1. Phylogeny  
   TRPM6, formally known as Transient Receptor Potential cation channel subfamily M member 6 or CHAK2, is phylogenetically nested within the TRPM (melastatin) subfamily of the larger TRP (Transient Receptor Potential) channel superfamily. Its evolutionary history is tightly linked to that of TRPM7, with which it shares a high degree of sequence similarity and common domain architecture, including the distinctive C-terminal α‐kinase domain. Phylogenetic analysis indicates that TRPM6 and TRPM7 emerged before the divergence of fish and land vertebrates, over 450 million years ago, thus placing them among evolutionarily conserved channel kinases in the vertebrate lineage (chubanov2005emergingrolesof pages 2-3, chubanov2005emergingrolesof pages 3-5). The kinase domain of TRPM6 is classified as part of the atypical α‐kinase family, a group clearly distinct from conventional serine/threonine kinases; within the kinome, the α‐kinases—including TRPM6 and TRPM7—are characterized by unusual catalytic cores and substrate recognition that preferentially target residues in α‐helical segments (middelbeek2010thealphakinasefamily pages 8-10). Orthologs of TRPM6 have been identified in several vertebrate species, including mammals such as mice and humans and extending to birds and fish, underscoring its conserved physiological importance in magnesium homeostasis (chubanov2005emergingrolesof pages 2-3).
2. Reaction Catalyzed  
   As a bifunctional protein, TRPM6 catalyzes two distinct reactions. In its role as an ion channel, TRPM6 facilitates the transmembrane flux of Mg²⁺ and other divalent cations, thereby directly influencing cytosolic magnesium concentrations. In parallel, its intracellular kinase domain catalyzes phosphorylation reactions whereby a phosphate moiety is transferred from ATP to specific serine and threonine residues on target protein substrates, including autophosphorylation of the channel itself and phosphorylation events that may modulate associated proteins such as TRPM7 (chubanov2005emergingrolesof pages 2-3, dorovkov2004phosphorylationofannexin pages 1-1). The general chemical reaction mediated by the kinase domain can be summarized as:  
     ATP + [protein] – OH → ADP + [protein] – O–PO₃²⁻ + H⁺  
   This dual reaction mechanism underlies its function as a “chanzyme” – both channel and enzyme – crucial for regulating magnesium absorption in epithelial cells (cai2017massspectrometricanalysis pages 13-13).
3. Cofactor Requirements  
   Activation of the kinase function in TRPM6 is dependent on specific cofactors. Like many kinases, TRPM6 requires Mg²⁺ as an essential cofactor to facilitate ATP binding and the phosphoryl transfer reaction (cao2008rack1inhibitstrpm6 pages 8-9). In the context of its ion channel activity, the permeability to Mg²⁺ coupled with regulation by intracellular concentrations of Mg²⁺ and Mg·ATP further underscores the dual sensitivity of TRPM6 to magnesium ions. Although Mn²⁺ could substitute in some phosphorylation reactions in other kinases, current data indicate that TRPM6 is highly specific for Mg²⁺ in both its channel and kinase activities (chubanov2005emergingrolesof pages 1-2).
4. Substrate Specificity  
   The substrate specificity of TRPM6’s kinase domain is determined by its classification within the atypical α‐kinase family. This group is known to phosphorylate serine and threonine residues, most notably within α‑helical regions of target proteins rather than in flexible loops typical of conventional kinases. Although our current literature does not enumerate an extensive list of physiological substrates, evidence suggests that TRPM6 shares overlapping substrate specificity with its close relative TRPM7. Studies have demonstrated phosphorylation events that modulate channel trafficking and activity, and there is support for phosphorylation of myosin II isoforms as a potential substrate in related systems (clark2008theα‐kinasestrpm6 pages 4-5, runnels2011trpm6andtrpm7 pages 2-3). In general, the consensus reaction involves the transfer of a phosphate group from ATP to hydroxyl groups on serine/threonine residues in substrates that may contain structural elements (such as α-helical domains) that permit binding by the unique catalytic site of TRPM6 (schmitz2005thechannelkinases pages 3-4).
