1. Phylogeny  
   TRPM7 is a member of the transient receptor potential (TRP) ion channel superfamily that falls within the melastatin (TRPM) subfamily, a group known for combining channel and kinase functions. It is evolutionarily conserved across vertebrate species and shares a high degree of sequence similarity with its closest homolog TRPM6, which likely diverged from a common ancestral TRPM gene early in vertebrate evolution (chubanov2005emergingrolesof pages 1-2). Phylogenetic analyses place TRPM7 within an evolutionary clade comprising proteins that serve as molecular sensors for divalent cations and participate in cell signaling, in alignment with kinase families that include classical serine/threonine kinases (middelbeek2010thealphakinasefamily pages 7-8). Its domain architecture and sequence conservation support its classification as a “chanzyme,” an ion channel equipped with an intrinsic alpha-kinase domain, situating TRPM7 in a unique branch of the eukaryotic kinome that is broadly conserved from fish to mammals (owsianik2006structure–functionrelationshipof pages 7-9, clapham2001thetrpion pages 7-8).
2. Reaction Catalyzed  
   The kinase activity of TRPM7 catalyzes the transfer of the γ-phosphate group from ATP to specific serine and threonine residues on protein substrates. The chemical reaction can be summarized as:  
     ATP + [protein] – (L-serine or L-threonine) → ADP + [protein] – (L-serine/threonine)-phosphate + H⁺  
   This reaction underpins the phosphorylation cascade mediated by TRPM7’s C-terminal kinase domain (chubanov2012theemergingrole pages 139-141).
3. Cofactor Requirements  
   The catalytic activity of the TRPM7 kinase domain is dependent on divalent cations, with Mg²⁺ serving as a critical cofactor. In the presence of Mg²⁺, TRPM7 utilizes ATP to phosphorylate its substrates, and both Mg²⁺ and Mg·ATP act as regulatory cofactors that inhibit the ion channel activity of TRPM7, thereby coupling ion conductance with its enzymatic function (chubanov2012theemergingrole pages 134-137).
4. Substrate Specificity  
   TRPM7 phosphorylates a variety of downstream targets including SMAD2, annexin A1, and various isoforms of myosin II, indicating that it recognizes serine/threonine residues within a context favorable to kinase activity. The kinase domain, which aligns with the atypical α-kinase family, tends to phosphorylate residues located within alpha-helical regions of substrate proteins. Although a distinct consensus motif has not been as thoroughly defined as in some classical kinases, the substrates of TRPM7 generally contain multiple serine/threonine sites, and its in vitro substrate specificity supports a broad but selective repertoire in phosphorylating proteins involved in cytoskeletal dynamics and signal transduction (chubanov2012theemergingrole pages 141-143, clapham2001thetrpion pages 8-9).
5. Structure  
   TRPM7 exhibits a composite structure that integrates an ion channel domain with an intracellular kinase domain. The ion channel portion is organized into six transmembrane helices (designated S1–S6) including a pore loop between S5 and S6 that is essential for ion permeability of divalent cations such as Ca²⁺, Mg²⁺, and Zn²⁺ (clapham2001thetrpion pages 7-8). Adjacent to the transmembrane segments, a conserved TRP domain is present near the C-terminus, which along with a coiled-coil region, facilitates subunit assembly into tetrameric complexes. The large intracellular N-terminal and C-terminal domains of TRPM7 contain regulatory motifs; most notably, the extreme C-terminus houses an atypical alpha-kinase domain that can autophosphorylate and phosphorylate other proteins. Key structural elements of the kinase include a nucleotide-binding region and a zinc-binding motif that is critical for its enzymatic activity, while the channel domain contains residues essential for ion selectivity and gating (owsianik2006structure–functionrelationshipof pages 6-7, clapham2001thetrpion pages 8-9).
6. Regulation  
   TRPM7 is under complex regulation that integrates its roles in ion conductance and kinase signaling. The channel portion is inhibited by intracellular Mg²⁺ and Mg·ATP, providing a feedback mechanism that links the metabolic state of the cell with ion flux (chubanov2012theemergingrole pages 134-137). In addition, phosphatidylinositol 4,5-bisphosphate (PIP₂) interactions are critical for channel gating; depletion of PIP₂, as can occur following phospholipase C activation, diminishes channel activity. Autophosphorylation of the kinase domain also regulates its catalytic function and may influence the coupling between the channel and kinase activities. Moreover, proteolytic cleavage of the kinase domain has been reported, with the cleaved fragment translocating to the nucleus to participate in additional signaling events. These post-translational modifications underscore the multifaceted regulatory mechanisms governing TRPM7 function and ensure tight control over its dual activity (chubanov2012theemergingrole pages 139-141, clapham2001thetrpion pages 7-8).
7. Function  
   TRPM7 is a bifunctional protein that plays a central role in maintaining cellular homeostasis by regulating divalent cation influx and subsequently modulating intracellular signaling pathways. Its ion channel activity is critical for the uptake of Mg²⁺, Ca²⁺, and Zn²⁺, which are essential for numerous cellular processes including enzyme activation, cytoskeletal organization, and energy metabolism. The kinase activity of TRPM7 enables it to phosphorylate substrates such as SMAD2, annexin A1, and various myosin II isoforms, thereby influencing cell motility, proliferation, and differentiation. Expression of TRPM7 is ubiquitous, and its function is vital during embryonic development, for immune cell function, and in the regulation of cell survival. In vivo studies have demonstrated that disruption of TRPM7 function leads to severe developmental defects and impaired Mg²⁺ homeostasis, underscoring its importance in physiological mineral ion transport and signal transduction (chubanov2012theemergingrole pages 141-143, nishida2006trpchannelsmolecular pages 5-6). Furthermore, TRPM7 contributes to signaling pathways that control cytoskeletal dynamics, thereby affecting cell adhesion and migration, which are key processes in both normal cellular turnover and in pathological conditions such as cancer.
8. Other Comments  
   Known inhibitors and pharmacological modulators of TRPM7 have been explored in studies because inhibition of TRPM7 has been associated with alterations in cellular Mg²⁺ and Ca²⁺ homeostasis that can affect cell proliferation and survival. Although specific small-molecule inhibitors are not as well characterized as for other kinases, modulation of TRPM7 activity is of interest in therapeutic contexts such as in cancer and cardiovascular diseases, where dysregulation of magnesium transport and kinase signaling can contribute to disease pathogenesis. Disease associations have been reported in the context of disrupted magnesium homeostasis, embryonic lethality, and altered immune responses. Mutations in TRPM7, or its dysregulation, are being investigated for their potential roles in neurodegenerative disorders and conditions linked to defective cellular ion balance (clapham2001thetrpion pages 7-8, nishida2006trpchannelsmolecular pages 14-15).
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