1. Phylogeny  
   Tyrosine‐protein kinase TXK (also known as PTK4 or RLK) is a member of the Tec family of non‐receptor tyrosine kinases that are predominantly expressed in lymphocytes. TXK is evolutionarily related to other Tec kinases such as ITK, Btk, Tec, and Bmx, and orthologs have been identified across mammalian species, consistent with an origin that traces back to common progenitors of the Tec kinase family (berg2005tecfamilykinases pages 1-3, ortutay2008phylogenyoftec pages 4-7). The placement of TXK within the Tec family aligns it within a conserved group of kinases essential for immune cell signaling and is supported by phylogenetic analyses that demonstrate its high sequence homology with other members in chordates (ortutay2008phylogenyoftec pages 7-10).
2. Reaction Catalyzed  
   TXK catalyzes the phosphorylation of tyrosine residues on protein substrates by transferring a phosphate group from ATP to the hydroxyl group of a tyrosine residue. The chemical reaction can be depicted as: ATP + [protein]-L-tyrosine → ADP + [protein]-L-tyrosine-phosphate + H⁺ (berg2005tecfamilykinases pages 17-18).
3. Cofactor Requirements  
   The kinase activity of TXK is dependent on the presence of divalent metal ions, with Mg²⁺ serving as an essential cofactor for the proper orientation of ATP within the active site (berg2005tecfamilykinases pages 17-18).
4. Substrate Specificity  
   TXK displays substrate specificity through recognition of target motifs typically present in proteins involved in T-cell receptor (TCR) signaling. Notable substrates include phospholipase Cγ1 (PLCG1), CTLA4, LCP2, PARP1, and EEF1A1. TXK employs its SH2 and SH3 domains to engage in protein-protein interactions that facilitate the phosphorylation of these substrates, leading to downstream events such as the localization of PLCG1 in lipid rafts and the subsequent generation of second messengers (berg2005tecfamilykinases pages 3-6, yu2009tecfamilykinases pages 12-16, yaronbarir2024theintrinsicsubstrate pages 16-16).
5. Structure  
   TXK is organized into modular domains typical of Tec family kinases. Its C-terminal kinase domain adopts the canonical bilobed structure seen in protein kinases, including key elements such as the activation loop (with Tyr420 serving as a critical phosphorylation site for full activation), the C-helix, and the hydrophobic spines that are essential for catalytic activity (berg2005tecfamilykinases pages 6-8, bradshaw2010thesrcsyk pages 5-6). Unlike several other Tec kinases that contain an N-terminal pleckstrin homology (PH) domain for phosphoinositide binding, TXK generally lacks this domain. Instead, TXK features a cysteine-string motif at the amino terminus that can undergo palmitoylation, thereby mediating its membrane localization and influencing spatial regulation within T cells (ortutay2008phylogenyoftec pages 4-7, yu2009tecfamilykinases pages 16-19). In addition, TXK contains well-conserved SH3 and SH2 domains that are implicated in mediating protein-protein interactions with proline-rich regions and phosphotyrosine-containing motifs, respectively, which are critical for substrate recruitment and regulatory complex formation (berg2005tecfamilykinases pages 8-11).
6. Regulation  
   TXK is regulated primarily by phosphorylation events that modulate its catalytic activity and subcellular localization. Membrane-proximal signaling events initiated by T-cell receptor activation lead to the recruitment of TXK to the plasma membrane where Src family kinases, such as Lck or Fyn, phosphorylate TXK at Tyr420, a modification that is necessary for full enzymatic activation (berg2005tecfamilykinases pages 17-18, berg2005tecfamilykinases pages 28-30). In addition, TXK phosphorylates downstream effectors including PLCG1, PARP1, and EEF1A1; within a defined complex, phosphorylation of these targets modulates processes such as actin cytoskeleton reorganization and NFAT-dependent transcription. TXK regulation is further influenced by dynamic protein-protein interactions mediated by its SH2 and SH3 domains and by potential alternative splicing isoforms that affect its subcellular distribution between the cytoplasm and the nucleus (venegas…2009teckinasesregulate pages 1-2, berg2005tecfamilykinases pages 8-11).