5. Structure  
   TRPM6 is characterized by a complex, multidomain architecture reflective of its bifunctional roles. At the N-terminus, TRPM6 contains regions typical of TRP channels including a long N-terminal cytosolic domain that often includes a coiled-coil region implicated in channel assembly. This is followed by six predicted transmembrane segments (S1–S6) that constitute the ion channel pore, with a pore loop located between S5 and S6 that confers selectivity for Mg²⁺ and Ca²⁺ (chubanov2005emergingrolesof pages 1-2, nilius2011thetransientreceptor pages 1-2). A conserved TRP box motif is typically found in the C-terminal tail near the transmembrane domain, and this region is critical for channel gating. The most distinctive feature of TRPM6 is its large intracellular C-terminal extension containing a catalytic α-kinase domain that bears structural similarity to that found in TRPM7. This kinase domain is flanked by regulatory regions that are subject to autophosphorylation and may serve to modulate the enzyme’s activity (middelbeek2010thealphakinasefamily pages 7-8, cai2017massspectrometricanalysis pages 13-13). Structural studies, including crystallographic analyses of the homologous TRPM7 kinase domain, support that TRPM6’s kinase fold comprises a conserved N-terminal lobe with a phosphate-binding P-loop and a C-terminal lobe that forms the substrate binding pocket. Key catalytic residues required for ATP binding and phosphoryl transfer are conserved, ensuring proper kinase function (chubanov2005emergingrolesof pages 3-5, schmitz2005thechannelkinases pages 8-9).
6. Regulation  
   Regulation of TRPM6 occurs at several levels, integrating both its channel and kinase functionalities. Autophosphorylation within its C-terminal kinase domain is a critical regulatory mechanism; specific residues, such as threonine 1851, have been identified as key autophosphorylation sites that influence channel activity and sensitivity to intracellular Mg²⁺ inhibition (cao2008rack1inhibitstrpm6 pages 8-9). In addition, protein–protein interactions play a significant regulatory role. For instance, the scaffolding protein RACK1 has been shown to interact with the α-kinase domain of TRPM6, thereby inhibiting its activity through modulation of phosphorylation state (cao2008rack1inhibitstrpm6 pages 8-9). Furthermore, while the precise mechanism controlling the switch between its channel and kinase activities remains under active investigation, there is evidence that TRPM6 requires association with TRPM7 for efficient trafficking to the plasma membrane and that heteromerization influences both gating and enzymatic function (chubanov2005emergingrolesof pages 1-2, runnels2011trpm6andtrpm7 pages 4-5). Modulation by intracellular levels of Mg²⁺ and Mg·ATP also contributes to the fine-tuning of TRPM6 activity, acting as a feedback signal to regulate the extent of both ion permeation and kinase-driven phosphorylation events (nilius2011thetransientreceptor pages 2-4).
7. Function  
   The biological role of TRPM6 is central to magnesium homeostasis in vertebrate organisms. Primarily expressed in epithelial cells of the renal distal convoluted tubule and the intestinal brush border, TRPM6 underpins active magnesium absorption—a process critical for maintaining cellular and systemic Mg²⁺ balance (voets2004trpm6formsthe pages 1-1, walder2002mutationoftrpm6 pages 2-3). Loss-of-function mutations in TRPM6 lead to familial hypomagnesemia with secondary hypocalcemia, a severe autosomal recessive disorder underscoring the protein’s physiological importance (walder2002mutationoftrpm6 pages 2-3). Beyond its channel function, the α-kinase domain of TRPM6 is implicated in intracellular signaling pathways through its capacity to phosphorylate specific downstream substrates. This dual functional capacity positions TRPM6 as a “chanzyme” that not only facilitates Mg²⁺ entry into cells but also modulates cellular processes via phosphorylation. The functional interplay between TRPM6 and TRPM7, with evidence supporting the formation of heteromeric complexes, may further fine-tune magnesium transport and intracellular signaling in response to environmental and metabolic cues (chubanov2005emergingrolesof pages 3-5, runnels2011trpm6andtrpm7 pages 1-2). The expression of TRPM6 is tissue-specific, and its activity is tightly regulated to ensure appropriate magnesium uptake in organs critical for electrolyte balance, ultimately influencing processes such as enzyme activity, signal transduction, and cellular metabolism (dorovkov2004phosphorylationofannexin pages 1-1).
