ	*Ficedula albicollis*	[28]

(TRPM homology region) (MHR1-MHR4) domain [36] and the C-terminal domain (CTD). In contrast to the structures from other TRP subfamilies, the N-terminal MHR domain and the C-terminal coiled-coil domains (CTD) [37] of TRPM constitute a unique intracellular architecture that is distinct from that of other TRP subfamilies [29–35]. The long N-terminal domain consists of four large MHR (MHR1-MHR4) domains with the shape of four peaks of the inverted crown, interacting with the TRP domain, pre-S1 helix, and the C-terminal domain. MHR1 and MHR2 form a single domain (MHR1/2) with an α/β fold, which is essential for channel assembly. The MHR3 and MHR4 are composed of stacked α-helices and mostly made up of helix-turn-helix (HTH) motifs, as MHR3 bridging between MHR1/2 and MHR4, MHR4 being the domain proximal to the TMD. The lower portion of MHR4 interacts with the TRP domain and the S2-S3 linker of TMD on the top with the rib helix of CTD and MHR3 on the bottom. MHR3-4 is linked to the transmembrane domain through MHR4, which clasps the TRP domain, thereby forming an interaction between the cytoplasmic domain and the transmembrane core.

The C-terminal domain of TRPM structures are also unique in that a connecting helix bridges the TRP domain and the conserved coiled-coil domain [20–28,37]. The CTD supports the architecture of protein, inserting into MHR domains horizontally and vertically, respectively (Fig. 1). The most notable feature of these structures is the umbrella-like CTD, the four C termini forming a homotetramer via parallel coiled-coils, preceding each coiled-coil helix being a connecting helix that bends to form an inverted 'L' with the coiled-coil helix (Fig. 2). Those four helices run into the same direction, forming a parallel coiled-coil domain. The four horizontal helix subunits are perpendicular to each other when viewed from the top, and link with the coiled-coils to form a central hole. The horizontal helix penetrates through a large tunnel formed by neighbouring MHR domains and has multiple hydrophobic and polar contacts with the MHR, contributing to channel assembly by the tethering together of the MHR domains.

3. Disulfide bond in TRPMs structures

Disulfide bond is essential for ion permeability and may be involved in the gating mechanism of TRPM ion channels, which is conserved across the available TRPM structures [38,39]. In *Dr*TRPM2 (*Dr: Danio rerio*), the pore loop is connected to the pore-lining helix S6 through a long loop in which Cys1012 and Cys1024 form a disulfide bond, stabilizing the integrity of the pore region (Fig. 3A) [20]. In *h*TRPM4 (*h: Homo sapiens*) structure, at the top of the permeation pathway, in the linker between the pore helix and S6, it is a conserved disulfide bond Cys993-Cys1011 and the loop is stabilized by a disulfide bond (Fig. 3B) [26]. In *m*TRPM7-Mg^{2+} (*m: Mus musculus*) bound structure, the conserved disulfide bond near the pore loop in TRPM7 (formed by Cys1056 and Cys1066) is closer to the S5-S6 helices than that of TRPM4 (Fig. 3C) [27]. Interestingly, these two cysteines are highly conserved in the pore domain of all TRPM subfamily members. In the case of TRPM7, when either or both cysteines are mutated to alanine, or the disulfide bond is chemically disrupted, the channel is nonfunctional [27]. Whether this is due to improper folding/assembly or a redox-sensitive gating mechanism requires more investigation.

