1. Phylogeny – TRPM6 is a member of the transient receptor potential melastatin (TRPM) subfamily of cation channels, an evolutionarily conserved group widely distributed among vertebrates, and its orthologs have been identified across various mammalian species (fleig2004thetrpmion pages 4-5). It is phylogenetically grouped together with TRPM7 due to their high sequence similarity, particularly in the transmembrane and C-terminal α-kinase domains, which distinguishes them from other TRPM channels (samanta2018transientreceptorpotential pages 10-13). TRPM6 and its close paralog TRPM7 belong to a distinct subgroup within the TRPM family characterized by dual functionality, combining ion conduction with intrinsic kinase activity (runnels2011trpm6andtrpm7 pages 1-2). Comparative evolutionary studies indicate that these channel-kinases emerged from an ancient duplication event in the TRPM lineage, and they have retained conserved domains such as the TRP box and coiled-coil assembly motifs, which underscores their evolutionary conservation and functional importance (fleig2004thetrpmion pages 1-2).
2. Reaction Catalyzed – The kinase domain of TRPM6 catalyzes phosphorylation reactions by transferring a phosphate group from ATP to serine and/or threonine residues on substrate proteins, and thus the general reaction can be represented as: ATP + [protein]–(Ser/Thr) → ADP + [protein]–(Ser/Thr-phosphate) + H⁺ (ryazanova2004characterizationofthe pages 6-7).
3. Cofactor Requirements – The catalytic activity of TRPM6’s kinase domain depends on divalent metal ions as essential cofactors, with Mg²⁺ being required for optimal ATP binding and phosphoryl transfer, and in some contexts Mn²⁺ may substitute as a cofactor though with differing efficacy (ryazanova2004characterizationofthe pages 6-7).
4. Substrate Specificity – Although detailed consensus substrate motifs for TRPM6 have not been fully elucidated in the available literature, its kinase domain is classified as an atypical α-kinase; such kinases typically target serine and threonine residues located within α-helical regions of protein substrates (harteneck2005functionandpharmacology pages 3-5). Experimental studies indicate that TRPM6, like its homolog TRPM7, phosphorylates substrates involved in cytoskeletal regulation and other intracellular signaling processes, although a precise amino acid consensus motif remains to be determined (runnels2011trpm6andtrpm7 pages 3-4).
5. Structure – TRPM6 is a bifunctional protein that exhibits a modular architecture comprising an extensive N-terminal cytosolic domain, six transmembrane helices (S1–S6) with a pore loop located between S5 and S6 that confers ion selectivity, and a C-terminal region that includes conserved coiled-coil domains and an atypical α-kinase domain (fleig2004thetrpmion pages 4-5). The transmembrane domain shows structural organization that is reminiscent of voltage-gated cation channels, wherein the S4 segment may function as a voltage-sensing element despite the protein exhibiting largely constitutive activity (nilius2014mammaliantransientreceptor pages 511-513). The kinase domain, fused at the C-terminus, adopts an α-kinase fold that is structurally distinct from conventional serine/threonine kinases; key catalytic residues and a zinc-binding module within the kinase domain contribute to its enzymatic function and stability (nilius2014mammaliantransientreceptor pages 508-511). Unique to TRPM6 is the integration of its channel and kinase domains into a single polypeptide, enabling it to potentially couple ion flux with immediate downstream phosphorylation events, an arrangement that is conserved in TRPM7 as well (runnels2011trpm6andtrpm7 pages 4-5).
6. Regulation – TRPM6 is regulated by several intracellular and extracellular signals that modulate both its channel and kinase activities; intracellular Mg²⁺ and Mg·ATP levels exert a negative regulatory influence on channel gating, thereby controlling divalent cation permeability (fleig2004thetrpmion pages 2-3). Furthermore, receptor-mediated signaling pathways, including those activated by epidermal growth factor (EGF), can upregulate TRPM6 expression and enhance its trafficking to the plasma membrane, which is critical for its function in epithelial Mg²⁺ absorption (jimenez2020trpmchannelsin pages 47-49). The kinase domain itself undergoes extensive autophosphorylation, and interactions with regulatory proteins such as RACK1 and the repressor of estrogen receptor activity (REA) have been shown to modulate channel activity through inhibitory protein–protein interactions (runnels2011trpm6andtrpm7 pages 5-6). In addition, signaling molecules that deplete phosphatidylinositol 4,5-bisphosphate (PIP₂) such as activated phospholipase C can inhibit TRPM6 channel function, thereby linking receptor activation to alterations in Mg²⁺ homeostasis (fleig2004thetrpmion pages 6-7).
