## Phylogeny

TRPM6 is a member of the melastatin-related (TRPM) subfamily within the transient receptor potential (TRP) ion-channel family (Azim et al., 2019; Chubanov & Gudermann, 2014). Kinome surveys place TRPM6 and its close homolog TRPM7 in the atypical α-kinase group, distinguished by fusion of an ion-channel module to a kinase domain (Chubanov et al., 2004; Schlingmann et al., 2007; Runnels, 2011). Orthologs are present in mouse, rat and zebrafish, indicating evolutionary conservation among vertebrates (Chubanov & Gudermann, 2014; Schmitz et al., 2005). TRPM6 and TRPM7 share ~77 % sequence identity in their kinase domains but are functionally non-redundant paralogs (Chubanov & Gudermann, 2014; Schmitz et al., 2005).

## Reaction Catalyzed

ATP + protein ⇌ ADP + phosphoprotein (Runnels, 2011; Schmitz et al., 2005; Schlingmann et al., 2007).  
The kinase domain uses ATP and does not accept GTP as phosphate donor (Runnels, 2011).

## Cofactor Requirements

Catalysis requires divalent cations: Mg²⁺ is essential and Mn²⁺ markedly stimulates activity (Azim et al., 2019; Chubanov & Gudermann, 2014; Chubanov et al., 2004; Runnels, 2011).

## Substrate Specificity

A consensus phosphorylation motif has not been defined (Runnels, 2011). TRPM6 phosphorylates serine or threonine residues, typically within α-helical regions (Chubanov & Gudermann, 2014; Runnels, 2011). Documented substrates (shared with TRPM7 in some cases) include myosin II heavy chains (IIA, IIB, IIC), annexin A1 and elongation-factor-2 kinase (Chubanov & Gudermann, 2014; Runnels, 2011).

## Structure

TRPM6 is a bifunctional protein comprising:  
• N-terminal ankyrin-like repeat domain  
• Six-transmembrane ion-channel core (S1–S6); the S5–S6 loop with a conserved EVY motif forms the pore (Chubanov & Gudermann, 2014)  
• C-terminal atypical α-kinase domain with distinct N- and C-lobes and a zinc-binding module that stabilises the fold (Chubanov & Gudermann, 2014; Runnels, 2011).

Structural information derives from homology modelling based on mouse TRPM7 kinase (PDB 1IA9), cryo-EM and AlphaFold models, highlighting key elements such as the activation loop and C-helix (Chubanov & Gudermann, 2014; Runnels, 2011; Schlingmann et al., 2007).

## Regulation

• Extensive Ser/Thr autophosphorylation (predominantly phosphoserine) enhances substrate recognition; Thr1851 autophosphorylation links kinase and channel functions (Chubanov & Gudermann, 2014; Runnels, 2011; Schmitz et al., 2005).  
• Mg-ATP positively modulates channel activity, whereas free intracellular Mg²⁺ is inhibitory (Azim et al., 2019; Chubanov & Gudermann, 2014).  
• TRPM6 can cross-phosphorylate TRPM7, but the reverse is not observed (Schmitz et al., 2005).  
• The scaffold protein RACK1 binds residues 1857–1885 and mediates inhibition (Runnels, 2011).  
• Epidermal growth factor up-regulates TRPM6 expression (Chubanov & Gudermann, 2014).

## Function

TRPM6 acts both as a Mg²⁺-permeable ion channel and as a Ser/Thr kinase, and is indispensable for systemic magnesium balance (Azim et al., 2019). It mediates active Mg²⁺ uptake in intestinal epithelium and reabsorption in the kidney distal convoluted tubule; expression is largely confined to these epithelia (Chubanov & Gudermann, 2014; Voets et al., 2004). Functional heterotetramers with ubiquitously expressed TRPM7 are required for proper membrane trafficking and activity (Chubanov et al., 2004; Schmitz et al., 2005). Additional interacting partners include RACK1, REA and MsrB1 (Chubanov & Gudermann, 2014).

## Inhibitors

Selective kinase inhibitors remain poorly characterised; few highly selective small molecules have been reported (Azim et al., 2019; Chubanov et al., 2004; Runnels, 2011; Schäffers et al., 2018). Channel conductance is voltage-dependently blocked by ruthenium red and is activated by 2-APB, opposite to the effect on TRPM7 (Schlingmann et al., 2007; Voets et al., 2004).

## Other Comments

Loss-of-function mutations in TRPM6 cause autosomal-recessive hypomagnesemia with secondary hypocalcemia, involving impaired intestinal absorption and renal Mg²⁺ wasting (Azim et al., 2019; Chubanov & Gudermann, 2014). Variants include missense (e.g., S141L), nonsense, frameshift and splice-site mutations that disrupt kinase function or TRPM6/TRPM7 complex formation (Azim et al., 2019; Chubanov et al., 2004; Schlingmann et al., 2007). Complete Trpm6 knockout in mice is embryonically lethal and causes neural tube defects, underscoring its developmental importance (Chubanov & Gudermann, 2014; Chubanov et al., 2016).

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