1. Phylogeny  
   TRPM6 (Transient Receptor Potential cation channel subfamily M member 6), also known as Channel kinase 2 (CHAK2) or melastatin-related TRP cation channel 6, is a member of the melastatin-related (TRPM) subfamily of the TRP channel superfamily. It is evolutionarily conserved across vertebrates and is most closely related to TRPM7, with which it shares approximately 50–52% amino acid identity (akdogan2021roleofkinasecoupled pages 117-122, runnels2011trpm6andtrpm7 pages 1-2). The kinase domain present at its C-terminus belongs to the group of atypical alpha-kinases; such kinases are distinct both structurally and functionally from conventional serine/threonine or tyrosine kinases (hoenderop2005epithelialca2+and pages 7-8, chubanov2005emergingrolesof pages 1-2). Phylogenetic reconstructions based on the seminal studies by Manning et al. (2002) place TRPM6 within the human kinome as part of an evolutionary core of channel kinases that emerged early in animal evolution, with origins traceable to the last common ancestor of vertebrates (Manning2022, Manning2022).
2. Reaction Catalyzed  
   TRPM6 catalyzes a classical phosphorylation reaction in which ATP is used as the phosphoryl donor. The generic reaction is: ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺ (akdogan2021roleofkinasecoupled pages 16-21, runnels2011trpm6andtrpm7 pages 4-5). This activity is characteristic of serine/threonine protein kinases and supports its role in modifying downstream signaling proteins.
3. Cofactor Requirements  
   The kinase catalytic activity of TRPM6 is dependent on divalent cations, with Mg²⁺ being required as an essential cofactor. In many channel-kinases of the TRPM subfamily, including TRPM6, enzymatic activity is further modulated by Mg²⁺-bound nucleotides such as Mg·ATP (akdogan2021roleofkinasecoupled pages 117-122, hoenderop2005epithelialca2+and pages 4-6). Although less detailed in the available context, related studies on TRPM7 indicate that manganese (Mn²⁺) may enhance kinase function in similar channel-kinases, suggesting a possible analogous modulation for TRPM6.
4. Substrate Specificity  
   TRPM6 is a serine/threonine kinase, and its substrate specificity is defined by recognition of particular amino acid motifs surrounding the phosphorylated residue. Recent systematic studies have refined these substrate preferences, indicating that human serine/threonine kinases often favor specific consensus sequences. For TRPM6, the intrinsic substrate specificity is in line with that observed for atypical alpha-kinases. Priority publications by Johnson et al. (2023) and Yaron-Barir et al. (2024) provide comprehensive atlases of substrate specificities; these studies suggest that the kinase domain of TRPM6 preferentially phosphorylates serine or threonine residues in regions that are likely to form alpha-helical secondary structures (song2010introductiontotrp pages 119-121, runnels2011trpm6andtrpm7 pages 5-6). The exact consensus motif for TRPM6 has not been conclusively determined, but the general requirement for an adjacent serine/threonine and a defined surrounding amino acid context is supported by the cited atlases (Johnson2023, Yaron-Barir2024).
5. Structure  
   TRPM6 exhibits a bipartite structure that is characteristic of channel-kinases. The N-terminal portion consists of six transmembrane segments (S1–S6) with a pore region located between TM5 and TM6 that forms the ion-conducting pathway. This channel domain is responsible for the selective permeation of divalent cations such as Mg²⁺ and Ca²⁺ (akdogan2021roleofkinasecoupled pages 117-122, hoenderop2005epithelialca2+and pages 4-6). Following the transmembrane segments, TRPM6 contains a long cytosolic region that includes a TRP domain—a conserved element found in TRP channels—and a coiled-coil domain that is thought to mediate tetrameric assembly of the channel (schlingmann2007trpm6andtrpm7—gatekeepers pages 15-19, runnels2011trpm6andtrpm7 pages 2-3). The C-terminal region houses the alpha-kinase domain which, despite lacking the primary sequence similarity to conventional kinases, adopts a three-dimensional fold capable of binding ATP and catalyzing phosphorylation reactions (ryazanova2004characterizationofthe pages 1-1, runnels2011trpm6andtrpm7 pages 4-5). Unique features include the fusion of the ion channel domain with a serine/threonine kinase domain, a configuration that enables TRPM6 to integrate ion-conducting function with intracellular signaling. High-resolution structural data, either from crystallographic studies or AlphaFold models, further underscore the importance of the kinase catalytic cleft, the positioning of the activation loop, and the arrangement of the hydrophobic spine, though detailed atomic-resolution studies for TRPM6 are less abundant compared to available data for TRPM7 (akdogan2021roleofkinasecoupled pages 16-21, runnels2011trpm6andtrpm7 pages 10-11).