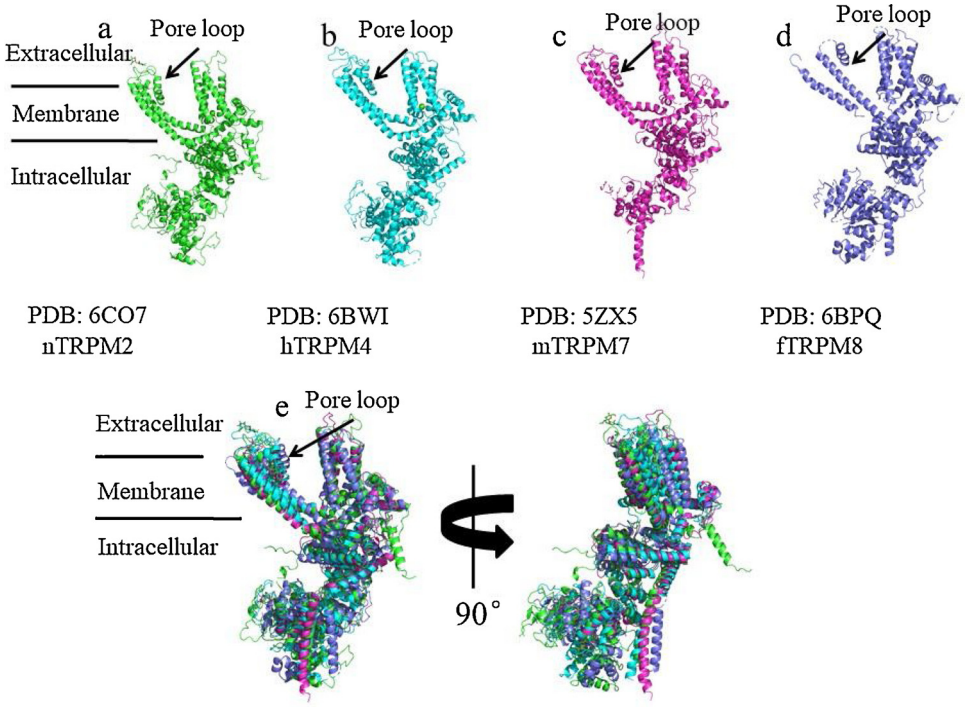

Fig. 1. Structures of TRPM channels.
(A) Cartoon representation of a *n*TRPM2 (*n: Nematostella vectensis*) protomer. (B) Cartoon representation of a *h*TRPM4 (*h: Homo sapiens*) protomer. (C) Cartoon representation of a *m*TRPM7 (*m: Mus musculus*) protomer. (D) Cartoon representation of a *f*TRPM8 (*f: Ficedula albicollis*) protomer. (E) Comparison of *n*TRPM2 (green), *h*TRPM4 (cyan), *m*TRPM7 (magentas) and *f*TRPM8 (slate).

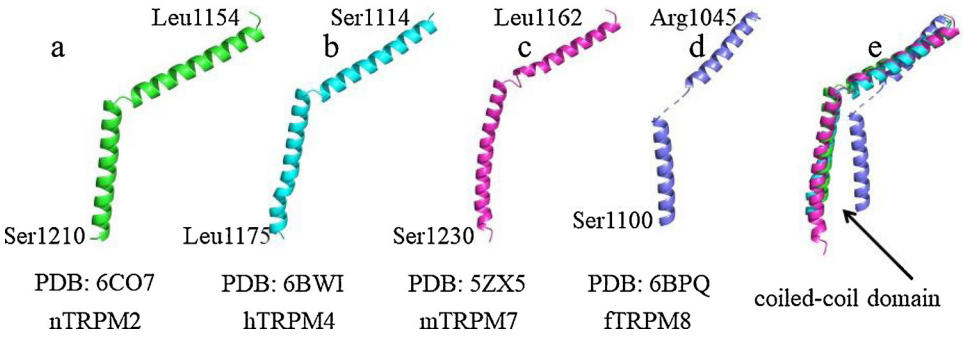

Fig. 2. Unique arrangements of the C-terminal α-helices in TRPMs.
(A) Side view of the *n*TRPM2 C-terminal in cartoon representation. (B) Side view of the *h*TRPM4 C-terminal in cartoon representation. (C) Side view of the *m*TRPM7 C-terminal in cartoon representation. (D) Side view of the *f*TRPM8 C-terminal in cartoon representation. (E) Comparison of TRPM HH and VH helices arranged in a coiled-coil structure. *n*TRPM2, *h*TRPM4, *m*TRPM7 and *f*TRPM8 are in green, cyan, magentas and slate, respectively.

