## Phylogeny

Tyrosine-protein kinase Mer (MERTK) is a member of the TAM receptor tyrosine kinase family, which also includes TYRO3 and AXL (ghosh2024intheeyes pages 13-15, huelse2020mertkincancer pages 1-2, keating2011mertk(cmerprotooncogene pages 1-3). This assignment places MERTK within the receptor tyrosine kinase (RTK) group, as classified by Manning et al. (huelse2020mertkincancer pages 1-2, tanim2024mertkinhibitionas pages 19-20, cummings2013molecularpathwaysmertk pages 6-7). The TAM family kinases share a unique KWIAIES sequence motif (huelse2020mertkincancer pages 1-2, keating2011mertk(cmerprotooncogene pages 1-3). MERTK is evolutionarily conserved across vertebrates, with known orthologs including murine Mertk, the RCS rat retinal dystrophy gene, the chicken v-eyk kinase, and the avian v-ryk/v-eyk retroviral oncogene (ghosh2024intheeyes pages 13-15, keating2011mertk(cmerprotooncogene pages 3-4, huelse2020mertkincancer pages 1-2, tanim2024mertkinhibitionas pages 4-5). Hominid MERTK has undergone evolutionary changes, resulting in leucine/isoleucine additions in the transmembrane domain that form leucine zipper-like motifs and may enhance receptor clustering (unknownauthors2016evaluationofmertk pages 98-102).

## Reaction Catalyzed

MERTK catalyzes the ATP-dependent transfer of a phosphate group to tyrosine residues on substrate proteins, yielding a phosphoprotein and ADP as products (ghosh2024intheeyes pages 13-15, huelse2020mertkincancer pages 6-7, nishi2019mertktyrosinekinase pages 21-23, tanim2024mertkinhibitionas pages 2-4).

## Cofactor Requirements

The kinase activity of MERTK requires divalent cations, such as Mg2+, as cofactors for ATP binding and catalysis (ghosh2024intheeyes pages 13-15, huelse2020mertkincancer pages 1-2, tanim2024mertkinhibitionas pages 1-2).

## Substrate Specificity

MERTK’s substrate specificity involves the recognition of a consensus phosphorylation motif around target tyrosine residues (tanim2024mertkinhibitionas pages 19-20, wu2024disturbedflowimpairs pages 15-15). The priority publication by Yaron-Barir et al. (2024) characterized substrate specificities for the human tyrosine kinome; however, the provided excerpts from this study do not detail the specific consensus motif for MERTK, nor do they confirm preferences for specific amino acid types at positions relative to the phosphorylated tyrosine (yaronbarir2024theintrinsicsubstrate pages 2-2, yaronbarir2024theintrinsicsubstrate pages 16-17, yaronbarir2024theintrinsicsubstrate pages 2-3, yaronbarir2024theintrinsicsubstrate pages 3-3).

## Structure

MERTK is a type I receptor tyrosine kinase with a multi-domain architecture (lahey2022mertkanemerging pages 1-3). The extracellular region contains two immunoglobulin-like (Ig) C2-type domains and two fibronectin type III (FNIII) domains responsible for ligand binding (keating2011mertk(cmerprotooncogene pages 1-3, huelse2020mertkincancer pages 1-2). This is followed by a single-pass transmembrane domain and an intracellular region containing the tyrosine kinase domain (huelse2020mertkincancer pages 1-2, keating2011mertk(cmerprotooncogene pages 1-3). Key features of the kinase domain include a TAM-specific KWIAIES motif, a C-helix, and an activation loop that are essential for catalytic activity and regulation (ghosh2024intheeyes pages 13-15, keating2011mertk(cmerprotooncogene pages 1-3, huelse2020mertkincancer pages 1-2). A critical lysine residue for kinase activity is located at position 614 (nishi2019mertktyrosinekinase pages 21-23). Three-dimensional structural models are available from the Protein Data Bank (PDB) and AlphaFold databases (ghosh2024intheeyes pages 13-15, tanim2024mertkinhibitionas pages 1-2).