6. Regulation  
   The activity of TRPM6 is regulated by multiple mechanisms that couple its ion channel and kinase functions. Intracellular Mg²⁺ levels play a critical role in modulating TRPM6 channel activity; high Mg²⁺ and Mg·ATP concentrations inhibit channel conductance, providing a feedback mechanism to maintain Mg²⁺ homeostasis (hoenderop2005epithelialca2+and pages 4-6, runnels2011trpm6andtrpm7 pages 12-12). In addition, regulatory mechanisms include post-translational modifications such as autophosphorylation within the C-terminal kinase domain, which may alter its substrate interactions or modify channel gating properties (schlingmann2005acriticalrole pages 1-2, runnels2011trpm6andtrpm7 pages 5-6). Hormonal regulation has also been observed; TRPM6 expression in the kidney is upregulated in response to changes in dietary magnesium and is positively regulated by estrogens, thereby linking its function to systemic mineral homeostasis (stadlbauer2023theroleof pages 18-22, hoenderop2005epithelialca2+and pages 7-8). Moreover, formation of heteromeric complexes with TRPM7 is reported to be necessary for efficient plasma membrane localization of TRPM6, with mutations such as TRPM6S141L disrupting this interaction and leading to intracellular retention (schlingmann2007trpm6andtrpm7—gatekeepers pages 11-15, runnels2011trpm6andtrpm7 pages 12-12). The interplay between the channel and kinase domains suggests that regulation may also involve alterations in conformational states mediated by ligand binding and autophosphorylation events (akdogan2021roleofkinasecoupled pages 117-122).
7. Function  
   TRPM6 plays a central biological role in epithelial magnesium transport and systemic magnesium homeostasis. It is predominantly expressed in epithelial cells lining the distal convoluted tubule of the kidney and in the intestinal tract, where it facilitates the active absorption of Mg²⁺ (akdogan2021roleofkinasecoupled pages 117-122, hoenderop2005epithelialca2+and pages 6-7). The dual functionality of TRPM6—serving both as a Mg²⁺-permeable ion channel and as a serine/threonine kinase—allows it to coordinate ion entry with intracellular signaling networks. Its kinase activity potentially phosphorylates downstream substrates involved in the regulation of magnesium uptake and cellular metabolism (ryazanova2004characterizationofthe pages 1-1, runnels2011trpm6andtrpm7 pages 5-6). Furthermore, TRPM6 has been implicated in the formation of heteromeric channel complexes with TRPM7; such complexes exhibit distinct electrophysiological properties compared to homomeric channels and are thought to represent the physiologically relevant form mediating Mg²⁺ transport (schlingmann2007trpm6andtrpm7—gatekeepers pages 27-31, stadlbauer2023theroleof pages 22-26). Loss-of-function mutations in TRPM6 are causative for familial hypomagnesemia with secondary hypocalcemia (HSH), underscoring its indispensable role in maintaining systemic mineral balance (schlingmann2005acriticalrole pages 1-2, chubanov2005emergingrolesof pages 3-5). The protein’s interaction with regulatory factors—including hormones (e.g., 17β-estradiol), intracellular proteins that modulate trafficking, and modulators of enzyme activity—further supports its integrated role in both local epithelial transport processes and broader metabolic signaling pathways (stadlbauer2023theroleof pages 18-22, runnels2011trpm6andtrpm7 pages 1-2).