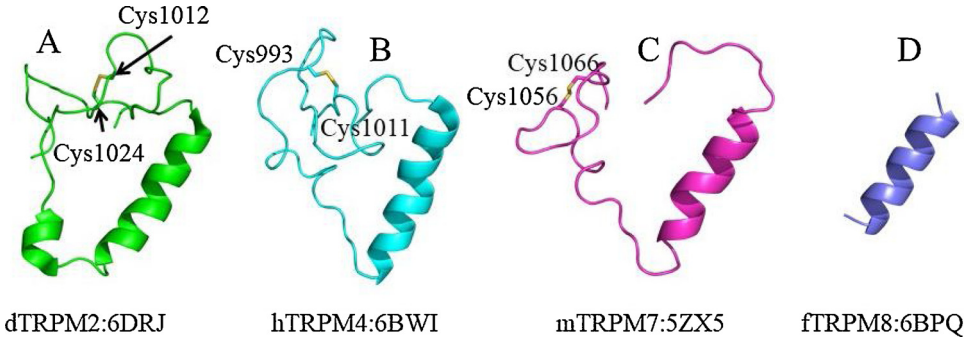

Fig. 3. Pore loop structures of TRPMs.
(A) Cartoon representation of the unique pore loop domain of *d*TRPM2. (B) Cartoon representation of the unique pore loop domain of *h*TRPM4 in closed state. Cysteine residues are shown in stick representation. (C) Cartoon representation of the unique pore loop domain of *m*TRPM7 in closed state. Cysteine residues are shown in stick representation. (D) Cartoon representation of the unique pore loop domain of *f*TRPM8. The pore loop of *f*TRPM8 is poorly resolved within the limitations of its lower resolution.

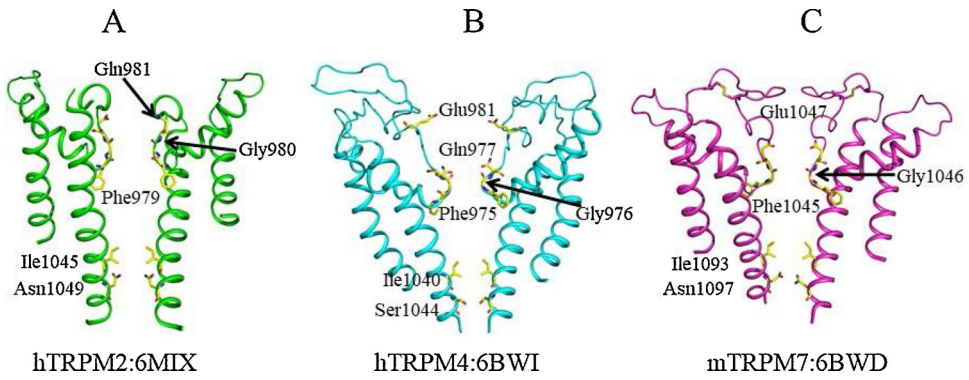

Fig. 4. Comparison of ion conducting pathways between TRPMs, front and rear subunits is removed for clarity, the key residues facing the pore are shown in yellow sticks. *h*TRPM2, *h*TRPM4 and *m*TRPM7 are in green, cyan and magentas respectively.

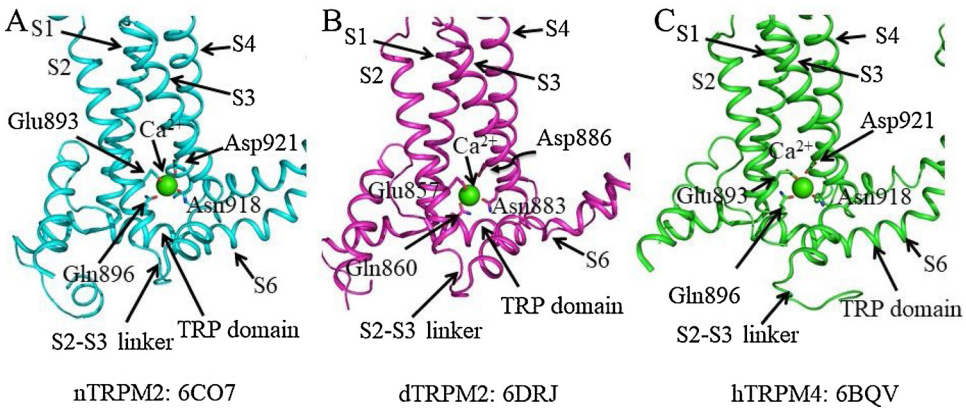

Fig. 5. Cartoon representation of the cation binding pocket in TRPMs transmembrane domain. The key residues involved in *n*TRPM2 (PDB: 6CO7, green) are Glu893, Gln896, Asn918 and Asp921 and cyan (TRPC5), involved in *d*TRPM2 (PDB: 6DRJ, magentas) are Glu857, Gln860, Asn883 and Asp886; involved in *h*TRPM4 (PDB: 6BQV, green) are Glu828, Gln831, Asn865 and Asp868. Residues are shown in sticks and calcium ions are shown in green spheres.