## Regulation

MERTK activity is regulated by ligand-induced receptor dimerization and subsequent autophosphorylation (huelse2020mertkincancer pages 1-2, keating2011mertk(cmerprotooncogene pages 1-3). The primary ligands, GAS6 and Protein S (PROS1), bridge MERTK to phosphatidylserine on the surface of apoptotic cells, triggering receptor homodimerization and activation (huelse2020mertkincancer pages 1-2, ghosh2024intheeyes pages 13-15, huelse2020mertkincancer pages 6-7). This leads to autophosphorylation on key intracellular tyrosine residues, including Y749, Y753, and Y754 within the activation loop, and Y867, which serves as a major docking site for signaling partners (keating2011mertk(cmerprotooncogene pages 1-3, shelby2013mertkinteractionswith pages 14-14). The phosphorylated Y872 residue serves as a binding site for the adaptor protein GRB2 (keating2011mertk(cmerprotooncogene pages 1-3). MERTK also undergoes glycosylation, and its extracellular domain can be shed by metalloproteinases, creating a soluble decoy receptor that inhibits signaling (keating2011mertk(cmerprotooncogene pages 1-3, keating2011mertk(cmerprotooncogene pages 3-4). Nuclear localization of MERTK has also been reported, implying non-canonical signaling functions (tanim2024mertkinhibitionas pages 5-7).

## Function

MERTK is expressed in various tissues, notably in the retinal pigment epithelium (RPE) and in hematopoietic cells such as macrophages, monocytes, dendritic cells, natural killer (NK) cells, and platelets (ghosh2024intheeyes pages 13-15, keating2011mertk(cmerprotooncogene pages 3-4, chen2021mertkinhibitionpotential pages 4-6). Upon activation, MERTK recruits downstream signaling partners including GRB2, PLCG2, VAV1, and the p85 subunit of PI3K (ghosh2024intheeyes pages 13-15, ghosh2024intheeyes pages 13-15, keating2011mertk(cmerprotooncogene pages 1-3). This engagement stimulates signaling pathways including PI3K/AKT, MAPK/ERK, and JAK/STAT (tanim2024mertkinhibitionas pages 4-5, huelse2020mertkincancer pages 6-7). The primary biological role of MERTK is mediating the phagocytosis of apoptotic cells (efferocytosis), a process critical for tissue homeostasis, modulation of the innate immune response, and clearance of shed photoreceptor outer segments in the RPE (ghosh2024intheeyes pages 13-15, huelse2020mertkincancer pages 1-2, shelby2013mertkinteractionswith pages 14-14). It also plays roles in platelet aggregation and thrombogenesis (chen2021mertkinhibitionpotential pages 4-6).

## Inhibitors

Several experimental small molecule inhibitors targeting MERTK have been identified, including UNC2025, MRX-2843, RXDX-106, UNC569, and UNC1062 (huelse2020mertkincancer pages 6-7, tanim2024mertkinhibitionas pages 15-16, tanim2024mertkinhibitionas pages 16-17, tanim2024mertkinhibitionas pages 19-20, cummings2013molecularpathwaysmertk pages 6-7). An antibody-drug conjugate, RGX-019-MMAE, has also been developed to target MERTK (tanim2024mertkinhibitionas pages 19-20).

## Other Comments

Loss-of-function germline mutations in MERTK cause retinal dystrophies, including Retinitis Pigmentosa (RP) (ghosh2024intheeyes pages 13-15, keating2011mertk(cmerprotooncogene pages 3-4). This pathology results from defective efferocytosis of photoreceptor outer segments by the retinal pigment epithelium, which leads to photoreceptor loss and retinal degeneration, as demonstrated in the Royal College of Surgeons (RCS) rat and various MERTK knockout mouse models (ghosh2024intheeyes pages 13-15). Aberrant or ectopic MERTK expression is implicated in the progression of numerous human cancers, including acute leukemias (AML, ALL), glioblastoma, melanoma, and carcinomas of the lung, colon, and breast, where it promotes cell survival, proliferation, and chemoresistance (huelse2020mertkincancer pages 1-2, huelse2020mertkincancer pages 6-7). MERTK dysfunction is also associated with autoimmune disorders such as systemic lupus erythematosus (chen2021mertkinhibitionpotential pages 4-6).

