## Phylogeny

Tyrosine-protein kinase TXK (gene TXK; also called PTK4 or RLK) belongs to the Tec family of non-receptor tyrosine kinases and is conserved across mammals. Phylogenetic analyses based on SH3, SH2 and catalytic (SH1) domains place TXK in a Tec sub-branch dedicated to T-cell receptor (TCR) signalling. Its closest paralogue is interleukin-2-inducible kinase (Itk), with which it shares partially redundant functions in T-cell activation (Bolen & Brugge, 1997, pp. 6-9; Mamand, 2018, pp. 32-35; Mahajan et al., 1995, pp. 7-8).

## Reaction Catalyzed

ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosine-phosphate + H⁺ (Template).

## Cofactor Requirements

Mg²⁺ is required for catalytic activity (Template).

## Substrate Specificity

TXK phosphorylates substrates central to T-cell activation, including:  
• Phospholipase C γ1 (PLCG1) at Tec-family sites to trigger Ca²⁺ release and NFAT activation (Min, 2008, pp. 35-39, 73-78).  
• Lymphocyte cytosolic protein 2 (LCP2), enhancing interleukin-2 production (Bolen & Brugge, 1997, pp. 9-11).  
• CTLA4 Tyr-201, promoting PI3-kinase recruitment (Min, 2008, pp. 39-44).  
Specificity is governed by long-range docking interactions involving TXK non-catalytic domains and complementary surfaces on the substrate rather than solely by local sequence motifs (Min, 2008, pp. 57-63).

## Structure

TXK exhibits the canonical Tec-kinase modular layout:  
1 N-terminal proline-/cysteine-rich segment (replaces the pleckstrin homology domain present in other Tec kinases) (Bolen & Brugge, 1997, pp. 6-9; Mahajan et al., 1995, pp. 7-8).  
2 SH3 domain (binds PxxP motifs).  
3 SH2 domain (engages substrates via non-canonical contacts) (Min, 2008, pp. 35-39, 73-78).  
4 C-terminal kinase (SH1) domain containing the activation loop; phosphorylation of Tyr-420 is required for full activity (Joseph et al., 2010, pp. 6-8; Min, 2008, pp. 63-73).  
No high-resolution crystal structure is available; biochemical and AlphaFold models indicate the standard bilobal kinase fold (Bolen & Brugge, 1997, pp. 6-9).

## Regulation

• Phosphorylation: membrane-recruited TXK is activated by autophosphorylation/ trans-phosphorylation on Tyr-420 following TCR engagement (Mamand, 2018, pp. 211-214).  
• Docking interactions: SH2-kinase domain interfaces and substrate SH2 docking enhance catalytic efficiency (Min, 2008, pp. 35-39, 73-78).  
• Allosteric control: assembly of a hydrophobic regulatory spine, stabilised by SH2-kinase contacts, gates activity (Joseph et al., 2010, pp. 6-8).

## Function

Predominantly expressed in T-lymphocytes, TXK propagates TCR signalling. Together with Itk, it regulates development and activation of conventional T cells and NKT cells. Key roles include:  
• Phosphorylation of PLCG1 → lipid-raft localisation → Ca²⁺ influx → NFAT-dependent transcription (Min, 2008, pp. 35-39, 78-82).  
• Phosphorylation of LCP2 → IL-2 production (Bolen & Brugge, 1997, pp. 9-11).  
• Phosphorylation of CTLA4 → PI3-kinase recruitment (Min, 2008, pp. 39-44).  
• Participation in a PARP1/EEF1A1 complex that activates IFNG transcription in Th1 cells (Mamand, 2018, pp. 32-35; Siveen et al., 2018, pp. 6-8).

## Inhibitors

Selective TXK inhibitors are not yet well characterised, but the kinase is considered a potential therapeutic target in immune disorders and haematological malignancies (Mamand, 2018, pp. 32-35; Bolen & Brugge, 1997, pp. 6-9).

## Other Comments

The absence of a pleckstrin homology domain may offer unique opportunities to develop TXK-selective inhibitors that disrupt its distinctive protein–protein interaction surfaces. Dysregulated Tec-family signalling contributes to autoimmune disease and T-cell malignancies, although direct TXK mutations are rare (Mamand, 2018, pp. 32-35; Bolen & Brugge, 1997, pp. 6-9).

## References

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