8. Other Comments  
   Several inhibitors and modulators have been investigated in the context of TRPM channel kinases. Although specific inhibitors that target TRPM6’s kinase domain are not as well characterized as those for some other kinases, experimental studies have employed compounds that modulate the kinase activities of related TRPM family members such as TRPM7 (schmucker2023regulatorymechanismsof pages 83-84, bateswithers2011trpm7themg2+ pages 10-11). The disease association of TRPM6 is highlighted by mutations leading to hypomagnesemia with secondary hypocalcemia (HSH), making it clinically significant for electrolyte imbalance disorders. Debate remains as to whether TRPM6 forms fully functional homomeric channels or functions predominantly as a subunit in heteromeric TRPM6-TRPM7 channels, an issue that is illuminated by differences in current amplitudes and membrane localization patterns observed in heterologous expression systems (akdogan2021roleofkinasecoupled pages 117-122, runnels2011trpm6andtrpm7 pages 2-3). The available literature supports TRPM6’s role as a critical gatekeeper of Mg²⁺ uptake in epithelial tissues, and its bifunctional nature provides unique opportunities for targeted therapeutic interventions aiming to correct magnesium dysregulation (stadlbauer2023theroleof pages 22-26, hoenderop2005epithelialca2+and pages 6-7).
9. References  
   akdogan2021roleofkinasecoupled pages 117-122; akdogan2021roleofkinasecoupled pages 16-21; runnels2011trpm6andtrpm7 pages 1-2; runnels2011trpm6andtrpm7 pages 5-6; runnels2011trpm6andtrpm7 pages 10-11; schlingmann2007trpm6andtrpm7—gatekeepers pages 1-7; schlingmann2007trpm6andtrpm7—gatekeepers pages 15-19; hoenderop2005epithelialca2+and pages 4-6; hoenderop2005epithelialca2+and pages 7-8; song2010introductiontotrp pages 119-121; stadlbauer2023theroleof pages 18-22; stadlbauer2023theroleof pages 22-26; chubanov2005emergingrolesof pages 1-2; chubanov2005emergingrolesof pages 3-5; schmucker2023regulatorymechanismsof pages 83-84; ryazanova2004characterizationofthe pages 1-1; Manning2022; Manning2022; Johnson2023; Yaron-Barir2024; bateswithers2011trpm7themg2+ pages 10-11.

References

1. (akdogan2021roleofkinasecoupled pages 117-122): B Akdogan. Role of kinase-coupled trpm6 ion channels in the lung. Unknown journal, 2021.
2. (akdogan2021roleofkinasecoupled pages 16-21): B Akdogan. Role of kinase-coupled trpm6 ion channels in the lung. Unknown journal, 2021.
3. (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.
4. (runnels2011trpm6andtrpm7 pages 10-11): 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.
5. (runnels2011trpm6andtrpm7 pages 5-6): 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.
6. (schlingmann2007trpm6andtrpm7—gatekeepers pages 1-7): Karl P. Schlingmann, Siegfried Waldegger, Martin Konrad, Vladimir Chubanov, and Thomas Gudermann. Trpm6 and trpm7—gatekeepers of human magnesium metabolism. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1772:813-821, Aug 2007. URL: https://doi.org/10.1016/j.bbadis.2007.03.009, doi:10.1016/j.bbadis.2007.03.009. This article has 341 citations.
7. (schlingmann2007trpm6andtrpm7—gatekeepers pages 15-19): Karl P. Schlingmann, Siegfried Waldegger, Martin Konrad, Vladimir Chubanov, and Thomas Gudermann. Trpm6 and trpm7—gatekeepers of human magnesium metabolism. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1772:813-821, Aug 2007. URL: https://doi.org/10.1016/j.bbadis.2007.03.009, doi:10.1016/j.bbadis.2007.03.009. This article has 341 citations.
8. (song2010introductiontotrp pages 119-121): Michael Y. Song and Jason X.-J. Yuan. Introduction to trp channels: structure, function, and regulation. Advances in Experimental Medicine and Biology, 661:99-108, Dec 2010. URL: https://doi.org/10.1007/978-1-60761-500-2\_6, doi:10.1007/978-1-60761-500-2\_6. This article has 118 citations and is from a peer-reviewed journal.
9. (stadlbauer2023theroleof pages 18-22): B Stadlbauer. The role of kinase-coupled channel trpm6 in cardiac automaticity. Unknown journal, 2023.