References

1. (ghosh2024intheeyes pages 13-15): Sourav Ghosh, Silvia C. Finnemann, Douglas Vollrath, and Carla V. Rothlin. In the eyes of the beholder—new mertk knockout mouse and re-evaluation of phagocytosis versus anti-inflammatory functions of mertk. International Journal of Molecular Sciences, 25:5299, May 2024. URL: https://doi.org/10.3390/ijms25105299, doi:10.3390/ijms25105299. This article has 2 citations and is from a peer-reviewed journal.
2. (huelse2020mertkincancer pages 1-2): Justus M. Huelse, Diana M Fridlyand, S. Earp, D. DeRyckere, and D. Graham. Mertk in cancer therapy: targeting the receptor tyrosine kinase in tumor cells and the immune system. Pharmacology & therapeutics, pages 107577, May 2020. URL: https://doi.org/10.1016/j.pharmthera.2020.107577, doi:10.1016/j.pharmthera.2020.107577. This article has 85 citations.
3. (huelse2020mertkincancer pages 6-7): Justus M. Huelse, Diana M Fridlyand, S. Earp, D. DeRyckere, and D. Graham. Mertk in cancer therapy: targeting the receptor tyrosine kinase in tumor cells and the immune system. Pharmacology & therapeutics, pages 107577, May 2020. URL: https://doi.org/10.1016/j.pharmthera.2020.107577, doi:10.1016/j.pharmthera.2020.107577. This article has 85 citations.
4. (keating2011mertk(cmerprotooncogene pages 1-3): AK Keating, RMA Linger, and DK Graham. Mertk (c-mer proto-oncogene tyrosine kinase). Atlas of Genetics and Cytogenetics in Oncology and Haematology, Nov 2011. URL: https://doi.org/10.4267/2042/44583, doi:10.4267/2042/44583. This article has 2 citations and is from a peer-reviewed journal.
5. (keating2011mertk(cmerprotooncogene pages 3-4): AK Keating, RMA Linger, and DK Graham. Mertk (c-mer proto-oncogene tyrosine kinase). Atlas of Genetics and Cytogenetics in Oncology and Haematology, Nov 2011. URL: https://doi.org/10.4267/2042/44583, doi:10.4267/2042/44583. This article has 2 citations and is from a peer-reviewed journal.
6. (nishi2019mertktyrosinekinase pages 21-23): Chihiro Nishi, Yuichi Yanagihashi, Katsumori Segawa, and S. Nagata. Mertk tyrosine kinase receptor together with tim4 phosphatidylserine receptor mediates distinct signal transduction pathways for efferocytosis and cell proliferation. The Journal of Biological Chemistry, 294:7221-7230, Mar 2019. URL: https://doi.org/10.1074/jbc.ra118.006628, doi:10.1074/jbc.ra118.006628. This article has 65 citations.
7. (shelby2013mertkinteractionswith pages 14-14): Shameka J Shelby, K. Colwill, S. Dhe-Paganon, T. Pawson, and Debra Thompson. Mertk interactions with sh2-domain proteins in the retinal pigment epithelium. PLoS ONE, Feb 2013. URL: https://doi.org/10.1371/journal.pone.0053964, doi:10.1371/journal.pone.0053964. This article has 47 citations and is from a peer-reviewed journal.
8. (tanim2024mertkinhibitionas pages 1-2): K.M. Tanim, Alisha Holtzhausen, Aashis Thapa, Justus M. Huelse, Douglas K. Graham, and H. Shelton Earp. Mertk inhibition as a targeted novel cancer therapy. International Journal of Molecular Sciences, 25:7660, Jul 2024. URL: https://doi.org/10.3390/ijms25147660, doi:10.3390/ijms25147660. This article has 4 citations and is from a peer-reviewed journal.
9. (tanim2024mertkinhibitionas pages 15-16): K.M. Tanim, Alisha Holtzhausen, Aashis Thapa, Justus M. Huelse, Douglas K. Graham, and H. Shelton Earp. Mertk inhibition as a targeted novel cancer therapy. International Journal of Molecular Sciences, 25:7660, Jul 2024. URL: https://doi.org/10.3390/ijms25147660, doi:10.3390/ijms25147660. This article has 4 citations and is from a peer-reviewed journal.
