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Recent progress in structural studies on canonical TRP ion channels

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ABSTRACT

Canonical TRP channels (TRPC) are non-selective cation channels that are involved in various important physiological processes. Currently, the structures of different TRPC ion channel family members are resolved by cryo-EM at resolutions ranging from 2.8 Å to 5.8 Å. These structures reveal the conserved architecture of TRPC ion channels as well as the specific features of each channel subtype. This review focuses on the structural differences in the extracellular portions, transmembrane domains and the cytoplasmic domains of TRPC channels.

1. Introduction

In 1989, the first TRP channel member, *Drosophila transient receptor potential* (*trp*), was cloned [1], which was then followed by the discovery of the mammalian canonical TRP channels (TRPC) [2–4]. Thereafter, other TRP channel family members such as TRPV [5–7] and TRPM [8,9] were also reported in mammals. TRPC channels are thus considered as the founding members of the mammalian TRP channel superfamily. These are the closest homologs to the Drosophila TRP channel, which is involved in photo transduction. There are six TRPC channels in human, TRPC1 and TRPC3-7, which are involved in many physiological processes (For a comprehensive review please see [10] on this topic). Importantly, gain-of-function genetic mutation of TRPC6 in human can cause familial focal segmental glomerulosclerosis (FSGS) [11,12] and therefore TRPC6 is a putative drug target of FSGS. TRPC5 is supposed to be a drug target for anxiety and depression [13]. Recently, pharmacological inhibition of TRPC5 in kidney is proposed to be beneficial for the treatment of FSGS [14]. Electrophysiologically, TRPC3, TRPC6, and TRPC7 can be activated by diacylglycerol (DAG) analogues from the intracellular side [15] and DAG is proposed to be the natural agonist for these channels. Therefore, TRPC3, TRPC6, and TRPC7 are considered as members of the DAG-activated TRPC subfamily. DAG is a second messenger that can be generated from the hydrolysis of PIP_2 which is catalyzed by G-protein-coupled receptors (GPCR) or receptor tyrosine kinase-coupled phospholipase C (PLC) [16]. In contrast, TRPC1, TRPC4 and TRPC5 cannot be activated by DAG and are considered as non-DAG-activated TRPC subfamily. The functional similarities within each subfamily channels correlate with their high sequence homologies, as evidenced by their clustering on the phylogenic tree (Fig. 1). This is further manifested by several distinct structural features between DAG-activated TRPCs and non-DAG-activated TRPCs as discussed below.

2. General structure of TRPC channels

Among various TRP superfamily members, the TRPC channels were the first cloned, but ironically, their structures were the last to be resolved to higher than 4 Å resolution, which permits *de novo* model building. To date, four research groups have reported the high-resolution structures of TRPC3 [17,18], TRPC4 [19,20], TRPC5 [21], and TRPC6 [18] homotetramers, and one research group has described the structures of the TRPC3 and TRPC6 cytoplasmic domains [22,23] (Table 1).

These structures reveal that TRPC channels share a common two-layer architecture, namely, the cytoplasmic domain layer (CTD) and the transmembrane domain layer (TMD). The CTD is folded by both N terminal and C terminal residues. The N terminal residues include a flexible N terminal loop, a linker helices domain and an ankyrin repeat domain. The C terminal residues contain a TRP helix, a flexible linker, two helices and some flexible residues at the end. The structure of the transmembrane domain is similar to that of other TRP channel members, which have the voltage sensor-like domain (VSLD) connected to

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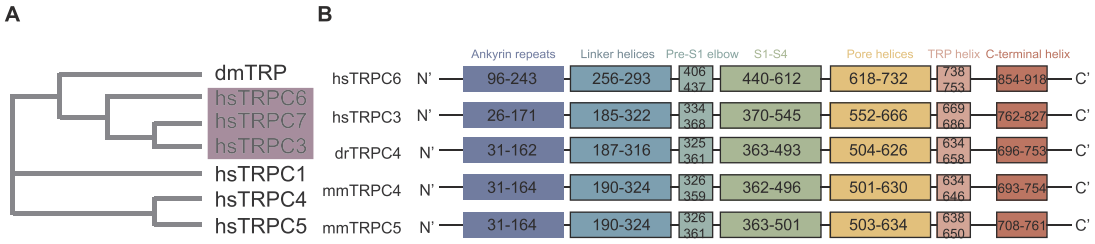

Fig. 1. Domain architecture of TRPC. **A,** Phylogenetic tree of TRPC ion channels generated using ClustalW2 [37]. The DAG-activated TRPC subfamily is shown with a pink background. **B,** the domain architecture of the published TRPC structures. Each domain is shown as a rectangle in different colors. The domain boundary is labeled on the box.