4. Selectivity filter

In the TRPMs known structures, the ion-conducting pore is controlled by two gates, selectivity filter close to the extracellular entrance and lower gate near the intracellular end lined by S6 [40,41]. The selectivity filter is formed by FGQ motif in TRPM2 and TRPM4 structures, while it is formed by FGE motif in TRPM7 structure (Fig. 4) [27]. TRPM4 and TRPM5, the only two monovalent-selective channels [6,7] in TRP family, are permeable to monovalent ions such as Na^+ and K^+, but poorly conduct divalent ions. However, the ion selectivity of

TRPM4 and TRPM5 remains elusive. TRPM4 and TRPM5 channels, the corresponding selectivity filter residues are FGQ, indicating the importance of Glu1047 in TRPM7's 'FGE filter' (Fig. 4C). Consistent with this interpretation, mutation of Glu1047 to Gln largely abolishes TRPM7 Ca^{2+} and Mg^{2+} permeation [41]. Thus, we propose that Glutamate acid residue in the selectivity filter is a key determinant in the mono-selectivity of TRPM channels.

Other features of the TRPM channels include a lower gate consisting of two constriction sites, Ile and Asn in TRPM2 and TRPM7 structures, Ile and Ser in TRPM4 structures (Fig. 4B). Interestingly, Asn1097 is conserved in a similar position in TRPM1-3, TRPM6 and TRPM7, but not in the more Na^{+}-selective TRPM4/5. Asn1097 is the only polar amino acid in the lower gate and appears to be responsible for coordinating Mg^{2+} entry by replacing the water molecules in the second hydration shell [27]. The side-chains of Asn1097 from each monomer form a polar ring that creates the substrate's entrance. Asparagine may fulfill this role better than acidic residues such as aspartate and glutamate because the negatively charged residues may bind strongly with the first hydration shell of Mg^{2+} and block the passage of ions [42].

5. Allosteric ion binding site

The activation of TRPM is dependent on Ca^{2+}. The first Ca^{2+} binding site was firstly described by TRPM4 structure (Fig. 5C) [25]. Interestingly, the Ca^{2+} binding site that is coordinated by four well conserved residues is found in both TRPM2 and TRPM4 (Fig. 5A, B) [20–22,25], while it is not observed in TRPM7 and TRPM8 [27,28]. It is probably due to the relative lower resolution or distinct activation mechanism between these TRPM channels.

The Ca^{2+} binding site in TRPM2 and TRPM4 structures [20–22,25], formed by the cytosolic ends of transmembrane helices S2 and S3, and the S2-S3 linker helix, is located within a hydrophilic pocket. This pocket is linked to the cytoplasmic space through a hydrophilic tunnel between the TRP domain and the S2-S3 linker. Also, the Ca^{2+} binding site is coordinated by two negative charged residues (Asp and Glu) and two neutral residues (Asn and Gln), which is large enough to accommodate additional water molecules for further coordination of the bound ion.

6. Conclusions and outlook

Members of TRPMs display considerable structural and functional homology. In this review, we have seen how evidence from structural studies can often be applied across the TRPM subfamily. Considering the level of sequence and structural similarity between members, it is not surprising that there is also cross-talk by open and close states within the group. A combination of traditional mutagenesis methods and some of the more recent developments will provide us with further insights, many of which will be widely applicable to the whole TRP channels. There are now 4 unique TRPM structures from over 20 PDB entries, which have presented many unprecedented findings in regard to the diversity of the structure, ion permeation and gating mechanism. Each new structure advances our understanding of the complexity of this channel subfamily, and there is still much to be learned about the 'control' of channel activation as most TRPM structures are in closed states. Encouragingly, researchers are continuously developing novel tools to aid TRP channels structure determination. For instance, the reconstitution of nanodiscs to be more amenable to cryo-EM should facilitate future channel-lipid complexes structures and improve resolution. Further advances in technology at phase plate will continue to extend the boundaries on sample molecular mass, while resolution and improvements in the quality of datasets will be of direct use for structure-based drug design approaches. Altogether, the future is bright for TRP channels structural biology as the rapid development of parallel techniques will undoubtedly bring forth many new biological insights and continue to accelerate structure-based drug design. We have entered into an exciting new era of TRP channel structural biology that is promising to answer many long-held questions on how TRPs work.

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