1. Phylogeny  
   TRPM7 is a member of the transient receptor potential melastatin (TRPM) subfamily and clusters with TRPM6 in a distinct subgroup characterized by the fusion of an ion channel domain with a C-terminal α‐kinase domain (clapham2001thetrpion pages 8-9, fleig2004thetrpmion pages 2-3). Orthologs of TRPM7 have been identified across a wide range of mammalian species, indicating strong evolutionary conservation. The kinase domain of TRPM7 is classified as an atypical α‐kinase and is positioned within the serine/threonine kinase branch of the kinome, as outlined by the seminal phylogenetic studies of Manning et al. (2002) (nilius2014mammaliantransientreceptor pages 520-523, clapham2001thetrpion pages 7-8). Its evolutionary origins extend back to ancient eukaryotes, and its orthologous relationships have been traced from mammals to lower vertebrates, reflecting its essential role in ion homeostasis and enzyme signaling.
2. Reaction Catalyzed  
   The kinase activity of TRPM7 catalyzes the phosphorylation reaction involving ATP and a protein substrate containing serine and/or threonine residues. The general chemical reaction is:  
   ATP + [protein]–(L-serine or L-threonine) → ADP + [protein]–(L-serine/threonine)-phosphate + H⁺ (clapham2001thetrpion pages 7-8, fleig2014trpm7 pages 9-12).  
   This reaction is typical of serine/threonine kinases and results in the transfer of the terminal phosphate group from ATP to the substrate protein.
3. Cofactor Requirements  
   The catalytic activity of TRPM7’s kinase domain is dependent on divalent cations, with Mg²⁺ being the primary cofactor required for efficient ATP binding and phosphotransfer (bateswithers2011trpm7themg2+ pages 1-2, ryazanova2004characterizationofthe pages 8-10). In some experimental conditions, Mn²⁺ can also support kinase activity, enhancing the catalytic efficiency; however, under physiological conditions, Mg²⁺ is the essential cofactor (nilius2014mammaliantransientreceptor pages 531-534).
4. Substrate Specificity  
   TRPM7 exhibits serine/threonine kinase activity and phosphorylates a variety of protein substrates. In vivo, TRPM7 phosphorylates substrates such as SMAD2, which suggests its role in activating SMAD signaling pathways (information section). In vitro studies have demonstrated that TRPM7 phosphorylates annexin A1 (ANXA1), several myosin II isoforms, and histone H3 (information section, fleig2014trpm7 pages 9-12). Although a precise consensus substrate motif for TRPM7 has not been fully defined in the available context, priority data from the atlas of substrate specificities for human serine/threonine kinases provides a framework for understanding that many serine/threonine kinases favor motifs with basic residues upstream of the phosphorylated residue (Johnson2023 example) and analogous insights have been extended to tyrosine kinases in related studies (Yaron-Barir2024 example). This information implies that TRPM7, as an atypical serine/threonine kinase, phosphorylates substrates that might share specific local sequence features conducive to phosphate transfer at serine and threonine residues (fleig2014trpm7 pages 9-12).
5. Structure  
   TRPM7 is organized as a bifunctional protein with two main domains. The N-terminal region forms the ion channel portion, which consists of six transmembrane segments (S1–S6) with a pore-forming loop between segments S5 and S6. Four TRPM7 subunits assemble to create a tetrameric channel capable of conducting divalent cations such as Ca²⁺, Mg²⁺, and Zn²⁺ (clapham2001thetrpion pages 8-9, fleig2014trpm7 pages 1-3). The C-terminal region contains the kinase domain, which belongs to the atypical α-kinase family and possesses structural features such as an ATP-binding cleft and several metal-binding sites for Zn and Mg (fleig2014trpm7 pages 3-6, nilius2014mammaliantransientreceptor pages 531-534). Within the kinase domain, critical residues are involved in autophosphorylation events and substrate binding, and a coiled-coil region upstream of the kinase facilitates proper channel assembly and trafficking (fleig2014trpm7 pages 6-9, nilius2014mammaliantransientreceptor pages 534-537). Although high-resolution crystal structures of the full-length protein are not available in the provided context, experimentally derived structures of individual domains and models based on analogous ion channels allow for characterization of the channel’s voltage-independent permeation properties and the atypical architecture of its kinase module.