Table 1
Summary of the reported cryo-EM structures of TRPC family channels.

TRPC subfamily name	Species	PDB	EMDB	Resolution	Citation
TRPC3	Homo sapiens	6CUD	EMD-7620	3.3 A°	[17]
TRPC3	Homo sapiens	5ZBG	EMD-6911	4.4 Å	[18]
TRPC6	Homo sapiens	5YX9	EMD-6856	3.8 Å	[18]
TRPC4	Mus musculus	5Z96	EMD-6901	3.3 Å	[19]
TRPC4	Danio rerio	6G1K	EMD-4339	3.6 Å	[20]
TRPC5	Mus musculus	6AEI	EMD-9615	2.8 Å	[21]
TRPC3 (CTD)	Homo sapiens	6D7L	EMD-7823	4.0 Å	[22]
TRPC3	Homo sapiens	6DJR (polyalanine) 6DJS (hybrid)	EMD-7940	5.8 Å	[22]
TRPC6 (CTD)	Mus musculus	6CV9	EMD-7637	3.8 Å	[23]

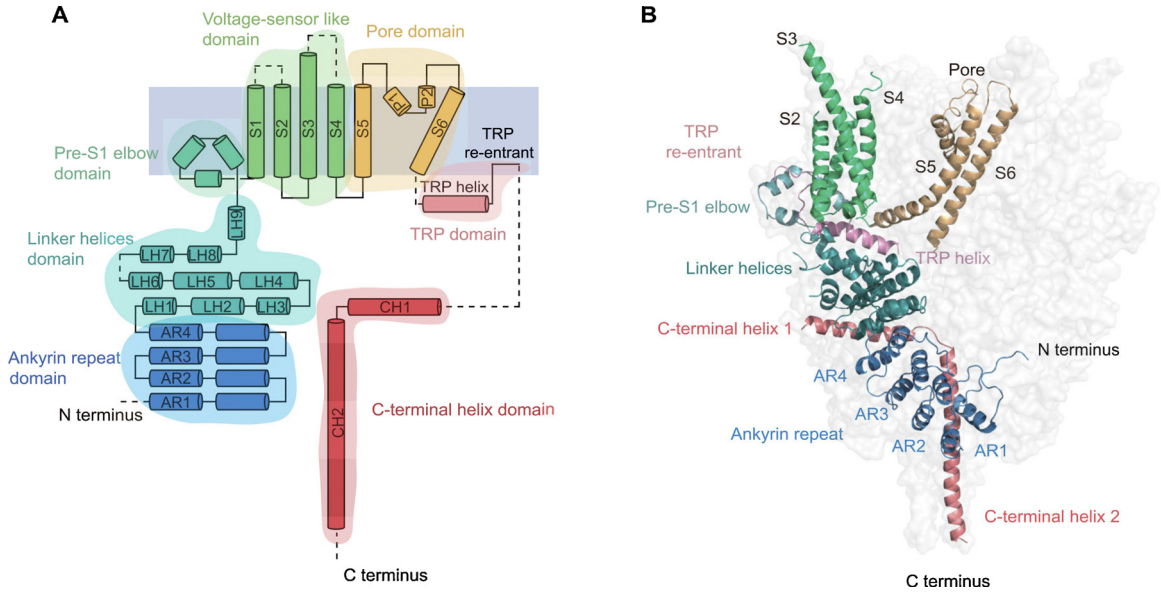

Fig. 2. The structure of TRPC channels. **A,** Topology and linear diagram of one TRPC subunit. As an example, TRPC6 has various domains that are colored differently according to Figure **1B**. **B,** The homotetramer structure of TRPC6. A single subunit is shown in cartoon with the surface of the whole TRPC channel shown in gray with transparency.

the pore domain by an S4-S5 linker in a domain-swapped fashion (Fig. 2). Among the TRP channels, the TMD structure of TRPC most closely resembles that of NOMPC [24] and TRPM [25–29], which have the pre-S1 elbow.

3. Extracellular portions

TRPC3/TRPC6 extracellular protrusions (TRPC-EPs) are structures consisting of continuous and exceptionally long S3 helices. Several extracellular loops such as S1-S2 and S3-S4 also contribute to the TRPC-EP (Fig. 3A). Sequence alignment shows that all DAG-activated TRPC channels, including TRPC3, TRPC6, and TRPC7 have the TRPC-EP, which apparently provides a unique structure for the binding of extracellular ligands such as ions, metabolites, or proteins. However, the function of TRPC-EP under physiological conditions remains unclear.

