Phylogeny  
- Assigned to the tyrosine-kinase (TK) group, Tec family, in the human kinome classification (unknownauthors2009tecfamilykinases pages 50-52, smith2001thetecfamily pages 7-9).  
- Mammalian orthologs confirmed in Homo sapiens (chromosome 4p12) and Mus musculus (Txk, chromosome 5); a homologous rat cDNA fragment has been reported, whereas the platypus genome lacks a Txk locus (haire1994txkanovel pages 3-4, haire1995themurineform pages 3-4, ortutay2008phylogenyoftec pages 4-7).  
- A single Tec-family gene (Btk29A) exists in Drosophila, but no direct TXK ortholog is present; Xenopus and zebrafish retain other Tec kinases yet show no dedicated Txk gene (ortutay2008phylogenyoftec pages 1-4).  
- Gene duplications that created the five vertebrate Tec kinases (BTK, BMX, ITK, TEC, TXK) occurred before vertebrate radiation, placing TXK on an evolutionary branch paralogous to ITK (ortutay2008phylogenyoftec pages 13-16).

Reaction Catalyzed  
- ATP + protein-L-tyrosine → ADP + protein-L-tyrosine-phosphate (ellis1998functionalanalysisof pages 3-4).

Cofactor Requirements  
- Maximal catalytic activity requires ≥5 mM Mg²⁺ or Mn²⁺; no strong preference between the two divalent cations (ellis1998functionalanalysisof pages 3-4, ellis1998functionalanalysisof pages 6-7).

Substrate Specificity  
- Comprehensive peptide screens show negligible phosphorylation of canonical Src-, Syk- or ZAP70-preferred motifs, indicating a distinct substrate repertoire (ellis1998functionalanalysisof pages 4-6).  
- The 2024 tyrosine-kinome atlas assigns TXK a unique intrinsic specificity without a simple consensus; preferred substrates contain hydrophobic residues at +1/+3 relative to the phosphotyrosine (yaronbarir2024theintrinsicsubstrate pages 16-16).  
- In cells, verified physiological substrates include PLC-γ1 and the adaptor SLP-76 during TCR signaling (chamorro2001requirementsforactivation pages 10-12).

Structure  
- Domain organization: N-terminal palmitoylated cysteine-string motif (membrane targeting) → proline-rich region with bipartite NLS → SH3 → SH2 → bilobal kinase domain lacking a PH domain (chamorro2001requirementsforactivation pages 1-2, haire1994txkanovel pages 1-2).  
- Activation loop contains the regulatory Tyr420 equivalent to Btk Tyr551; flanked by divergent residues relative to other Tec kinases (chamorro2001requirementsforactivation pages 2-4).  
- AlphaFold model AF-P42681-F1 shows canonical TK fold with conserved C-helix, HRD catalytic loop, DFG motif and intact hydrophobic spine (unknownauthors2007exploringstructureand pages 27-28).  
- No experimental crystal or NMR structure reported to date; structural inference derives from homology with solved Tec-family kinase domains (unknownauthors2007exploringstructureand pages 138-143).

Regulation  
- Src-family kinases Fyn and Lck bind the N-terminal proline-rich motif and trans-phosphorylate Tyr420, generating full catalytic activation (chamorro2001requirementsforactivation pages 2-4, chamorro2001requirementsforactivation pages 10-12).  
- Autophosphorylation occurs in vitro, contributing to basal activity (ellis1998functionalanalysisof pages 3-4).  
- S-palmitoylation of clustered N-terminal cysteines is essential for constitutive lipid-raft localization; this process is independent of Tyr420 phosphorylation (chamorro2001requirementsforactivation pages 1-2).  
- Phosphorylation accelerates proteolytic turnover, suggesting ubiquitin-mediated degradation downstream of activation, although the E3 ligase is not yet defined (chamorro2001requirementsforactivation pages 10-12).  
- PI3K activity is dispensable for both membrane recruitment and phosphorylation, distinguishing TXK from PH-domain-containing Tec kinases (chamorro2001requirementsforactivation pages 1-2).  
- Following TCR engagement, the inherent NLS directs a pool of active TXK to the nucleus where it binds promoter DNA (mihara2007roleoftxk pages 1-4).

Function  
- Expression: High in thymocytes, peripheral T-cells, NK cells and mast cells; minimal in B-cells and non-hematopoietic tissues (haire1994txkanovel pages 3-4, ellis1998functionalanalysisof pages 1-2).  
- Upstream activators: TCR-proximal Src kinases Fyn/Lck (chamorro2001requirementsforactivation pages 2-4).  
- Downstream substrates and partners: PLC-γ1, SLP-76, LAT, VAV1 and actin-regulatory complexes, enabling Ca²⁺ mobilization and cytoskeletal remodeling (chamorro2001requirementsforactivation pages 10-12, unknownauthors2009teckinasesregulate pages 1-2).  
- Functional overlap with ITK; dual Itk/Txk deficiency severely compromises PLC-γ1 phosphorylation and downstream signaling (unknownauthors2009teckinasesregulate pages 1-2).  
- Nuclear role: Binds −53/−39 IFNG promoter element in Th1 cells, enhancing IFN-γ transcription and promoting Th1 differentiation (mihara2007roleoftxk pages 1-4).  
- Contributes to development and function of invariant NKT cells, corroborated by combined Itk/Txk knockout phenotypes (ortutay2008phylogenyoftec pages 4-7).

Other Comments  
- Elevated TXK expression is observed in Th1-dominant autoimmune disorders such as rheumatoid arthritis and Behçet’s disease; reduced levels correlate with Th2-skewed conditions including asthma and atopic dermatitis (mihara2007roleoftxk pages 1-4).

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