## Phylogeny

TRPM7 belongs to the melastatin (TRPM) subfamily of transient receptor potential channels and is classed as a “chanzyme” because its C-terminus encodes an intrinsic α-kinase. It is highly conserved from fish to mammals and is most closely related to TRPM6, with both proteins thought to have arisen from an ancestral vertebrate TRPM gene (Chubanov et al., 2005; Middelbeek et al., 2010). Phylogenetic analyses group TRPM7 with other molecular sensors of divalent cations and place its kinase domain within the unusual α-kinase branch of the eukaryotic kinome (Owsianik et al., 2006).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Chubanov et al., 2012).

## Cofactor Requirements

Mg²⁺ is essential; Mg²⁺ and Mg·ATP also act as feedback inhibitors of the channel (Chubanov et al., 2012).

## Substrate Specificity

The α-kinase domain phosphorylates serine/threonine residues within α-helical regions of diverse proteins including SMAD2, annexin A1, and several myosin II isoforms, indicating a broad but selective substrate range without a strict consensus motif (Chubanov et al., 2012).

## Structure

TRPM7 forms tetramers. Each subunit contains:  
• Six transmembrane helices (S1–S6) with a pore loop between S5–S6 that conducts Ca²⁺, Mg²⁺ and Zn²⁺ (Clapham et al., 2001).  
• A conserved TRP domain and a C-terminal coiled-coil that mediate assembly (Owsianik et al., 2006).  
• Large cytosolic N- and C-termini; the extreme C-terminus houses an atypical α-kinase with a nucleotide-binding pocket and a Zn²⁺-binding motif required for catalysis (Owsianik et al., 2006).

## Regulation

Channel activity is inhibited by intracellular Mg²⁺ and Mg·ATP, linking cellular energy status to ion flux (Chubanov et al., 2012). Phosphatidylinositol-4,5-bisphosphate sustains gating; its depletion suppresses currents (Clapham et al., 2001). Autophosphorylation modulates kinase output, and proteolytic cleavage can release the kinase fragment for nuclear signalling (Chubanov et al., 2012).

## Function

TRPM7 couples divalent-cation entry with kinase signalling to maintain Mg²⁺, Ca²⁺ and Zn²⁺ homeostasis. Ubiquitously expressed, it is indispensable for embryonic development, immune cell function and cell survival. By phosphorylating substrates such as SMAD2, annexin A1 and myosin II, TRPM7 influences cytoskeletal dynamics, cell migration, proliferation and differentiation (Chubanov et al., 2012; Nishida et al., 2006).

## Inhibitors

Small-molecule inhibitors and other modulators have been reported, but no highly selective compounds are yet established. Pharmacological suppression of TRPM7 alters cellular Mg²⁺/Ca²⁺ handling and is being explored in cancer and cardiovascular contexts (Clapham et al., 2001; Nishida et al., 2006).

## Other Comments

Mutations or dysregulation of TRPM7 are linked to disrupted magnesium balance, developmental defects, immune abnormalities and possible roles in neurodegeneration. Interest in targeting TRPM7 stems from its combined channel–kinase activities and implication in disease (Chubanov et al., 2005; Nishida et al., 2006).

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