In contrast to the DAG-activated TRPC channels, the extracellular surfaces of TRPC4/5 are rather flat. A pair of cysteine residues, C549 and C554, sit on the loop between S5 and the pore helix of mTRPC4 (Fig. 3B). This pair of cysteines is conserved between TRPC4 and TRPC5. Sequence alignment shows that the two cysteines are also conserved in TRPC1. Notably, these conserved intra-subunit disulfide bonds are only present in non-DAG-activated TRPC channels (TRPC1/4/5) but are absent in the DAG-activated TRPC channels (TRPC3/6/7). Structurally, these extracellular disulfide bonds stabilize the conformations of the loops between S5 and pore helix, which form the

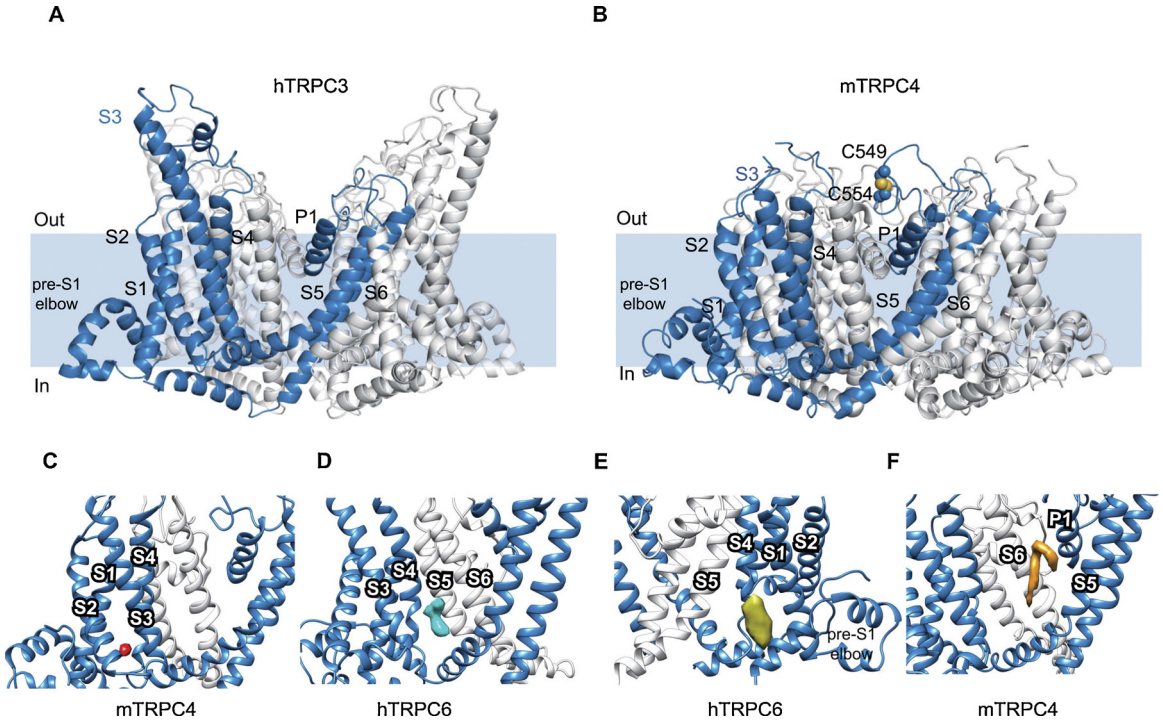

Fig. 3. Structure of TRPC transmembrane domains. **A,** Side view of human TRPC3 TMD. A single subunit transmembrane helices is indicated in blue. The other TMD is shown in gray. The putative membrane is shown in light blue. **B,** Side view of mouse TRPC4 TMD. One subunit of transmembrane helices is colored in blue. The two cysteine residues C549 and C554 out of the pore are shown as spheres. **C-F**, The putative ligand densities in TRPCs. **C,** A putative sodium density in mTRPC4 is colored in red. **D,** The inhibitor BTDM in hTRPC6 is shown in cyan. **E**, The density of the putative CHS in hTRPC6 is shown in yellow. **F**, Phosphatidic acid (PA) in mTRPC4 is highlighted in orange.

extracellular entrance of the pore, and there are a few highly charged residues on this loop which might affect the local electrostatic environment and thus affect ion permeability of the channel. These disulfide bonds provide a possible sensory mechanism for extracellular reductive/oxidative potentials based on the observation that a reduction of disulfide bonds in TRPC5 activates the channel [30].

