## Phylogeny

Tyrosine-protein kinase ITK belongs to the Tec family of non-receptor tyrosine kinases, which forms an independent branch of the vertebrate kinome devoted largely to adaptive immunity (Zhong et al., 2014). Orthologs are present in mammals and earlier vertebrates, and the conserved catalytic core and multi-domain architecture have been maintained throughout vertebrate evolution (Devkota et al., 2017).

## Reaction Catalyzed

ATP + protein-(L-tyrosine) ⇌ ADP + protein-(L-tyrosine-phosphate) + H⁺ (Zhong et al., 2014).

## Cofactor Requirements

Mg²⁺ is required to coordinate ATP and support phosphoryl transfer (Zhong et al., 2014; Howe et al., 2019).

## Substrate Specificity

ITK preferentially phosphorylates tyrosine residues in key T-cell signaling proteins, including PLCG1, LAT, LCP2/SLP-76, and the transcription factor TBX21 at Tyr530. Although no strict consensus sequence has been defined, substrates generally participate in T-cell receptor signaling complexes (Basu, 2023; Kannan, 2015).

## Structure

ITK exhibits a modular fold: an N-terminal PH domain that binds PIP₃, a Tec Homology (TH) region containing a zinc-binding BH motif and proline-rich segments, followed by SH3 and SH2 domains, and a C-terminal kinase (SH1) domain. Activation loop residue Tyr511 within the kinase domain is phosphorylated by LCK, while autophosphorylation on Tyr180 in the SH3 domain further modulates activity. Structural studies and benzothiazole inhibitors highlight the ATP-binding pocket as a selectivity determinant (Devkota et al., 2017; Mackinnon et al., 2013; Zhong et al., 2014).

## Regulation

In resting T cells, intramolecular contacts among PH, TH, SH3, and SH2 domains maintain ITK in an autoinhibited conformation. T-cell receptor engagement activates PI3K, generating PIP₃ that recruits ITK to the plasma membrane via its PH domain. Subsequent phosphorylation of Tyr511 by LCK and autophosphorylation of Tyr180 release autoinhibition, producing the catalytically competent kinase. Additional conformational shifts and domain rearrangements fine-tune activity (Devkota et al., 2017; Hsu et al., 2023; Zhong et al., 2014).

## Function

ITK is selectively expressed in αβ T cells, γδ T cells, and NKT cells, where it is essential for development, activation, and differentiation. Upon antigen recognition, active ITK phosphorylates PLCG1, leading to IP₃/DAG production and Ca²⁺ signaling; it also phosphorylates LAT and LCP2, scaffolding downstream effectors such as VAV1. Phosphorylation of TBX21 modulates T-helper lineage decisions. Collectively, these events drive cytokine production, proliferation, and subset specification of T lymphocytes (Huang, 2014; Kannan, 2015; Lechner et al., 2020; Zhong et al., 2014).

## Inhibitors

Selective ATP-competitive ITK inhibitors—including benzothiazole derivatives and other covalent or non-covalent compounds—display sub-nanomolar potency and high isoform specificity (Kaur et al., 2012; Mackinnon et al., 2013; Hsu et al., 2023).

## Other Comments

Aberrant ITK signaling is implicated in autoimmune disease, allergic asthma, and lymphoproliferative disorders, while ITK deficiency causes immunodeficiency. Pharmacological modulation of ITK is therefore a promising therapeutic strategy (Lechner et al., 2020; Kaur et al., 2012).

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