7. Function – TRPM6 plays a crucial role in maintaining systemic magnesium homeostasis primarily through its function in epithelial Mg²⁺ transport in the kidney and gut; its activity underlies the active absorption of Mg²⁺ from the intestinal lumen and contributes to renal reabsorption in the distal convoluted tubule (fleig2004thetrpmion pages 4-5). The protein’s dual functionality enables it to both conduct Mg²⁺ through its ion channel pore and modulate downstream signaling pathways via its kinase activity, aspects that are essential for cellular magnesium balance and overall metabolic regulation (jimenez2020trpmchannelsin pages 25-27). Loss-of-function mutations in TRPM6 are directly linked to the autosomal recessive disorder familial hypomagnesemia with secondary hypocalcemia, a condition characterized by impaired intestinal and renal Mg²⁺ transport, which underscores the protein’s importance in mineral homeostasis (nilius2007transientreceptorpotential pages 12-13). TRPM6 is predominantly expressed in colon and kidney epithelia, and its proper function is necessary for sustaining physiological levels of Mg²⁺ required for numerous enzymatic processes and general cellular function (harteneck2005functionandpharmacology pages 7-8).
8. Other Comments – Although debate remains regarding whether TRPM6 forms fully functional homomeric channels in isolation or predominantly operates as a component of heteromeric TRPM6–TRPM7 complexes, the current consensus indicates that channel assembly and plasma membrane localization may be more efficient in the heteromeric state (fleig2004thetrpmion pages 6-7, nilius2014mammaliantransientreceptor pages 520-523). Several inhibitors known to affect related TRPM channels, such as ruthenium red and rottlerin, have been observed to modulate TRPM6 activity, although selective pharmacological tools that target TRPM6 specifically remain underdeveloped (runnels2011trpm6andtrpm7 pages 8-9). Mutations in TRPM6 that impair either channel conductance or kinase activity are associated with severe magnesium deficiency syndromes, and ongoing research continues to elucidate the mechanistic details of how such mutations disrupt its dual functions (nilius2007transientreceptorpotential pages 4-5, runnels2011trpm6andtrpm7 pages 9-10). No definitive consensus sequence for substrate recognition by the TRPM6 kinase domain has been established, and further biochemical studies are required to fully map its phosphorylation targets (harteneck2005functionandpharmacology pages 3-5).
9. References
10. fleig2004thetrpmion pages 4-5
11. fleig2004thetrpmion pages 6-7
12. fleig2004thetrpmion pages 1-2
13. fleig2004thetrpmion pages 2-3
14. harteneck2005functionandpharmacology pages 3-5
15. harteneck2005functionandpharmacology pages 7-8
16. jimenez2020trpmchannelsin pages 25-27
17. jimenez2020trpmchannelsin pages 47-49
18. nilius2014mammaliantransientreceptor pages 511-513
19. nilius2014mammaliantransientreceptor pages 520-523
20. nilius2007transientreceptorpotential pages 12-13
21. nilius2014mammaliantransientreceptor pages 503-505
22. runnels2011trpm6andtrpm7 pages 1-2
23. runnels2011trpm6andtrpm7 pages 4-5
24. runnels2011trpm6andtrpm7 pages 5-6
25. runnels2011trpm6andtrpm7 pages 8-9
26. runnels2011trpm6andtrpm7 pages 9-10
27. samanta2018transientreceptorpotential pages 10-13
28. ryazanova2004characterizationofthe pages 6-7
29. clapham2001thetrpion pages 8-9
30. geiger2023rolesoftransient pages 60-61
31. jimenez2020trpmchannelsin pages 20-23
32. jimenez2020trpmchannelsin pages 3-6
33. jimenez2020trpmchannelsin pages 46-47
34. huang2020astructuraloverview pages 11-11

References

1. (fleig2004thetrpmion pages 4-5): Andrea Fleig and Reinhold Penner. The trpm ion channel subfamily: molecular, biophysical and functional features. Trends in Pharmacological Sciences, 25:633-639, Dec 2004. URL: https://doi.org/10.1016/j.tips.2004.10.004, doi:10.1016/j.tips.2004.10.004. This article has 360 citations and is from a highest quality peer-reviewed journal.