4. The transmembrane domain

Similar to many other TRP channels, the TMD of TRPC channels is capable of binding diverse ligands or lipids and is the major target of synthetic drugs. High-resolution structures have revealed that TRPC4/TRPC5 have ion-binding sites within the VSLD. The putative ion sits in the pocket surrounded by S2 and S3 (Fig. 3C), possibly a sodium ion in TRPC4 [19], whereas this might be a calcium ion in TRPC5 [21]. The exact identity and function of this ion remain elusive. BTDM is a high-affinity allosteric inhibitor of TRPC3/6 [18]. Cryo-EM map of TRPC6 in complex with BTDM has shown that the BTDM binding site is encircled by the S3–S4 and S4–S5 linker of one subunit and S5 and S6 of the adjacent subunit (Fig. 3D). The BTDM binding site in TRPC6 is similar to the resiniferatoxin and the capsaicin binding site in TRPV1 [31]. The BTDM binding site is the first structurally identified high affinity inhibitor binding pocket in hTRPC6 and will be of general interest for the design and optimization of drugs targeting FSGS caused by hTRPC6 mutations.

Similar to many other membrane proteins, lipids play important roles in TRPC channel function, particularly PIP_2 and its metabolite, DAG. Cryo-EM maps of TRPC3/4/5/6 have shown two lipid-binding sites in the TRPC channels. One binding pocket is surrounded by the pre-S1 elbow, S1, S4, and S4–S5 linker from one subunit and S5 from the adjacent subunit [17–21]. The electron density is supposed to be a cholesteryl hemisuccinate (CHS) molecule, which is added during the protein purification of TRPC3 in nanodiscs /4/5/6 (Fig. 3E) [18–21]. This site in the TRPC3 structure solved in digitonin micelle is occupied by phospholipids [17], which suggests that this pocket can bind to either cholesterol or phospholipids in the plasma membrane. Mutagenesis studies have shown that mutations in this site do not affect the activation of the membrane-permeable DAG analogue 1-oleoyl-2-acetyl-sn glycerol (OAG) of TRPC6, which indicates that this is not the site responsible for DAG binding and activation [18]. The second lipid-binding site is close to the S5 and pore helix from one subunit and S6 helix from the adjacent subunit. This site is occupied by phospholipids in the TRPC3/4/5 structures [17,19–21] (Fig. 3F). Mutations around this site suggest it will affect the activation by a photo-switchable DAG analogue, OptoDArG [32]. However, this lipid binding site is close to the outer leaflet of the membrane, and DAG generated from PIP_2 hydrolysis would be in the inner leaflet of the membrane, at least initially. Therefore, whether this lipid binding site is responsible for physiological activation of TRPC3/6/7 by DAG remains elusive.

5. The cytoplasmic domain

In TRPC channels, the last two C-terminal helices, CH1 and CH2, fold back into the structural scaffold formed by the N terminal residues to form the large CTD structure, which caps below the TMD. The CTD provides a structural platform to sense diverse intracellular signals and might have associated conformational changes. TRPC3 CTD shows marked structural differences with various sample preparation conditions. In the structure of TRPC3 in nanodiscs, CH1 and CH2 assemble in a domain-swapped manner [18], while in the structure of TRPC3 in digitonin detergent, CH1 and CH2 assemble in a non-domain-swapped manner [17] (Fig. 4). Moreover, the CTD of TRPC3 in nanodiscs shows a compact structure, whereas that in digitonin is relatively relaxed. The TRPC4/5/6 structures reported so far resemble TRPC3 in nanodiscs. However, the exact reason for this conformational difference is currently unknown, although it implies that the TRPC CTD can undergo conformational changes that are probably associated with different functional states. It is reported that phosphorylation of several residues