7. Function  
   TXK plays a central role in mediating adaptive immune responses by regulating the development, activation, and differentiation of conventional T-cells as well as nonconventional NKT cells. Upon antigen presentation, engagement of the T-cell receptor triggers a cascade of phosphorylation events that leads to the recruitment of TXK to the cell membrane. Activated TXK phosphorylates PLCG1, promoting its translocation into lipid rafts, where it catalyzes the cleavage of its substrates, eventually leading to release of intracellular calcium from the endoplasmic reticulum and subsequent nuclear translocation of the nuclear factor of activated T-cells (NFAT) (berg2005tecfamilykinases pages 39-41, berg2005tecfamilykinases pages 17-18). In addition, TXK contributes to the positive regulation of IFNG transcription in T-helper 1 (Th1) cells by forming a complex with PARP1 and EEF1A1 and phosphorylating both components, thereby enhancing IFNG promoter activity (berg2005tecfamilykinases pages 39-41, suzuki2006skewedth1responses pages 5-5). TXK also phosphorylates LCP2, which is involved in the up-regulation of the Th1-preferred cytokine IL-2, and phosphorylates Tyr-201 of CTLA4, a modification that facilitates PI-3 kinase association with the CTLA4 receptor, further influencing T-cell co-stimulatory signaling (berg2005tecfamilykinases pages 39-41, venegas…2009teckinasesregulate pages 5-7).
8. Other Comments  
   TXK has been implicated in immunological disease processes through genetic and pharmacological studies. Although specific disease-causing mutations in TXK have not been extensively documented, its functional redundancy with ITK is evidenced by the exacerbated defects observed in double knockout mouse models. Furthermore, genetic association studies and Open Targets data have linked TXK to platelet-related phenotypes and autoimmune diseases, including vitiligo and alopecia areata (OpenTargets Search). Clinically, TXK is considered a candidate target for therapeutic intervention, as exemplified by the small-molecule inhibitor ritlecitinib tosylate, which targets multiple Tec family kinases including TXK (castelosoccio2023proteinkinasesdrug pages 15-16, bradshaw2010thesrcsyk pages 3-5). TXK also shares a conserved cysteine residue in the kinase domain that is exploited by covalent inhibitors developed for related kinases, further supporting its potential for drug targeting (schnute2012brutonstyrosinekinase pages 18-20).
9. References  
   berg2005tecfamilykinases pages 1-3; berg2005tecfamilykinases pages 3-6; berg2005tecfamilykinases pages 6-8; berg2005tecfamilykinases pages 8-11; berg2005tecfamilykinases pages 13-15; berg2005tecfamilykinases pages 17-18; berg2005tecfamilykinases pages 28-30; berg2005tecfamilykinases pages 39-41; ortutay2008phylogenyoftec pages 4-7; ortutay2008phylogenyoftec pages 7-10; venegas…2009teckinasesregulate pages 1-2; venegas…2009teckinasesregulate pages 5-7; yu2009tecfamilykinases pages 12-16; yu2009tecfamilykinases pages 16-19; yu2009tecfamilykinases pages 50-52; bradshaw2010thesrcsyk pages 3-5; bradshaw2010thesrcsyk pages 5-6; castelosoccio2023proteinkinasesdrug pages 15-16; schnute2012brutonstyrosinekinase pages 18-20; yaronbarir2024theintrinsicsubstrate pages 16-16.

References

1. (berg2005tecfamilykinases pages 3-6): Leslie J. Berg, Lisa D. Finkelstein, Julie A. Lucas, and Pamela L. Schwartzberg. Tec family kinases in t lymphocyte development and function. Annual Review of Immunology, 23:549-600, Apr 2005. URL: https://doi.org/10.1146/annurev.immunol.22.012703.104743, doi:10.1146/annurev.immunol.22.012703.104743. This article has 426 citations and is from a highest quality peer-reviewed journal.
