Phylogeny  
TRPM6 is a member of the transient receptor potential melastatin (TRPM) family that is broadly conserved in vertebrates (Fleig & Penner, 2004). It clusters most closely with its paralogue TRPM7, sharing high sequence identity in the six-transmembrane core and the C-terminal α-kinase region (Samanta, Hughes, & Moiseenkova-Bell, 2018). Comparative analyses indicate both channel-kinases arose from an early gene-duplication event and have retained conserved TRP boxes and coiled-coil assembly motifs (Runnels, 2011).

Reaction Catalyzed  
ATP + [protein]-(Ser/Thr) ⇌ ADP + H⁺ + [protein]-(Ser/Thr-phosphate) (Ryazanova et al., 2004).

Cofactor Requirements  
Mg²⁺ is essential; Mn²⁺ can substitute with reduced efficiency (Ryazanova et al., 2004).

Substrate Specificity  
The C-terminal α-kinase is an atypical Ser/Thr kinase that preferentially targets residues embedded in α-helical regions. A strict consensus motif has not yet been defined, but, by analogy with TRPM7, substrates involved in cytoskeletal regulation and intracellular signalling are recognised (Harteneck, 2005; Runnels, 2011).

Structure  
TRPM6 is a bifunctional, single-chain protein comprising a large cytosolic N-terminus, six transmembrane segments (S1–S6) with a pore loop between S5 and S6, and a C-terminal module that contains coiled-coil domains followed by an atypical α-kinase fold (Fleig & Penner, 2004). The transmembrane core resembles voltage-gated cation channels, with S4 acting as a putative voltage sensor, while the kinase domain bears a distinct α-kinase architecture with catalytic, zinc-binding and regulatory elements (Nilius & Flockerzi, 2014). Channel and kinase domains are covalently linked, permitting coordinated ion permeation and phosphorylation (Runnels, 2011).

Regulation  
• Channel gating is negatively regulated by intracellular Mg²⁺ and Mg·ATP (Fleig & Penner, 2004).  
• Epidermal growth factor signalling up-regulates expression and plasma-membrane trafficking (Jimenez et al., 2020).  
• Autophosphorylation of the kinase domain and binding of RACK1 or REA provide additional control (Runnels, 2011).  
• Depletion of phosphatidylinositol-4,5-bisphosphate through PLC activation inhibits channel activity, linking receptor signalling to Mg²⁺ transport (Fleig & Penner, 2004).

Function  
TRPM6 is essential for systemic Mg²⁺ homeostasis. It is highly expressed in intestinal epithelium and in the distal convoluted tubule of the kidney, where it mediates active Mg²⁺ uptake and reabsorption (Fleig & Penner, 2004; Harteneck, 2005). Its dual channel/kinase activities coordinate Mg²⁺ influx with downstream signalling pathways required for metabolic regulation (Jimenez et al., 2020). Loss-of-function mutations cause familial hypomagnesemia with secondary hypocalcaemia (Nilius, Owsianik, Voets, & Peters, 2007).

Inhibitors  
Ruthenium red and rottlerin reduce TRPM6 activity, but selective pharmacological tools remain limited (Runnels, 2011; Fleig & Penner, 2004).

Other Comments  
TRPM6 can assemble as homomers or as heteromeric complexes with TRPM7; the latter appear more efficiently trafficked to the plasma membrane (Nilius & Flockerzi, 2014). Disease-linked mutations may impair either the ion-channel pore or the kinase active site, underscoring the importance of both functional modules (Runnels, 2011; Nilius et al., 2007). A definitive substrate consensus motif for the kinase has not yet been established (Harteneck, 2005).

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