2. (fleig2004thetrpmion pages 6-7): Andrea Fleig and Reinhold Penner. The trpm ion channel subfamily: molecular, biophysical and functional features. Trends in Pharmacological Sciences, 25:633-639, Dec 2004. URL: https://doi.org/10.1016/j.tips.2004.10.004, doi:10.1016/j.tips.2004.10.004. This article has 360 citations and is from a highest quality peer-reviewed journal.
3. (harteneck2005functionandpharmacology pages 3-5): Christian Harteneck. Function and pharmacology of trpm cation channels. Naunyn-Schmiedeberg’s Archives of Pharmacology, 371:307-314, Apr 2005. URL: https://doi.org/10.1007/s00210-005-1034-x, doi:10.1007/s00210-005-1034-x. This article has 201 citations.
4. (jimenez2020trpmchannelsin pages 25-27): Ivanka Jimenez, Yolanda Prado, Felipe Marchant, Carolina Otero, Felipe Eltit, Claudio Cabello-Verrugio, Oscar Cerda, and Felipe Simon. Trpm channels in human diseases. Cells, 9:2604, Dec 2020. URL: https://doi.org/10.3390/cells9122604, doi:10.3390/cells9122604. This article has 65 citations and is from a peer-reviewed journal.
5. (nilius2014mammaliantransientreceptor pages 503-505): B. Nilius and V. Flockerzi. Mammalian transient receptor potential (trp) cation channels. Handbook of Experimental Pharmacology, Jan 2014. URL: https://doi.org/10.1007/978-3-642-54215-2, doi:10.1007/978-3-642-54215-2. This article has 228 citations and is from a peer-reviewed journal.
6. (nilius2014mammaliantransientreceptor pages 508-511): B. Nilius and V. Flockerzi. Mammalian transient receptor potential (trp) cation channels. Handbook of Experimental Pharmacology, Jan 2014. URL: https://doi.org/10.1007/978-3-642-54215-2, doi:10.1007/978-3-642-54215-2. This article has 228 citations and is from a peer-reviewed journal.
7. (nilius2014mammaliantransientreceptor pages 511-513): B. Nilius and V. Flockerzi. Mammalian transient receptor potential (trp) cation channels. Handbook of Experimental Pharmacology, Jan 2014. URL: https://doi.org/10.1007/978-3-642-54215-2, doi:10.1007/978-3-642-54215-2. This article has 228 citations and is from a peer-reviewed journal.
8. (nilius2014mammaliantransientreceptor pages 520-523): B. Nilius and V. Flockerzi. Mammalian transient receptor potential (trp) cation channels. Handbook of Experimental Pharmacology, Jan 2014. URL: https://doi.org/10.1007/978-3-642-54215-2, doi:10.1007/978-3-642-54215-2. This article has 228 citations and is from a peer-reviewed journal.
9. (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.
10. (samanta2018transientreceptorpotential pages 10-13): Amrita Samanta, Taylor E. T. Hughes, and Vera Y. Moiseenkova-Bell. Transient receptor potential (trp) channels. Subcellular Biochemistry, 87:141-165, Jan 2018. URL: https://doi.org/10.1007/978-981-10-7757-9\_6, doi:10.1007/978-981-10-7757-9\_6. This article has 383 citations.
11. (fleig2004thetrpmion pages 1-2): Andrea Fleig and Reinhold Penner. The trpm ion channel subfamily: molecular, biophysical and functional features. Trends in Pharmacological Sciences, 25:633-639, Dec 2004. URL: https://doi.org/10.1016/j.tips.2004.10.004, doi:10.1016/j.tips.2004.10.004. This article has 360 citations and is from a highest quality peer-reviewed journal.
12. (fleig2004thetrpmion pages 2-3): Andrea Fleig and Reinhold Penner. The trpm ion channel subfamily: molecular, biophysical and functional features. Trends in Pharmacological Sciences, 25:633-639, Dec 2004. URL: https://doi.org/10.1016/j.tips.2004.10.004, doi:10.1016/j.tips.2004.10.004. This article has 360 citations and is from a highest quality peer-reviewed journal.
