1. Phylogeny  
   TRPM7 belongs to the transient receptor potential melastatin (TRPM) subfamily of ion channels and is evolutionarily conserved across vertebrates, with orthologs identifiable in mammals, birds, amphibians, and fish (cai2018thefunctionalinterplay pages 8-12, luo2024trpm7inneurodevelopment pages 2-3). It shares a close evolutionary relationship with TRPM6, another channel‐kinase that arose early in vertebrate evolution approximately 450 million years ago, indicating that both proteins emerged before the divergence of fish and land vertebrates (gao2022palmitoylationandregulationa pages 49-53, beesetty2018consequencesoftrpm7 pages 27-32). Phylogenetically, TRPM7 is classified within an atypical branch of serine/threonine kinases, the so‐called “α-kinases,” which are evolutionarily distinct from classical protein kinases and are found ubiquitously in eukaryotes (cai2018thefunctionalinterplay pages 12-16, schmucker2023regulatorymechanismsof pages 14-18).
2. Reaction Catalyzed  
   The kinase domain of TRPM7 catalyzes the transfer of a phosphate group from ATP to specific serine and threonine residues on substrate proteins, a reaction that can be summarized as: ATP + protein → ADP + phosphorylated protein + H⁺ (beesetty2018consequencesoftrpm7 pages 23-27). In addition to autophosphorylation of its own serine/threonine-rich region—a process that modulates its protein stability and trafficking—TRPM7 phosphorylates several downstream targets (e.g., annexin A1, myosin II isoforms and SMAD2), thereby linking ion conduction with intracellular signaling events that influence processes such as cell motility, differentiation, and immune function (beesetty2018consequencesoftrpm7 pages 27-32, cai2018thefunctionalinterplay pages 118-121).
3. Cofactor Requirements  
   The phosphotransferase activity of the TRPM7 kinase domain is strictly dependent on divalent cations, most notably Mg²⁺, which serves both as a cofactor for the kinase catalytic process and as a regulator for the ion channel domain (zou2019trpm7magnesiumand pages 1-3, turlova2018cellularandmolecular pages 51-54). The activity is further modulated by Mg-ATP complexes, with intracellular Mg²⁺ and Mg-ATP levels critically determining both channel gating and kinase activity (chubanov2020mappingtrpm7function pages 1-3, gav2022palmitoylationandregulation pages 46-49). In some experimental systems, additional metal ions such as Mn²⁺ or Zn²⁺ can support or modulate kinase activity; however, Mg²⁺ is the predominant cofactor in physiological contexts (cai2017massspectrometricanalysis pages 1-3, beesetty2018consequencesoftrpm7 pages 16-23).
4. Substrate Specificity  
   TRPM7 exhibits a broad substrate specificity typical of atypical α-kinases, phosphorylating serine/threonine residues within structured α-helical regions rather than the canonical motifs recognized by classical kinases (cai2017massspectrometricanalysis pages 3-3, beesetty2018consequencesoftrpm7 pages 23-27). Known physiological substrates include SMAD2, which links TRPM7 activity to TGF-β signaling cascades, as well as annexin A1 and various isoforms of myosin II, which underline its role in cytoskeletal rearrangements and cell motility (beesetty2018consequencesoftrpm7 pages 27-32, cai2018thefunctionalinterplay pages 118-121). Although a consensus phosphorylation motif for TRPM7 has not been as clearly defined as for classical serine/threonine kinases, its substrate recognition appears to depend on specific structural features within the target proteins that allow binding and correct positioning in the active site of the kinase domain (cai2017massspectrometricanalysis pages 13-13, schmucker2023regulatorymechanismsofc pages 14-18).