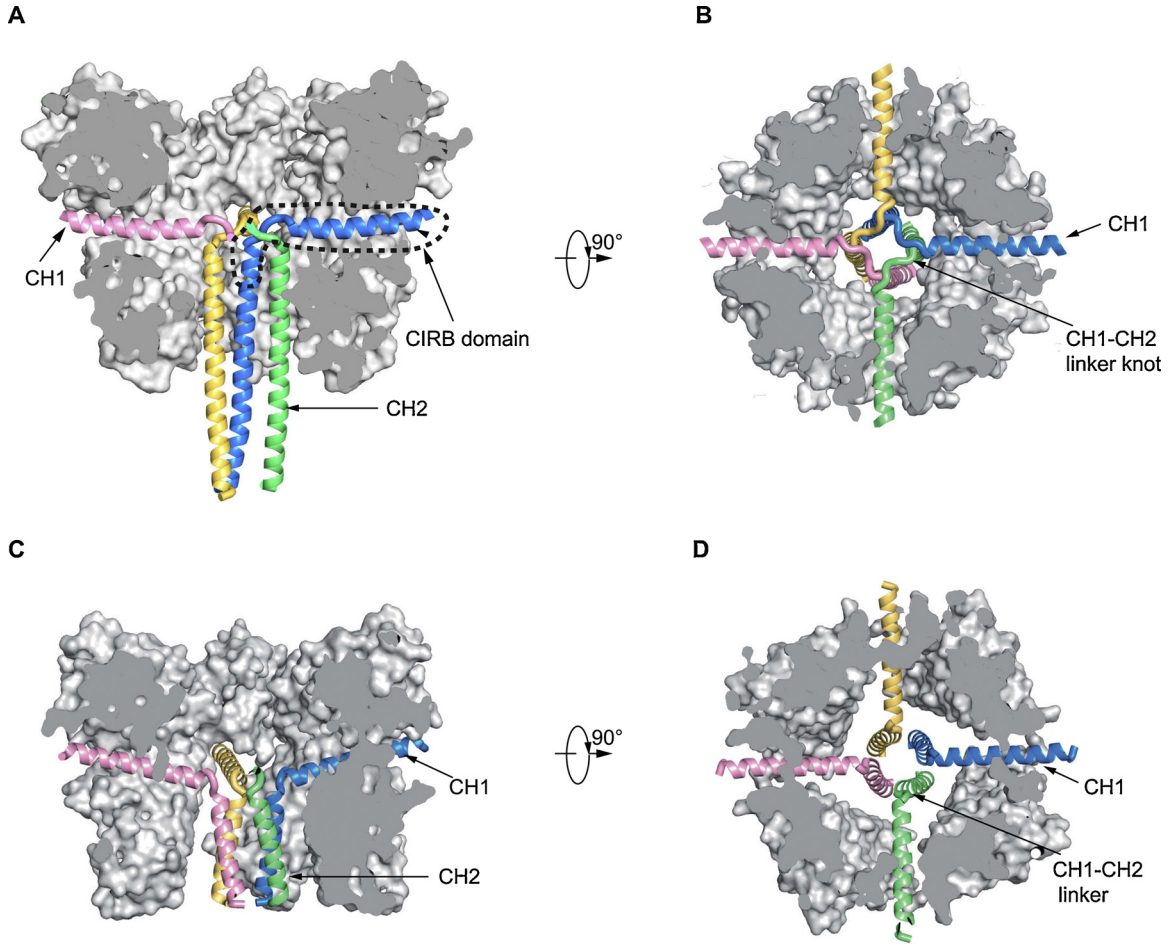

Fig. 4. Structure of TRPC cytoplasmic domains. A, Cross-section of the CTD of TRPC3 in nanodiscs. CH1 and CH2 are shown in cartoon and colored in pink, yellow, blue and green for different subunits. The other parts of CTD are shown in surface and colored in grey. The CIRB domain is marked by dash line. **B,** Top view of the CH1 and CH2 location. The CH1 and CH1-CH2 linker knot are marked by arrows. **C,D,** Side view and top view of CTD of TRPC3 in digitonin buffer. Each parts of the CTD are shown the same as in Fig. 4A. The location of CH1, CH2 and CH1-CH2 linker are highlighted by arrows.

plays an important role in TRPC activation [33]. It is also reported that calmodulin can bind and modulate the channel activity [34,35]. The calmodulin/IP3 receptor binding (CIRB) region is mapped to be on the CH1 and part of CH2 helices (761–795 aa in hTRPC3) [36]. Interestingly, in all of the currently available structures of TRPC channels, the CH1 and CH2 helices are shielded from the molecular surface of TRPCs by the N terminal scaffolds and would be inaccessible for calmodulin binding. Therefore, the calmodulin modulation might happen in a distinct and yet-unresolved conformational state or a folding intermediate where the calmodulin binding sites are exposed.

6. Outlook

Recent progress on the structural studies on TRPC ion channels provide novel information on the architecture and assembly of TRPC channels; however, structure-based mechanistic details are relatively scarce. Several functional hallmarks of TRPC channels, such as lipid activation, await further structural elucidation and structures of the same TRPC channels in distinct functional states are required. Moreover, high resolution structures of TRPC channels in complex with small molecules that are of high pharmaceutical value will certainly pave the way for structure-based drug design targeting related human diseases.

Declaration of Competing Interest

The authors declare no competing interest.

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