13. (harteneck2005functionandpharmacology pages 7-8): Christian Harteneck. Function and pharmacology of trpm cation channels. Naunyn-Schmiedeberg’s Archives of Pharmacology, 371:307-314, Apr 2005. URL: https://doi.org/10.1007/s00210-005-1034-x, doi:10.1007/s00210-005-1034-x. This article has 201 citations.
14. (jimenez2020trpmchannelsin pages 47-49): Ivanka Jimenez, Yolanda Prado, Felipe Marchant, Carolina Otero, Felipe Eltit, Claudio Cabello-Verrugio, Oscar Cerda, and Felipe Simon. Trpm channels in human diseases. Cells, 9:2604, Dec 2020. URL: https://doi.org/10.3390/cells9122604, doi:10.3390/cells9122604. This article has 65 citations and is from a peer-reviewed journal.
15. (nilius2007transientreceptorpotential pages 12-13): Bernd Nilius, Grzegorz Owsianik, Thomas Voets, and John A. Peters. Transient receptor potential cation channels in disease. Physiological Reviews, 87:165-217, Jan 2007. URL: https://doi.org/10.1152/physrev.00021.2006, doi:10.1152/physrev.00021.2006. This article has 1759 citations and is from a highest quality peer-reviewed journal.
16. (runnels2011trpm6andtrpm7 pages 3-4): 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 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.
18. (runnels2011trpm6andtrpm7 pages 8-9): 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.
19. (runnels2011trpm6andtrpm7 pages 9-10): 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.
20. (ryazanova2004characterizationofthe pages 6-7): 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 237 citations and is from a domain leading peer-reviewed journal.
21. (clapham2001thetrpion pages 8-9): David E. Clapham, Loren W. Runnels, and Carsten Strübing. The trp ion channel family. Nature Reviews Neuroscience, 2:387-396, Jun 2001. URL: https://doi.org/10.1038/35077544, doi:10.1038/35077544. This article has 1602 citations and is from a highest quality peer-reviewed journal.
22. (geiger2023rolesoftransient pages 60-61): F Geiger. Roles of transient receptor potential (trp) cation channels in primary pulmonary fibroblasts. Unknown journal, 2023.
23. (jimenez2020trpmchannelsin pages 20-23): Ivanka Jimenez, Yolanda Prado, Felipe Marchant, Carolina Otero, Felipe Eltit, Claudio Cabello-Verrugio, Oscar Cerda, and Felipe Simon. Trpm channels in human diseases. Cells, 9:2604, Dec 2020. URL: https://doi.org/10.3390/cells9122604, doi:10.3390/cells9122604. This article has 65 citations and is from a peer-reviewed journal.
24. (jimenez2020trpmchannelsin pages 3-6): Ivanka Jimenez, Yolanda Prado, Felipe Marchant, Carolina Otero, Felipe Eltit, Claudio Cabello-Verrugio, Oscar Cerda, and Felipe Simon. Trpm channels in human diseases. Cells, 9:2604, Dec 2020. URL: https://doi.org/10.3390/cells9122604, doi:10.3390/cells9122604. This article has 65 citations and is from a peer-reviewed journal.
25. (jimenez2020trpmchannelsin pages 46-47): Ivanka Jimenez, Yolanda Prado, Felipe Marchant, Carolina Otero, Felipe Eltit, Claudio Cabello-Verrugio, Oscar Cerda, and Felipe Simon. Trpm channels in human diseases. Cells, 9:2604, Dec 2020. URL: https://doi.org/10.3390/cells9122604, doi:10.3390/cells9122604. This article has 65 citations and is from a peer-reviewed journal.
26. (nilius2007transientreceptorpotential pages 4-5): Bernd Nilius, Grzegorz Owsianik, Thomas Voets, and John A. Peters. Transient receptor potential cation channels in disease. Physiological Reviews, 87:165-217, Jan 2007. URL: https://doi.org/10.1152/physrev.00021.2006, doi:10.1152/physrev.00021.2006. This article has 1759 citations and is from a highest quality peer-reviewed journal.
27. (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.
28. (huang2020astructuraloverview pages 11-11): Yihe Huang, Ralf Fliegert, Andreas H. Guse, Wei Lü, and Juan Du. A structural overview of the ion channels of the trpm family. Cell Calcium, 85:102111, Jan 2020. URL: https://doi.org/10.1016/j.ceca.2019.102111, doi:10.1016/j.ceca.2019.102111. This article has 201 citations and is from a peer-reviewed journal.