5. Structure  
   TRPM7 is a bifunctional protein with a complex domain organization that integrates both ion channel and kinase functionalities. The N-terminal region consists of several melastatin homology regions (MHRs) that play roles in channel trafficking and possibly in establishing subunit interactions (cai2018thefunctionalinterplay pages 8-12, beesetty2018consequencesoftrpm7 pages 16-23). This is followed by six transmembrane segments (S1–S6) that together form the ion channel pore, with the loop between S5 and S6 conferring selectivity to divalent cations such as Ca²⁺, Mg²⁺, and Zn²⁺ (chubanov2020mappingtrpm7function pages 1-3, turlova2018cellularandmolecular pages 51-54). Adjacent to the pore, a conserved TRP domain contributes to the channel’s gating properties, particularly in response to intracellular Mg²⁺ and phosphatidylinositol 4,5-bisphosphate (PIP2) levels (gao2022palmitoylationandregulation pages 58-62). C-terminal to the transmembrane region lies a coiled-coil domain that is critical for tetramerization and proper assembly of the channel complex (solivio2024characterizingtherole pages 22-26, stadlbauer2023theroleof pages 18-22). Finally, the C-terminal region houses the α-kinase domain, which is atypical in structure relative to conventional kinases; it contains unique features such as an ATP-grasp fold and serine/threonine-rich autophosphorylation sites that are crucial for modulating its enzymatic activity and, indirectly, the channel’s function (gao2022palmitoylationandregulationa pages 53-58, cai2017massspectrometricanalysis pages 1-3). Key catalytic residues within the kinase domain, including those involved in binding Mg²⁺ and ATP, are essential for phosphotransferase activity, while additional residues contribute to dimerization and regulatory autophosphorylation (cai2017massspectrometricanalysis pages 13-13, beesetty2018consequencesoftrpm7 pages 27-32).
6. Regulation  
   The activity of TRPM7 is intricately regulated by multiple mechanisms acting on both its ion channel and kinase domains. Intracellular Mg²⁺ and Mg-ATP serve as negative regulators for channel gating, forming a feedback loop that adjusts ion flux in response to cellular metabolic status (turlova2018cellularandmolecular pages 51-54, zou2019trpm7magnesiumand pages 1-3). In addition, the kinase domain undergoes extensive autophosphorylation at serine/threonine-rich regions; specific phosphorylation events, such as those at residues S1360 and S1403, have been shown to modulate channel stability by affecting interactions with proteins like 14-3-3θ, thereby influencing intracellular trafficking and degradation (cai2018thefunctionalinterplay pages 114-118, beesetty2018consequencesoftrpm7 pages 23-27). Furthermore, regulatory inputs include modulation by PIP2 levels: hydrolysis of PIP2 via receptor-mediated activation of phospholipase C lowers channel activity, particularly under conditions of low intracellular Mg²⁺, while mechanical stimuli and extracellular pH shifts can also impact channel conductance (chubanov2020mappingtrpm7function pages 1-3, schmucker2023regulatorymechanismsofc pages 9-14). Additional regulation occurs via protein–protein interactions with modulatory partners such as ARL15 and CNNMs, which selectively suppress either channel or kinase activity without necessarily affecting the other domain (bousova2023interactionofcalmodulin pages 11-12, solivio2024characterizingtheroleb pages 22-26).
7. Function  
   As a bifunctional protein, TRPM7 plays critical roles in maintaining cellular homeostasis. Its ion channel activity regulates the influx of divalent cations (Ca²⁺, Mg²⁺, Zn²⁺), which is fundamental for processes such as embryonic development, cell proliferation, migration, and differentiation (beesetty2018consequencesoftrpm7 pages 16-23, zou2019trpm7magnesiumand pages 1-3). Moreover, TRPM7’s kinase domain contributes to cellular signaling by phosphorylating downstream targets such as SMAD2, which implicates TRPM7 in TGF-β signaling and gene regulation, and by modifying proteins involved in cytoskeletal dynamics (e.g., annexin A1, myosin II isoforms) (beesetty2018consequencesoftrpm7 pages 23-27, cai2018thefunctionalinterplay pages 118-121). In immune cells, TRPM7 is essential for proper lymphocyte function, influencing B cell receptor (BCR) signaling and actin cytoskeletal rearrangements that govern antigen processing and cell migration (solivio2024characterizingtherolea pages 26-32, preez2021potentialimplicationsof pages 2-4). Additionally, by controlling intracellular Mg²⁺ levels, TRPM7 regulates a spectrum of cellular activities including cell cycle progression and survival, and disruptions in its function have been associated with pathologies ranging from metabolic disorders to cancer (beesetty2018consequencesoftrpm7 pages 16-23, schmucker2023regulatorymechanismsofb pages 90-92). Its dual role as both an ion channel and kinase thus positions TRPM7 as a central integrator of ion homeostasis and phosphorylation-mediated signal transduction.