8. Other Comments  
   TRPM6 is of considerable clinical interest due to its direct involvement in hereditary disorders of magnesium homeostasis. Mutations in the TRPM6 gene are genetically linked to hypomagnesemia with secondary hypocalcemia, providing a clear link between channel-kinase dysfunction and disease (walder2002mutationoftrpm6 pages 2-3). Despite extensive research, the debate continues over whether TRPM6 can form fully functional homomeric channels on its own or whether its primary physiological role is as a subunit within heteromeric TRPM6-TRPM7 complexes (chubanov2005emergingrolesof pages 1-2, runnels2011trpm6andtrpm7 pages 2-3). This controversy further emphasizes the importance of precise regulatory mechanisms that govern both its ion channel and kinase activities. Ongoing studies are directed at elucidating the complete substrate repertoire of the TRPM6 kinase domain and deciphering the exact molecular mechanisms by which its phosphorylation events impact downstream signaling pathways. Inhibitor development targeting TRPM6 is also an area of active research, with the potential to modulate magnesium absorption in disease states; however, the dual functionality of TRPM6 complicates the development of highly specific inhibitors that can differentially affect its channel versus kinase activities (cao2008rack1inhibitstrpm6 pages 8-9). Furthermore, current research focuses on determining how phosphorylation of specific residues influences channel trafficking and gating, which may ultimately reveal novel therapeutic opportunities for the treatment of magnesium-related disorders (ferioli2017trpm6andtrpm7 pages 1-2).
9. References
10. chubanov2005emergingrolesof pages 1-2
11. chubanov2005emergingrolesof pages 2-3
12. chubanov2005emergingrolesof pages 3-5
13. middelbeek2010thealphakinasefamily pages 8-10
14. cao2008rack1inhibitstrpm6 pages 8-9
15. dorovkov2004phosphorylationofannexin pages 1-1
16. ferioli2017trpm6andtrpm7 pages 1-2
17. nilius2011thetransientreceptor pages 2-4
18. runnels2011trpm6andtrpm7 pages 2-3
19. schmitz2005thechannelkinases pages 1-2
20. schmitz2005thechannelkinases pages 3-4
21. clark2008theα‐kinasestrpm6 pages 4-5
22. voets2004trpm6formsthe pages 1-1
23. walder2002mutationoftrpm6 pages 2-3

References

1. (chubanov2005emergingrolesof pages 1-2): V. Chubanov, M. Mederos y Schnitzler, J. Wäring, A. Plank, and T. Gudermann. Emerging roles of trpm6/trpm7 channel kinase signal transduction complexes. Naunyn-Schmiedeberg’s Archives of Pharmacology, 371:334-341, May 2005. URL: https://doi.org/10.1007/s00210-005-1056-4, doi:10.1007/s00210-005-1056-4. This article has 60 citations.
2. (chubanov2005emergingrolesof pages 2-3): V. Chubanov, M. Mederos y Schnitzler, J. Wäring, A. Plank, and T. Gudermann. Emerging roles of trpm6/trpm7 channel kinase signal transduction complexes. Naunyn-Schmiedeberg’s Archives of Pharmacology, 371:334-341, May 2005. URL: https://doi.org/10.1007/s00210-005-1056-4, doi:10.1007/s00210-005-1056-4. This article has 60 citations.
3. (chubanov2005emergingrolesof pages 3-5): V. Chubanov, M. Mederos y Schnitzler, J. Wäring, A. Plank, and T. Gudermann. Emerging roles of trpm6/trpm7 channel kinase signal transduction complexes. Naunyn-Schmiedeberg’s Archives of Pharmacology, 371:334-341, May 2005. URL: https://doi.org/10.1007/s00210-005-1056-4, doi:10.1007/s00210-005-1056-4. This article has 60 citations.
4. (middelbeek2010thealphakinasefamily pages 8-10): Jeroen Middelbeek, Kristopher Clark, Hanka Venselaar, Martijn A. Huynen, and Frank N. van Leeuwen. The alpha-kinase family: an exceptional branch on the protein kinase tree. Cellular and Molecular Life Sciences, 67:875-890, Dec 2010. URL: https://doi.org/10.1007/s00018-009-0215-z, doi:10.1007/s00018-009-0215-z. This article has 150 citations and is from a domain leading peer-reviewed journal.
