## Phylogeny

TXK (also called RLK) is a member of the tyrosine-kinase (TK) group, Tec family, within the human kinome (Unknown Authors, 2009; Smith et al., 2001). Orthologous genes are confirmed in Homo sapiens (chromosome 4p12) and Mus musculus (Txk, chromosome 5), with a rat cDNA fragment also reported; the platypus genome lacks a Txk locus (Haire et al., 1994; Haire & Litman, 1995; Ortutay et al., 2008). Invertebrates such as Drosophila possess a single Tec-family gene (Btk29A) but no direct TXK ortholog, and amphibian/fish genomes encode other Tec kinases yet lack a dedicated Txk gene (Ortutay et al., 2008). Gene duplications that created the five vertebrate Tec kinases (BTK, BMX, ITK, TEC, TXK) pre-dated vertebrate radiation, placing TXK on a branch paralogous to ITK (Ortutay et al., 2008).

## Reaction Catalyzed

ATP + protein-L-tyrosine → ADP + protein-L-tyrosine-phosphate (Ellis et al., 1998).

## Cofactor Requirements

Maximal activity requires ≥ 5 mM Mg²⁺ or Mn²⁺, with no marked preference between the two divalent cations (Ellis et al., 1998).

## Substrate Specificity

Peptide-array screening shows minimal phosphorylation of motifs preferred by Src, Syk or ZAP70 kinases, indicating a distinct specificity (Ellis et al., 1998). A recent tyrosine-kinome atlas assigns TXK an intrinsic but non-consensus preference, favouring hydrophobic residues at +1 and +3 relative to the Tyr to be phosphorylated (Yaron-Barir et al., 2024). Verified cellular substrates during T-cell-receptor (TCR) signalling include PLC-γ1 and the adaptor SLP-76 (Chamorro et al., 2001).

## Structure

The protein comprises an N-terminal palmitoylated cysteine string (membrane targeting), a proline-rich region containing a bipartite nuclear localisation signal, followed by SH3, SH2 and a bilobal kinase domain; unlike other Tec kinases, it lacks a PH domain (Haire et al., 1994; Chamorro et al., 2001). The activation loop harbours Tyr420 (equivalent to BTK Tyr551) flanked by divergent residues (Chamorro et al., 2001). An AlphaFold model (AF-P42681-F1) exhibits the canonical TK fold with conserved C-helix, HRD, DFG and hydrophobic spine (Unknown Authors, 2007). No experimental crystal or NMR structure is yet available; structural insight is inferred from homology models of Tec-family kinase domains (Unknown Authors, 2007).

## Regulation

• Src-family kinases Fyn and Lck bind the N-terminal proline-rich motif and trans-phosphorylate Tyr420 to achieve full activation (Chamorro et al., 2001).  
• Autophosphorylation contributes to basal activity in vitro (Ellis et al., 1998).  
• S-palmitoylation of clustered N-terminal cysteines drives constitutive lipid-raft localisation independently of Tyr420 phosphorylation (Chamorro et al., 2001).  
• Phosphorylation promotes proteolytic turnover, suggesting ubiquitin-mediated degradation, although the responsible E3 ligase is unknown (Chamorro et al., 2001).  
• PI3K activity is not required for membrane recruitment or activation, distinguishing TXK from PH-domain-containing Tec kinases (Chamorro et al., 2001).  
• After TCR engagement, the intrinsic NLS directs a fraction of active TXK to the nucleus where it binds promoter DNA (Mihara & Suzuki, 2007).

## Function

Expression is high in thymocytes, peripheral T cells, NK cells and mast cells, but low in B cells and most non-haematopoietic tissues (Haire et al., 1994; Ellis et al., 1998).  
Upstream activators: TCR-proximal Src kinases Fyn and Lck (Chamorro et al., 2001).  
Downstream substrates/partners: PLC-γ1, SLP-76, LAT, VAV1 and actin-regulatory complexes, facilitating Ca²⁺ mobilisation and cytoskeletal remodelling (Chamorro et al., 2001; Unknown Authors, 2009).  
Functional overlap with ITK: combined Itk/Txk deficiency severely impairs PLC-γ1 phosphorylation and T-cell signalling (Unknown Authors, 2009).  
Nuclear role: binds the −53/−39 IFNG promoter element in Th1 cells to enhance IFN-γ transcription and promote Th1 differentiation (Mihara & Suzuki, 2007).  
Contributes to development and function of invariant NKT cells (Ortutay et al., 2008).

## Other Comments

Elevated TXK expression is associated with Th1-dominant autoimmune disorders (e.g., rheumatoid arthritis, Behçet’s disease), whereas reduced levels correlate with Th2-skewed conditions such as asthma and atopic dermatitis (Mihara & Suzuki, 2007).

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