8. Other Comments  
   Several small molecules have been identified as modulators of TRPM7 activity. For instance, TG100-115 is noted as an inhibitor of the TRPM7 kinase activity with an IC₅₀ in the low micromolar range; additionally, activators such as naltriben have been reported to stimulate channel function even under conditions where intracellular Mg²⁺ concentrations are high (chubanov2017assessmentoftrpm7 pages 6-6, zou2020regulationofthe pages 33-36). Mutations such as S1107E in the TRP domain have been observed to produce a constitutively active channel, emphasizing the structural determinants critical for gating and regulation (turlova2018cellularandmolecular pages 51-54, beesetty2018consequencesoftrpm7 pages 27-32). Pathologically, dysregulated TRPM7 expression or function has been implicated in various diseases, including cancer (with overexpression correlating with tumor grade and metastasis), cardiovascular disorders such as hypertension owing to altered vascular smooth muscle function, and neurological conditions related to abnormal Ca²⁺ influx (gao2022palmitoylationandregulation pages 58-62, preez2021potentialimplicationsof pages 2-4). Ongoing research efforts are focused on dissecting the interplay between the channel and kinase activities to develop more selective inhibitors that may serve therapeutic purposes. Current studies utilizing kinase-dead knock-in models continue to clarify the relative contributions of channel versus kinase functions in both development and disease (schmucker2023regulatorymechanismsofd pages 90-92, solivio2024characterizingtheroleb pages 26-32).
9. References  
   Beesetty2018ConsequencesOFTRPM7 pages 16-23, Beesetty2018ConsequencesOFTRPM7 pages 23-27, Beesetty2018ConsequencesOFTRPM7 pages 27-32, Cai2018TheFunctionalInterplay pages 8-12, Cai2018TheFunctionalInterplay pages 12-16, Cai2018TheFunctionalInterplay pages 114-118, Chubanov2020MappingTRPM7Function pages 1-3, Gao2022PalmitoylationAndRegulation pages 46-49, Gao2022PalmitoylationAndRegulation pages 53-58, Gao2022PalmitoylationAndRegulation pages 58-62, Gao2022PalmitoylationAndRegulationA pages 49-53, Gao2022PalmitoylationAndRegulationA pages 53-58, Gong2020Calcineurinasa pages 8-14, Gong2020Calcineurinasa pages 14-18, Krishnamoorthy2018TheRoleOF pages 41-46, Luo2024TRPM7InNeurodevelopment pages 2-3, Preez2021PotentialImplicationsOF pages 2-4, Schmucker2023RegulatoryMechanismsof pages 14-18, Schmucker2023RegulatoryMechanismsof pages 90-92, Schmucker2023RegulatoryMechanismsofA pages 90-92, Schmucker2023RegulatoryMechanismsofB pages 14-18, Schmucker2023RegulatoryMechanismsofB pages 90-92, Schmucker2023RegulatoryMechanismsofC pages 9-14, Schmucker2023RegulatoryMechanismsofC pages 14-18, Schmucker2023RegulatoryMechanismsofC pages 90-92, Schmucker2023RegulatoryMechanismsofD pages 9-14, Schmucker2023RegulatoryMechanismsofD pages 14-18, Schmucker2023RegulatoryMechanismsofD pages 90-92, Solivio2024CharacterizingTheRole pages 22-26, Solivio2024CharacterizingTheRole pages 26-32, Solivio2024CharacterizingTheRoleA pages 22-26, Solivio2024CharacterizingTheRoleA pages 26-32, Solivio2024CharacterizingTheRoleB pages 22-26, Solivio2024CharacterizingTheRoleB pages 26-32, Solivio2024CharacterizingTheRoleC pages 22-26, Solivio2024CharacterizingTheRoleC pages 26-32, Stadlbauer2023TheRoleOF pages 18-22, Stadlbauer2023TheRoleOFb pages 18-22, Tetteh2022RegulationOFTRPM7A pages 7-13, Turlova2018CellularAndMolecular pages 51-54, Turlova2018CellularAndMolecular pages 54-58, Zou2019TRPM7MagnesiumAnd pages 1-3, Zou2020RegulationOFThe pages 33-36, Bousova2023InteractionOfCalmodulin pages 11-12, Cai2017MassSpectrometricAnalysis pages 1-3, Cai2017MassSpectrometricAnalysis pages 13-13.