6. Regulation  
   TRPM7 is subject to complex regulatory mechanisms that integrate both its ion channel and kinase functions. The channel domain is regulated by intracellular free Mg²⁺ and Mg·ATP, which inhibit its activity by binding to distinct inhibitory sites on both the channel and the kinase domains (nilius2014mammaliantransientreceptor pages 529-531, park2014thepathophysiologicroles pages 1-2). Activation of phospholipase C (PLC) and subsequent hydrolysis of PIP₂ lead to channel inactivation, linking TRPM7 to receptor-mediated signaling pathways (clapham2001thetrpion pages 8-9, park2014thepathophysiologicroles pages 2-3). Furthermore, autophosphorylation of the kinase domain can modulate the enzyme’s activity and in turn affect the channel function, although deletion or mutation of the kinase domain significantly reduces channel currents (fleig2014trpm7 pages 9-12, bateswithers2011trpm7themg2+ pages 5-7). Several pharmacological agents have been reported to inhibit TRPM7 channel activity, including compounds such as waixenicin A and 2-APB; these inhibitors affect either the channel’s ion conductance or its kinase functions, thereby interfering with the regulatory cascade (park2014thepathophysiologicroles pages 1-2, cordier2021trpm7ionchannel pages 6-7).
7. Function  
   TRPM7 plays a central role in cellular ion homeostasis by mediating the influx of divalent cations with a particular emphasis on Mg²⁺, Ca²⁺, and Zn²⁺. Its ion channel activity contributes to maintaining intracellular concentrations of these ions, which are critical for diverse cellular processes including cell proliferation, motility, differentiation, and survival (clapham2001thetrpion pages 7-8, fleig2004thetrpmion pages 2-3). In addition, the kinase domain of TRPM7 phosphorylates downstream proteins such as SMAD2, ANXA1, and myosin II isoforms, thereby linking ion transport to intracellular signaling pathways involved in embryonic development, immune responses, and cytoskeletal reorganization (information section, fleig2014trpm7 pages 9-12, jimenez2020trpmchannelsin pages 47-49). Expression of TRPM7 is ubiquitous with high transcript levels observed in the brain, heart, kidney, liver, lung, and various other tissues (clapham2001thetrpion pages 8-9, jimenez2020trpmchannelsin pages 51-52). Genetic studies using knockout models have demonstrated that complete deletion of TRPM7 or its kinase domain results in embryonic lethality and defects in organogenesis, underscoring its essential role in development and cell viability (park2014thepathophysiologicroles pages 2-3, fleig2014trpm7 pages 6-9).
8. Other Comments  
   Several inhibitors have been employed experimentally to dissect TRPM7 function. In addition to 2-APB, inhibitors such as waixenicin A, NS8593, and sphingosine analogues have been utilized to selectively inhibit either the channel or kinase activities of TRPM7, highlighting its potential as a therapeutic target in pathologies associated with aberrant divalent cation homeostasis (park2014thepathophysiologicroles pages 1-2, cordier2021trpm7ionchannel pages 6-7). TRPM7 has been implicated in a variety of disease states, including cancer progression, ischemic neuronal injury, cardiovascular disorders, and hypomagnesemia. Specific mutations, such as those affecting the kinase domain, have been associated with alterations in Mg²⁺ sensitivity and have been reported in conditions such as Guamanian amyotrophic lateral sclerosis and Parkinsonism-dementia (park2014thepathophysiologicroles pages 6-7, ryazanova2004characterizationofthe pages 8-10). The multifunctional nature of TRPM7, combining ion transport and kinase signaling, positions it centrally in the regulation of cellular processes and supports its investigation as a candidate for targeted pharmacological intervention.
9. References
10. clapham2001thetrpion pages 7-8
11. clapham2001thetrpion pages 8-9
12. fleig2004thetrpmion pages 2-3
13. fleig2014trpm7 pages 1-3
14. fleig2014trpm7 pages 9-12
15. jimenez2020trpmchannelsin pages 47-49
16. nilius2014mammaliantransientreceptor pages 520-523
17. nilius2014mammaliantransientreceptor pages 531-534
18. park2014thepathophysiologicroles pages 1-2
19. park2014thepathophysiologicroles pages 2-3
20. ryazanova2004characterizationofthe pages 8-10
21. bateswithers2011trpm7themg2+ pages 1-2
22. cordier2021trpm7ionchannel pages 6-7

(For substrate specificity details, refer to Johnson2023 and Yaron-Barir2024 as integrated data sources for serine/threonine and tyrosine kinase substrate preferences, and for phylogeny refer to Manning et al. 2002 as outlined in the template.)

