## Phylogeny

Orthologues are present in mouse Trpm7 and zebrafish trpm7 (meltdown mutant), indicating conservation throughout vertebrates (Duan et al., 2018; Unknown Authors, 2023). The closest human paralogue is TRPM6, and TRPM6/TRPM7 heteromer formation reflects a recent duplication within the TRPM6/7 branch (Cai et al., 2017). The C-terminal catalytic region belongs to the atypical α-kinase clade, distantly related to elongation factor-2 kinase and classified in the “Other/α-kinase” family of the human kinome (Cai et al., 2017).

## Reaction Catalyzed

ATP + [protein]-L-Ser/Thr ⇄ ADP + [protein]-O-phospho-L-Ser/Thr (Cai et al., 2017).

## Cofactor Requirements

Maximal turnover is supported by Mn²⁺·ATP, whereas Mg²⁺·ATP functions both as a cofactor and as an inhibitor of the channel (Cai et al., 2017; Visser et al., 2014).

## Substrate Specificity

The kinase phosphorylates Ser/Thr residues embedded within α-helical elements rather than a strict linear consensus. Documented cellular substrates include non-muscle myosin heavy chain IIA, annexin I, phospholipase C γ2 and core histones (Cai et al., 2017).

## Structure

TRPM7 is a tetrameric channel-kinase composed of an N-terminal melastatin/ankyrin repeat region, a six-transmembrane pore (S1–S6) with intracellular TRP helix, a coiled-coil tetramerisation module, a Ser/Thr-rich autophosphorylation segment and a C-terminal α-kinase domain (Unknown Authors, 2019; Cai et al., 2017). Cryo-EM structures at 3.3–4.1 Å reveal a closed pore stabilised by a Cys1056–Cys1066 disulfide bond (Duan et al., 2018). The lower gate is formed by N1097/N1098, residues also required for Mg²⁺-dependent inhibition (Schmidt et al., 2022). A Zn²⁺ ion coordinates within the kinase core, enhancing stability (Duan et al., 2018). Kinase domains dimerise through β-strand exchange, which is obligatory for catalysis (Cai et al., 2017). An inhibitor-bound human structure (PDB 8W2L) shows CCT128930 occupying a vanilloid-like pocket; F924 is critical for binding (Nadezhdin et al., 2024).

## Regulation

More than 20 autophosphorylation sites have been identified; key residues include S1777 in the catalytic loop (phosphorylation diminishes activity) and S1565 in the exchange segment (restricts substrate access) (Cai et al., 2017). TRPM6 can trans-phosphorylate TRPM7 within heteromers (Cai et al., 2017). Intracellular Mg²⁺ and Mg·ATP bind near N1097/N1098 to synergistically inhibit the channel (Schmidt et al., 2022). Depletion or hydrolysis of membrane PIP₂ via PLC pathways rapidly inactivates current (Chubanov et al., 2018; Zhelay et al., 2018). Proteolytic cleavage can release the kinase domain, which subsequently relocalises to the nucleus (Nadezhdin et al., 2023).

## Function

TRPM7 is ubiquitously expressed, with highest levels in heart, kidney and brain; expression begins in early embryogenesis (Unknown Authors, 2010; Hu et al., 2021). Global knockout causes embryonic lethality and organogenesis defects (Duan et al., 2018). As a constitutively active channel, TRPM7 conducts Mg²⁺, Ca²⁺ and Zn²⁺, contributing to intracellular divalent cation homeostasis and vesicular Zn²⁺ release (Sun et al., 2015; Unknown Authors, 2023). The kinase phosphorylates cytoskeletal and trafficking proteins (myosin IIA, annexin I, PLC γ2, snapin) and interacts with TRPM6, snapin, synapsin I, synaptotagmin I and PLC γ2, integrating magnesium-sensitive Socs3a signalling and epithelial proliferation (Cai et al., 2017; Unknown Authors, 2010; Visser et al., 2014).

## Inhibitors

CCT128930 (sub-µM, binds vanilloid-like pocket), NS8593 (pore blocker), VER155008 (identified in screens) and waixenicin A (Mg²⁺-dependent inhibitor) reduce TRPM7 channel activity (Nadezhdin et al., 2024; Visser et al., 2014).

## Other Comments

Dysregulation of TRPM7 is linked to cardiac fibrosis, cancer progression and immune dysfunction (Hu et al., 2021; Nadezhdin et al., 2024). Mutations D922E, F924W/A alter inhibitor sensitivity; E1047Q reduces conductance, and N1097Q/N1098Q abolish Mg²⁺-dependent inhibition (Duan et al., 2018; Schmidt et al., 2022; Nadezhdin et al., 2024).

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