10. (tanim2024mertkinhibitionas pages 16-17): K.M. Tanim, Alisha Holtzhausen, Aashis Thapa, Justus M. Huelse, Douglas K. Graham, and H. Shelton Earp. Mertk inhibition as a targeted novel cancer therapy. International Journal of Molecular Sciences, 25:7660, Jul 2024. URL: https://doi.org/10.3390/ijms25147660, doi:10.3390/ijms25147660. This article has 4 citations and is from a peer-reviewed journal.
11. (tanim2024mertkinhibitionas pages 19-20): K.M. Tanim, Alisha Holtzhausen, Aashis Thapa, Justus M. Huelse, Douglas K. Graham, and H. Shelton Earp. Mertk inhibition as a targeted novel cancer therapy. International Journal of Molecular Sciences, 25:7660, Jul 2024. URL: https://doi.org/10.3390/ijms25147660, doi:10.3390/ijms25147660. This article has 4 citations and is from a peer-reviewed journal.
12. (tanim2024mertkinhibitionas pages 2-4): K.M. Tanim, Alisha Holtzhausen, Aashis Thapa, Justus M. Huelse, Douglas K. Graham, and H. Shelton Earp. Mertk inhibition as a targeted novel cancer therapy. International Journal of Molecular Sciences, 25:7660, Jul 2024. URL: https://doi.org/10.3390/ijms25147660, doi:10.3390/ijms25147660. This article has 4 citations and is from a peer-reviewed journal.
13. (tanim2024mertkinhibitionas pages 4-5): K.M. Tanim, Alisha Holtzhausen, Aashis Thapa, Justus M. Huelse, Douglas K. Graham, and H. Shelton Earp. Mertk inhibition as a targeted novel cancer therapy. International Journal of Molecular Sciences, 25:7660, Jul 2024. URL: https://doi.org/10.3390/ijms25147660, doi:10.3390/ijms25147660. This article has 4 citations and is from a peer-reviewed journal.
14. (tanim2024mertkinhibitionas pages 5-7): K.M. Tanim, Alisha Holtzhausen, Aashis Thapa, Justus M. Huelse, Douglas K. Graham, and H. Shelton Earp. Mertk inhibition as a targeted novel cancer therapy. International Journal of Molecular Sciences, 25:7660, Jul 2024. URL: https://doi.org/10.3390/ijms25147660, doi:10.3390/ijms25147660. This article has 4 citations and is from a peer-reviewed journal.
15. (unknownauthors2016evaluationofmertk pages 98-102): Evaluation of MERTK evolution and efferocytosis signalling
16. (chen2021mertkinhibitionpotential pages 4-6): Chao-Ju Chen and Yu-Peng Liu. Mertk inhibition: potential as a treatment strategy in egfr tyrosine kinase inhibitor-resistant non-small cell lung cancer. Pharmaceuticals, 14:130, Feb 2021. URL: https://doi.org/10.3390/ph14020130, doi:10.3390/ph14020130. This article has 24 citations and is from a peer-reviewed journal.
17. (cummings2013molecularpathwaysmertk pages 6-7): Christopher T. Cummings, Deborah DeRyckere, H. Shelton Earp, and Douglas K. Graham. Molecular pathways: mertk signaling in cancer. Clinical Cancer Research, 19:5275-5280, Oct 2013. URL: https://doi.org/10.1158/1078-0432.ccr-12-1451, doi:10.1158/1078-0432.ccr-12-1451. This article has 149 citations and is from a highest quality peer-reviewed journal.
18. (lahey2022mertkanemerging pages 1-3): Kevin C. Lahey, Varsha Gadiyar, Amanda Hill, Samuel Desind, Ziren Wang, Viralkumar Davra, Radhey Patel, Ahnaf Zaman, David Calianese, and Raymond B. Birge. Mertk: an emerging target in cancer biology and immuno-oncology. International Review of Cell and Molecular Biology, 368:35-59, Jan 2022. URL: https://doi.org/10.1016/bs.ircmb.2022.04.004, doi:10.1016/bs.ircmb.2022.04.004. This article has 27 citations and is from a peer-reviewed journal.
19. (wu2024disturbedflowimpairs pages 15-15): Jinzi Wu, Shijie Liu, Oishani Banerjee, Hang Shi, Bingzhong Xue, and Zufeng Ding. Disturbed flow impairs mertk-mediated efferocytosis in aortic endothelial cells during atherosclerosis. Theranostics, 14:2427-2441, Mar 2024. URL: https://doi.org/10.7150/thno.93036, doi:10.7150/thno.93036. This article has 19 citations and is from a domain leading peer-reviewed journal.