2. (berg2005tecfamilykinases pages 1-3): Leslie J. Berg, Lisa D. Finkelstein, Julie A. Lucas, and Pamela L. Schwartzberg. Tec family kinases in t lymphocyte development and function. Annual Review of Immunology, 23:549-600, Apr 2005. URL: https://doi.org/10.1146/annurev.immunol.22.012703.104743, doi:10.1146/annurev.immunol.22.012703.104743. This article has 426 citations and is from a highest quality peer-reviewed journal.
3. (berg2005tecfamilykinases pages 28-30): Leslie J. Berg, Lisa D. Finkelstein, Julie A. Lucas, and Pamela L. Schwartzberg. Tec family kinases in t lymphocyte development and function. Annual Review of Immunology, 23:549-600, Apr 2005. URL: https://doi.org/10.1146/annurev.immunol.22.012703.104743, doi:10.1146/annurev.immunol.22.012703.104743. This article has 426 citations and is from a highest quality peer-reviewed journal.
4. (berg2005tecfamilykinases pages 6-8): Leslie J. Berg, Lisa D. Finkelstein, Julie A. Lucas, and Pamela L. Schwartzberg. Tec family kinases in t lymphocyte development and function. Annual Review of Immunology, 23:549-600, Apr 2005. URL: https://doi.org/10.1146/annurev.immunol.22.012703.104743, doi:10.1146/annurev.immunol.22.012703.104743. This article has 426 citations and is from a highest quality peer-reviewed journal.
5. (berg2005tecfamilykinases pages 8-11): Leslie J. Berg, Lisa D. Finkelstein, Julie A. Lucas, and Pamela L. Schwartzberg. Tec family kinases in t lymphocyte development and function. Annual Review of Immunology, 23:549-600, Apr 2005. URL: https://doi.org/10.1146/annurev.immunol.22.012703.104743, doi:10.1146/annurev.immunol.22.012703.104743. This article has 426 citations and is from a highest quality peer-reviewed journal.
6. (ortutay2008phylogenyoftec pages 4-7): Csaba Ortutay, Beston F. Nore, Mauno Vihinen, and C.I. Edvard Smith. Phylogeny of tec family kinases: identification of a premetazoan origin of btk, bmx, itk, tec, txk, and the btk regulator sh3bp5. Advances in Genetics, 64:51-80, Jan 2008. URL: https://doi.org/10.1016/s0065-2660(08)00803-1, doi:10.1016/s0065-2660(08)00803-1. This article has 38 citations and is from a peer-reviewed journal.
7. (venegas…2009teckinasesregulate pages 1-2): AM Venegas… JA Readinger, KL Mueller. Tec kinases regulate t‐lymphocyte development and function: new insights into the roles of itk and rlk/txk. Unknown journal, 2009. URL: https://doi.org/10.1111/j.1600-065x.2008.00757, doi:10.1111/j.1600-065x.2008.00757.
8. (yu2009tecfamilykinases pages 12-16): L Yu. Tec family kinases: transcriptional and posttranslational regulation. Unknown journal, 2009.
9. (yu2009tecfamilykinases pages 16-19): L Yu. Tec family kinases: transcriptional and posttranslational regulation. Unknown journal, 2009.
10. (yu2009tecfamilykinases pages 50-52): L Yu. Tec family kinases: transcriptional and posttranslational regulation. Unknown journal, 2009.
11. (berg2005tecfamilykinases pages 17-18): Leslie J. Berg, Lisa D. Finkelstein, Julie A. Lucas, and Pamela L. Schwartzberg. Tec family kinases in t lymphocyte development and function. Annual Review of Immunology, 23:549-600, Apr 2005. URL: https://doi.org/10.1146/annurev.immunol.22.012703.104743, doi:10.1146/annurev.immunol.22.012703.104743. This article has 426 citations and is from a highest quality peer-reviewed journal.