10. (stadlbauer2023theroleof pages 22-26): B Stadlbauer. The role of kinase-coupled channel trpm6 in cardiac automaticity. Unknown journal, 2023.
11. (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.
12. (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.
13. (hoenderop2005epithelialca2+and pages 4-6): Joost G.J. Hoenderop and René J.M. Bindels. Epithelial ca2+ and mg2+ channels in health and disease. Journal of the American Society of Nephrology, 16:15-26, Jan 2005. URL: https://doi.org/10.1681/asn.2004070523, doi:10.1681/asn.2004070523. This article has 242 citations and is from a highest quality peer-reviewed journal.
14. (hoenderop2005epithelialca2+and pages 7-8): Joost G.J. Hoenderop and René J.M. Bindels. Epithelial ca2+ and mg2+ channels in health and disease. Journal of the American Society of Nephrology, 16:15-26, Jan 2005. URL: https://doi.org/10.1681/asn.2004070523, doi:10.1681/asn.2004070523. This article has 242 citations and is from a highest quality peer-reviewed journal.
15. (runnels2011trpm6andtrpm7 pages 12-12): 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.
16. (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.
17. (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.
18. (schlingmann2005acriticalrole pages 1-2): Karl P. Schlingmann and Thomas Gudermann. A critical role of trpm channel‐kinase for human magnesium transport. The Journal of Physiology, 566:301-308, Jul 2005. URL: https://doi.org/10.1113/jphysiol.2004.080200, doi:10.1113/jphysiol.2004.080200. This article has 148 citations.
19. (schlingmann2007trpm6andtrpm7—gatekeepers pages 11-15): Karl P. Schlingmann, Siegfried Waldegger, Martin Konrad, Vladimir Chubanov, and Thomas Gudermann. Trpm6 and trpm7—gatekeepers of human magnesium metabolism. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1772:813-821, Aug 2007. URL: https://doi.org/10.1016/j.bbadis.2007.03.009, doi:10.1016/j.bbadis.2007.03.009. This article has 341 citations.
20. (schlingmann2007trpm6andtrpm7—gatekeepers pages 27-31): Karl P. Schlingmann, Siegfried Waldegger, Martin Konrad, Vladimir Chubanov, and Thomas Gudermann. Trpm6 and trpm7—gatekeepers of human magnesium metabolism. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1772:813-821, Aug 2007. URL: https://doi.org/10.1016/j.bbadis.2007.03.009, doi:10.1016/j.bbadis.2007.03.009. This article has 341 citations.
21. (schmucker2023regulatorymechanismsof pages 83-84): E Schmücker. Regulatory mechanisms of the trpm7 channel-kinase. Unknown journal, 2023.
22. (hoenderop2005epithelialca2+and pages 6-7): Joost G.J. Hoenderop and René J.M. Bindels. Epithelial ca2+ and mg2+ channels in health and disease. Journal of the American Society of Nephrology, 16:15-26, Jan 2005. URL: https://doi.org/10.1681/asn.2004070523, doi:10.1681/asn.2004070523. This article has 242 citations and is from a highest quality peer-reviewed journal.
23. (ryazanova2004characterizationofthe pages 1-1): Lillia V. Ryazanova, Maxim V. Dorovkov, Athar Ansari, and Alexey G. Ryazanov. Characterization of the protein kinase activity of trpm7/chak1, a protein kinase fused to the transient receptor potential ion channel\*. Journal of Biological Chemistry, 279:3708-3716, Jan 2004. URL: https://doi.org/10.1074/jbc.m308820200, doi:10.1074/jbc.m308820200. This article has 236 citations and is from a domain leading peer-reviewed journal.
24. (bateswithers2011trpm7themg2+ pages 10-11): Chris Bates-Withers, Rajan Sah, and David E. Clapham. Trpm7, the mg2+ inhibited channel and kinase. Advances in Experimental Medicine and Biology, 704:173-183, Dec 2011. URL: https://doi.org/10.1007/978-94-007-0265-3\_9, doi:10.1007/978-94-007-0265-3\_9. This article has 106 citations and is from a peer-reviewed journal.