5. (cai2017massspectrometricanalysis pages 13-13): Na Cai, Zhiyong Bai, Vikas Nanda, and Loren W. Runnels. Mass spectrometric analysis of trpm6 and trpm7 phosphorylation reveals regulatory mechanisms of the channel-kinases. Scientific Reports, Feb 2017. URL: https://doi.org/10.1038/srep42739, doi:10.1038/srep42739. This article has 38 citations and is from a poor quality or predatory journal.
6. (cao2008rack1inhibitstrpm6 pages 8-9): Gang Cao, Stéphanie Thébault, Jenny van der Wijst, AnneMiete van der Kemp, Edwin Lasonder, René J.M. Bindels, and Joost G.J. Hoenderop. Rack1 inhibits trpm6 activity via phosphorylation of the fused α-kinase domain. Current Biology, 18:168-176, Feb 2008. URL: https://doi.org/10.1016/j.cub.2007.12.058, doi:10.1016/j.cub.2007.12.058. This article has 74 citations and is from a highest quality peer-reviewed journal.
7. (dorovkov2004phosphorylationofannexin pages 1-1): Maxim V. Dorovkov and Alexey G. Ryazanov. Phosphorylation of annexin i by trpm7 channel-kinase\*. Journal of Biological Chemistry, 279:50643-50646, Dec 2004. URL: https://doi.org/10.1074/jbc.c400441200, doi:10.1074/jbc.c400441200. This article has 279 citations and is from a domain leading peer-reviewed journal.
8. (ferioli2017trpm6andtrpm7 pages 1-2): Silvia Ferioli, Susanna Zierler, Joanna Zaißerer, Johann Schredelseker, Thomas Gudermann, and Vladimir Chubanov. Trpm6 and trpm7 differentially contribute to the relief of heteromeric trpm6/7 channels from inhibition by cytosolic mg2+ and mg·atp. Scientific Reports, Aug 2017. URL: https://doi.org/10.1038/s41598-017-08144-1, doi:10.1038/s41598-017-08144-1. This article has 87 citations and is from a poor quality or predatory journal.
9. (middelbeek2010thealphakinasefamily pages 7-8): Jeroen Middelbeek, Kristopher Clark, Hanka Venselaar, Martijn A. Huynen, and Frank N. van Leeuwen. The alpha-kinase family: an exceptional branch on the protein kinase tree. Cellular and Molecular Life Sciences, 67:875-890, Dec 2010. URL: https://doi.org/10.1007/s00018-009-0215-z, doi:10.1007/s00018-009-0215-z. This article has 150 citations and is from a domain leading peer-reviewed journal.
10. (nilius2011thetransientreceptor pages 1-2): Bernd Nilius and Grzegorz Owsianik. The transient receptor potential family of ion channels. Genome Biology, 12:218-218, Mar 2011. URL: https://doi.org/10.1186/gb-2011-12-3-218, doi:10.1186/gb-2011-12-3-218. This article has 1155 citations and is from a highest quality peer-reviewed journal.
11. (nilius2011thetransientreceptor pages 2-4): Bernd Nilius and Grzegorz Owsianik. The transient receptor potential family of ion channels. Genome Biology, 12:218-218, Mar 2011. URL: https://doi.org/10.1186/gb-2011-12-3-218, doi:10.1186/gb-2011-12-3-218. This article has 1155 citations and is from a highest quality peer-reviewed journal.
12. (runnels2011trpm6andtrpm7 pages 1-2): Loren W. Runnels. Trpm6 and trpm7: a mul-trp-plik-cation of channel functions. Current Pharmaceutical Biotechnology, 12:42-53, Jan 2011. URL: https://doi.org/10.2174/138920111793937880, doi:10.2174/138920111793937880. This article has 105 citations and is from a peer-reviewed journal.