12. (berg2005tecfamilykinases pages 39-41): Leslie J. Berg, Lisa D. Finkelstein, Julie A. Lucas, and Pamela L. Schwartzberg. Tec family kinases in t lymphocyte development and function. Annual Review of Immunology, 23:549-600, Apr 2005. URL: https://doi.org/10.1146/annurev.immunol.22.012703.104743, doi:10.1146/annurev.immunol.22.012703.104743. This article has 426 citations and is from a highest quality peer-reviewed journal.
13. (bradshaw2010thesrcsyk pages 3-5): J. Michael Bradshaw. The src, syk, and tec family kinases: distinct types of molecular switches. Cellular Signalling, 22:1175-1184, Aug 2010. URL: https://doi.org/10.1016/j.cellsig.2010.03.001, doi:10.1016/j.cellsig.2010.03.001. This article has 364 citations and is from a peer-reviewed journal.
14. (bradshaw2010thesrcsyk pages 5-6): J. Michael Bradshaw. The src, syk, and tec family kinases: distinct types of molecular switches. Cellular Signalling, 22:1175-1184, Aug 2010. URL: https://doi.org/10.1016/j.cellsig.2010.03.001, doi:10.1016/j.cellsig.2010.03.001. This article has 364 citations and is from a peer-reviewed journal.
15. (castelosoccio2023proteinkinasesdrug pages 15-16): Leslie Castelo-Soccio, Hanna Kim, Massimo Gadina, Pamela L. Schwartzberg, Arian Laurence, and John J. O’Shea. Protein kinases: drug targets for immunological disorders. Nature Reviews Immunology, 23:787-806, May 2023. URL: https://doi.org/10.1038/s41577-023-00877-7, doi:10.1038/s41577-023-00877-7. This article has 74 citations and is from a highest quality peer-reviewed journal.
16. (ortutay2008phylogenyoftec pages 7-10): Csaba Ortutay, Beston F. Nore, Mauno Vihinen, and C.I. Edvard Smith. Phylogeny of tec family kinases: identification of a premetazoan origin of btk, bmx, itk, tec, txk, and the btk regulator sh3bp5. Advances in Genetics, 64:51-80, Jan 2008. URL: https://doi.org/10.1016/s0065-2660(08)00803-1, doi:10.1016/s0065-2660(08)00803-1. This article has 38 citations and is from a peer-reviewed journal.
17. (suzuki2006skewedth1responses pages 5-5): N. Suzuki, K. Nara, and Tomoko Suzuki. Skewed th1 responses caused by excessive expression of txk, a member of the tec family of tyrosine kinases, in patients with behcet’s disease. Clinical Medicine & Research, 4:147-151, Jun 2006. URL: https://doi.org/10.3121/cmr.4.2.147, doi:10.3121/cmr.4.2.147. This article has 53 citations.
18. (berg2005tecfamilykinases pages 13-15): Leslie J. Berg, Lisa D. Finkelstein, Julie A. Lucas, and Pamela L. Schwartzberg. Tec family kinases in t lymphocyte development and function. Annual Review of Immunology, 23:549-600, Apr 2005. URL: https://doi.org/10.1146/annurev.immunol.22.012703.104743, doi:10.1146/annurev.immunol.22.012703.104743. This article has 426 citations and is from a highest quality peer-reviewed journal.
19. (schnute2012brutonstyrosinekinase pages 18-20): MARK E. SCHNUTE, ADRIAN HUANG, and EDDINE SAIAH. Bruton’s tyrosine kinase (btk). Anti-Inflammatory Drug Discovery, pages 297-326, Jul 2012. URL: https://doi.org/10.1039/9781849735346-00297, doi:10.1039/9781849735346-00297. This article has 3 citations.
20. (yaronbarir2024theintrinsicsubstrate pages 16-16): 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 50 citations and is from a highest quality peer-reviewed journal.
21. (venegas…2009teckinasesregulate pages 5-7): AM Venegas… JA Readinger, KL Mueller. Tec kinases regulate t‐lymphocyte development and function: new insights into the roles of itk and rlk/txk. Unknown journal, 2009. URL: https://doi.org/10.1111/j.1600-065x.2008.00757, doi:10.1111/j.1600-065x.2008.00757.