20. (yaronbarir2024theintrinsicsubstrate pages 2-2): Tomer M. Yaron-Barir, Brian A. Joughin, Emily M. Huntsman, Alexander Kerelsky, Daniel M. Cizin, Benjamin M. Cohen, Amit Regev, Junho Song, Neil Vasan, Ting-Yu Lin, Jose M. Orozco, Christina Schoenherr, Cari Sagum, Mark T. Bedford, R. Max Wynn, Shih-Chia Tso, David T. Chuang, Lei Li, Shawn S.-C. Li, Pau Creixell, Konstantin Krismer, Mina Takegami, Harin Lee, Bin Zhang, Jingyi Lu, Ian Cossentino, Sean D. Landry, Mohamed Uduman, John Blenis, Olivier Elemento, Margaret C. Frame, Peter V. Hornbeck, Lewis C. Cantley, Benjamin E. Turk, Michael B. Yaffe, and Jared L. Johnson. The intrinsic substrate specificity of the human tyrosine kinome. Nature, 629:1174-1181, May 2024. URL: https://doi.org/10.1038/s41586-024-07407-y, doi:10.1038/s41586-024-07407-y. This article has 59 citations and is from a highest quality peer-reviewed journal.
21. (yaronbarir2024theintrinsicsubstrate pages 16-17): Tomer M. Yaron-Barir, Brian A. Joughin, Emily M. Huntsman, Alexander Kerelsky, Daniel M. Cizin, Benjamin M. Cohen, Amit Regev, Junho Song, Neil Vasan, Ting-Yu Lin, Jose M. Orozco, Christina Schoenherr, Cari Sagum, Mark T. Bedford, R. Max Wynn, Shih-Chia Tso, David T. Chuang, Lei Li, Shawn S.-C. Li, Pau Creixell, Konstantin Krismer, Mina Takegami, Harin Lee, Bin Zhang, Jingyi Lu, Ian Cossentino, Sean D. Landry, Mohamed Uduman, John Blenis, Olivier Elemento, Margaret C. Frame, Peter V. Hornbeck, Lewis C. Cantley, Benjamin E. Turk, Michael B. Yaffe, and Jared L. Johnson. The intrinsic substrate specificity of the human tyrosine kinome. Nature, 629:1174-1181, May 2024. URL: https://doi.org/10.1038/s41586-024-07407-y, doi:10.1038/s41586-024-07407-y. This article has 59 citations and is from a highest quality peer-reviewed journal.
22. (yaronbarir2024theintrinsicsubstrate pages 2-3): Tomer M. Yaron-Barir, Brian A. Joughin, Emily M. Huntsman, Alexander Kerelsky, Daniel M. Cizin, Benjamin M. Cohen, Amit Regev, Junho Song, Neil Vasan, Ting-Yu Lin, Jose M. Orozco, Christina Schoenherr, Cari Sagum, Mark T. Bedford, R. Max Wynn, Shih-Chia Tso, David T. Chuang, Lei Li, Shawn S.-C. Li, Pau Creixell, Konstantin Krismer, Mina Takegami, Harin Lee, Bin Zhang, Jingyi Lu, Ian Cossentino, Sean D. Landry, Mohamed Uduman, John Blenis, Olivier Elemento, Margaret C. Frame, Peter V. Hornbeck, Lewis C. Cantley, Benjamin E. Turk, Michael B. Yaffe, and Jared L. Johnson. The intrinsic substrate specificity of the human tyrosine kinome. Nature, 629:1174-1181, May 2024. URL: https://doi.org/10.1038/s41586-024-07407-y, doi:10.1038/s41586-024-07407-y. This article has 59 citations and is from a highest quality peer-reviewed journal.
23. (yaronbarir2024theintrinsicsubstrate pages 3-3): Tomer M. Yaron-Barir, Brian A. Joughin, Emily M. Huntsman, Alexander Kerelsky, Daniel M. Cizin, Benjamin M. Cohen, Amit Regev, Junho Song, Neil Vasan, Ting-Yu Lin, Jose M. Orozco, Christina Schoenherr, Cari Sagum, Mark T. Bedford, R. Max Wynn, Shih-Chia Tso, David T. Chuang, Lei Li, Shawn S.-C. Li, Pau Creixell, Konstantin Krismer, Mina Takegami, Harin Lee, Bin Zhang, Jingyi Lu, Ian Cossentino, Sean D. Landry, Mohamed Uduman, John Blenis, Olivier Elemento, Margaret C. Frame, Peter V. Hornbeck, Lewis C. Cantley, Benjamin E. Turk, Michael B. Yaffe, and Jared L. Johnson. The intrinsic substrate specificity of the human tyrosine kinome. Nature, 629:1174-1181, May 2024. URL: https://doi.org/10.1038/s41586-024-07407-y, doi:10.1038/s41586-024-07407-y. This article has 59 citations and is from a highest quality peer-reviewed journal.