References

1. (clapham2001thetrpion pages 7-8): 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 1598 citations and is from a highest quality peer-reviewed journal.
2. (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 1598 citations and is from a highest quality peer-reviewed journal.
3. (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.
4. (fleig2014trpm7 pages 1-3): Andrea Fleig and Vladimir Chubanov. Trpm7. Handbook of Experimental Pharmacology, pages 521-546, Jan 2014. URL: https://doi.org/10.1007/978-3-642-54215-2\_21, doi:10.1007/978-3-642-54215-2\_21. This article has 127 citations and is from a peer-reviewed journal.
5. (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 227 citations and is from a peer-reviewed journal.
6. (park2014thepathophysiologicroles pages 1-2): Hyun Soo Park, Chansik Hong, Byung Joo Kim, and Insuk So. The pathophysiologic roles of trpm7 channel. The Korean Journal of Physiology & Pharmacology, 18:15, Jan 2014. URL: https://doi.org/10.4196/kjpp.2014.18.1.15, doi:10.4196/kjpp.2014.18.1.15. This article has 73 citations.
7. (park2014thepathophysiologicroles pages 6-7): Hyun Soo Park, Chansik Hong, Byung Joo Kim, and Insuk So. The pathophysiologic roles of trpm7 channel. The Korean Journal of Physiology & Pharmacology, 18:15, Jan 2014. URL: https://doi.org/10.4196/kjpp.2014.18.1.15, doi:10.4196/kjpp.2014.18.1.15. This article has 73 citations.
8. (bateswithers2011trpm7themg2+ pages 1-2): 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.
9. (bateswithers2011trpm7themg2+ pages 5-7): 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.
10. (cordier2021trpm7ionchannel pages 6-7): Clément Cordier, Natalia Prevarskaya, and V’yacheslav Lehen’kyi. Trpm7 ion channel: oncogenic roles and therapeutic potential in breast cancer. Cancers, 13:6322, Dec 2021. URL: https://doi.org/10.3390/cancers13246322, doi:10.3390/cancers13246322. This article has 28 citations and is from a peer-reviewed journal.
11. (fleig2014trpm7 pages 3-6): Andrea Fleig and Vladimir Chubanov. Trpm7. Handbook of Experimental Pharmacology, pages 521-546, Jan 2014. URL: https://doi.org/10.1007/978-3-642-54215-2\_21, doi:10.1007/978-3-642-54215-2\_21. This article has 127 citations and is from a peer-reviewed journal.
12. (fleig2014trpm7 pages 6-9): Andrea Fleig and Vladimir Chubanov. Trpm7. Handbook of Experimental Pharmacology, pages 521-546, Jan 2014. URL: https://doi.org/10.1007/978-3-642-54215-2\_21, doi:10.1007/978-3-642-54215-2\_21. This article has 127 citations and is from a peer-reviewed journal.
13. (fleig2014trpm7 pages 9-12): Andrea Fleig and Vladimir Chubanov. Trpm7. Handbook of Experimental Pharmacology, pages 521-546, Jan 2014. URL: https://doi.org/10.1007/978-3-642-54215-2\_21, doi:10.1007/978-3-642-54215-2\_21. This article has 127 citations and is from a peer-reviewed journal.
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. (jimenez2020trpmchannelsin pages 51-52): 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.
16. (nilius2014mammaliantransientreceptor pages 529-531): 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 227 citations and is from a peer-reviewed journal.
17. (nilius2014mammaliantransientreceptor pages 531-534): 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 227 citations and is from a peer-reviewed journal.
18. (nilius2014mammaliantransientreceptor pages 534-537): 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 227 citations and is from a peer-reviewed journal.
19. (park2014thepathophysiologicroles pages 2-3): Hyun Soo Park, Chansik Hong, Byung Joo Kim, and Insuk So. The pathophysiologic roles of trpm7 channel. The Korean Journal of Physiology & Pharmacology, 18:15, Jan 2014. URL: https://doi.org/10.4196/kjpp.2014.18.1.15, doi:10.4196/kjpp.2014.18.1.15. This article has 73 citations.
20. (ryazanova2004characterizationofthe pages 8-10): 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.