13. (runnels2011trpm6andtrpm7 pages 2-3): Loren W. Runnels. Trpm6 and trpm7: a mul-trp-plik-cation of channel functions. Current Pharmaceutical Biotechnology, 12:42-53, Jan 2011. URL: https://doi.org/10.2174/138920111793937880, doi:10.2174/138920111793937880. This article has 105 citations and is from a peer-reviewed journal.
14. (runnels2011trpm6andtrpm7 pages 4-5): Loren W. Runnels. Trpm6 and trpm7: a mul-trp-plik-cation of channel functions. Current Pharmaceutical Biotechnology, 12:42-53, Jan 2011. URL: https://doi.org/10.2174/138920111793937880, doi:10.2174/138920111793937880. This article has 105 citations and is from a peer-reviewed journal.
15. (schmitz2005thechannelkinases pages 1-2): Carsten Schmitz, Maxim V. Dorovkov, Xiaoyun Zhao, Bennett J. Davenport, Alexey G. Ryazanov, and Anne-Laure Perraud. The channel kinases trpm6 and trpm7 are functionally nonredundant. Journal of Biological Chemistry, 280:37763-37771, Nov 2005. URL: https://doi.org/10.1074/jbc.m509175200, doi:10.1074/jbc.m509175200. This article has 247 citations and is from a domain leading peer-reviewed journal.
16. (schmitz2005thechannelkinases pages 3-4): Carsten Schmitz, Maxim V. Dorovkov, Xiaoyun Zhao, Bennett J. Davenport, Alexey G. Ryazanov, and Anne-Laure Perraud. The channel kinases trpm6 and trpm7 are functionally nonredundant. Journal of Biological Chemistry, 280:37763-37771, Nov 2005. URL: https://doi.org/10.1074/jbc.m509175200, doi:10.1074/jbc.m509175200. This article has 247 citations and is from a domain leading peer-reviewed journal.
17. (schmitz2005thechannelkinases pages 8-9): Carsten Schmitz, Maxim V. Dorovkov, Xiaoyun Zhao, Bennett J. Davenport, Alexey G. Ryazanov, and Anne-Laure Perraud. The channel kinases trpm6 and trpm7 are functionally nonredundant. Journal of Biological Chemistry, 280:37763-37771, Nov 2005. URL: https://doi.org/10.1074/jbc.m509175200, doi:10.1074/jbc.m509175200. This article has 247 citations and is from a domain leading peer-reviewed journal.
18. (voets2004trpm6formsthe pages 1-1): Thomas Voets, Bernd Nilius, Susan Hoefs, Annemiete W.C.M. van der Kemp, Guy Droogmans, Rene J.M. Bindels, and Joost G.J. Hoenderop. Trpm6 forms the mg2+ influx channel involved in intestinal and renal mg2+ absorption\*. Journal of Biological Chemistry, 279:19-25, Jan 2004. URL: https://doi.org/10.1074/jbc.m311201200, doi:10.1074/jbc.m311201200. This article has 771 citations and is from a domain leading peer-reviewed journal.
19. (walder2002mutationoftrpm6 pages 2-3): Roxanne Y. Walder, Daniel Landau, Peter Meyer, Hanna Shalev, Maria Tsolia, Zvi Borochowitz, Melanie Barbara Boettger, Gretel E. Beck, Richard K. Englehardt, Rivka Carmi, and Val C. Sheffield. Mutation of trpm6 causes familial hypomagnesemia with secondary hypocalcemia. Nature Genetics, 31:171-174, May 2002. URL: https://doi.org/10.1038/ng901, doi:10.1038/ng901. This article has 687 citations and is from a highest quality peer-reviewed journal.
20. (clark2008theα‐kinasestrpm6 pages 4-5): Kristopher Clark, Jeroen Middelbeek, Maxim V. Dorovkov, Carl G. Figdor, Alexey G. Ryazanov, Edwin Lasonder, and Frank N. van Leeuwen. The α‐kinases trpm6 and trpm7, but not eef‐2 kinase, phosphorylate the assembly domain of myosin iia, iib and iic. FEBS Letters, 582:2993-2997, Aug 2008. URL: https://doi.org/10.1016/j.febslet.2008.07.043, doi:10.1016/j.febslet.2008.07.043. This article has 115 citations and is from a peer-reviewed journal.