References

1. (beesetty2018consequencesoftrpm7 pages 16-23): P Beesetty. Consequences of trpm7 kinase inactivation in immune cells. Unknown journal, 2018.
2. (beesetty2018consequencesoftrpm7 pages 23-27): P Beesetty. Consequences of trpm7 kinase inactivation in immune cells. Unknown journal, 2018.
3. (beesetty2018consequencesoftrpm7 pages 27-32): P Beesetty. Consequences of trpm7 kinase inactivation in immune cells. Unknown journal, 2018.
4. (cai2018thefunctionalinterplay pages 118-121): Na Cai. The functional interplay between tprm7 channel-kinase autophosphorylation and its cellular regulation. Unknown journal, 2018. URL: https://doi.org/10.7282/t3fx7dwq, doi:10.7282/t3fx7dwq. This article has 0 citations.
5. (cai2018thefunctionalinterplay pages 12-16): Na Cai. The functional interplay between tprm7 channel-kinase autophosphorylation and its cellular regulation. Unknown journal, 2018. URL: https://doi.org/10.7282/t3fx7dwq, doi:10.7282/t3fx7dwq. This article has 0 citations.
6. (cai2018thefunctionalinterplay pages 8-12): Na Cai. The functional interplay between tprm7 channel-kinase autophosphorylation and its cellular regulation. Unknown journal, 2018. URL: https://doi.org/10.7282/t3fx7dwq, doi:10.7282/t3fx7dwq. This article has 0 citations.
7. (chubanov2020mappingtrpm7function pages 1-3): Vladimir Chubanov and Thomas Gudermann. Mapping trpm7 function by ns8593. International Journal of Molecular Sciences, 21:7017, Sep 2020. URL: https://doi.org/10.3390/ijms21197017, doi:10.3390/ijms21197017. This article has 28 citations and is from a peer-reviewed journal.
8. (gao2022palmitoylationandregulation pages 58-62): X Gao. Palmitoylation and regulation of divalent cation transport by trpm7 and trpm6. Unknown journal, 2022.
9. (gao2022palmitoylationandregulationa pages 49-53): X Gao. Palmitoylation and regulation of divalent cation transport by trpm7 and trpm6. Unknown journal, 2022.
10. (gao2022palmitoylationandregulationa pages 53-58): X Gao. Palmitoylation and regulation of divalent cation transport by trpm7 and trpm6. Unknown journal, 2022.
11. (luo2024trpm7inneurodevelopment pages 2-3): Zhengwei Luo, Xinyang Zhang, Andrea Fleig, Daniel Romo, Kenneth G. Hull, F. David Horgen, Hong-Shuo Sun, and Zhong-Ping Feng. Trpm7 in neurodevelopment and therapeutic prospects for neurodegenerative disease. Cell Calcium, 120:102886, Jun 2024. URL: https://doi.org/10.1016/j.ceca.2024.102886, doi:10.1016/j.ceca.2024.102886. This article has 0 citations and is from a peer-reviewed journal.
12. (preez2021potentialimplicationsof pages 2-4): Stanley Du Preez, Helene Cabanas, Donald Staines, and Sonya Marshall-Gradisnik. Potential implications of mammalian transient receptor potential melastatin 7 in the pathophysiology of myalgic encephalomyelitis/chronic fatigue syndrome: a review. International Journal of Environmental Research and Public Health, 18:10708, Oct 2021. URL: https://doi.org/10.3390/ijerph182010708, doi:10.3390/ijerph182010708. This article has 7 citations and is from a poor quality or predatory journal.
13. (schmucker2023regulatorymechanismsof pages 14-18): E Schmücker. Regulatory mechanisms of the trpm7 channel-kinase. Unknown journal, 2023.
14. (schmucker2023regulatorymechanismsofb pages 90-92): E Schmücker. Regulatory mechanisms of the trpm7 channel-kinase. Unknown journal, 2023.
15. (schmucker2023regulatorymechanismsofc pages 14-18): E Schmücker. Regulatory mechanisms of the trpm7 channel-kinase. Unknown journal, 2023.
16. (schmucker2023regulatorymechanismsofc pages 9-14): E Schmücker. Regulatory mechanisms of the trpm7 channel-kinase. Unknown journal, 2023.
17. (schmucker2023regulatorymechanismsofd pages 90-92): E Schmücker. Regulatory mechanisms of the trpm7 channel-kinase. Unknown journal, 2023.
18. (solivio2024characterizingtherole pages 22-26): A Solivio. Characterizing the role of trpm7 kinase in early b cell activation. Unknown journal, 2024.
19. (solivio2024characterizingtherolea pages 26-32): A Solivio. Characterizing the role of trpm7 kinase in early b cell activation. Unknown journal, 2024.
20. (solivio2024characterizingtheroleb pages 22-26): A Solivio. Characterizing the role of trpm7 kinase in early b cell activation. Unknown journal, 2024.
21. (solivio2024characterizingtheroleb pages 26-32): A Solivio. Characterizing the role of trpm7 kinase in early b cell activation. Unknown journal, 2024.
22. (stadlbauer2023theroleof pages 18-22): B Stadlbauer. The role of kinase-coupled channel trpm6 in cardiac automaticity. Unknown journal, 2023.
23. (turlova2018cellularandmolecular pages 51-54): E Turlova. Cellular and molecular mechanisms of transient receptor potential melastatin 7 (trpm7) channel in neuronal development and injury. Unknown journal, 2018.
24. (zou2019trpm7magnesiumand pages 1-3): Zhi-Guo Zou, Francisco J. Rios, Augusto C. Montezano, and Rhian M. Touyz. Trpm7, magnesium, and signaling. International Journal of Molecular Sciences, 20:1877, Apr 2019. URL: https://doi.org/10.3390/ijms20081877, doi:10.3390/ijms20081877. This article has 162 citations and is from a peer-reviewed journal.
25. (zou2020regulationofthe pages 33-36): Z Zou. Regulation of the mg2+ transporter trpm7 by growth factors-implications in vascular function in health and disease. Unknown journal, 2020.
26. (bousova2023interactionofcalmodulin pages 11-12): Kristyna Vydra Bousova, Monika Zouharova, Katerina Jiraskova, and Veronika Vetyskova. Interaction of calmodulin with trpm: an initiator of channel modulation. International Journal of Molecular Sciences, 24:15162, Oct 2023. URL: https://doi.org/10.3390/ijms242015162, doi:10.3390/ijms242015162. This article has 5 citations and is from a peer-reviewed journal.
27. (cai2017massspectrometricanalysis pages 1-3): 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.
28. (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.
29. (cai2017massspectrometricanalysis pages 3-3): 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.
30. (cai2018thefunctionalinterplay pages 114-118): Na Cai. The functional interplay between tprm7 channel-kinase autophosphorylation and its cellular regulation. Unknown journal, 2018. URL: https://doi.org/10.7282/t3fx7dwq, doi:10.7282/t3fx7dwq. This article has 0 citations.
31. (chubanov2017assessmentoftrpm7 pages 6-6): Vladimir Chubanov, Silvia Ferioli, and Thomas Gudermann. Assessment of trpm7 functions by drug-like small molecules. Cell Calcium, 67:166-173, Nov 2017. URL: https://doi.org/10.1016/j.ceca.2017.03.004, doi:10.1016/j.ceca.2017.03.004. This article has 40 citations and is from a peer-reviewed journal.