

Tec

Key References

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Overview

Tec kinases represent the second largest family of nonreceptor tyrosine kinases and are activated in response to cellular stimulation by antigen receptors, integrins, growth factors, cytokines and G protein-coupled receptors. The mammalian Tec family consists of five members: Tec, Btk, Itk/Emt/Tsk, Rlk/Txk and Bmx/Etk. Tec kinases are defined by a common protein domain organization including a COOH-terminal kinase domain, preceded by Src homology-2 and 3 protein interaction domains and a Tec homology domain that includes one or two proline-rich regions that interact intramolecularly or intermolecularly with SH3 domains and contribute to kinase regulation. Importantly, most Tec kinases possess an amino terminal pleckstrin homology (PH) domain that distinguishes them from all other identified tyrosine kinases. The Tec kinases' PH domains bind to phosphatidylinositol (3,4,5) trisphosphate (PIP₃), and are therefore regulated by PI3 kinase and the phosphatases SHIP and PTEN. The atypical Tec kinase Rlk/Txk lacks a PH domain and instead contains a palmitoylated series of cysteines.

With some exceptions, Tec kinases are expressed primarily in cells of hematopoietic lineages. Btk is expressed in most hematopoietic cells except T cells, whereas Itk expression is limited to mast cells, T-, NK-, and NKT cells, and Rlk is restricted to T- and mast cells. In contrast, Tec is most widely expressed and is found in liver, developing embryo, brain, endothelium and melanocytes, in addition to hematopoietic cells. Bmx is expressed in granulocytes, monocytes, and in cells of epithelial and endothelial lineages.

Activation of Tec kinases requires two major steps: 1) membrane targeting, via interac-

tions of their PH domains with PIP₃ or other proteins and 2) tyrosine phosphorylation within the kinase activation loop. Protein interactions via the SH2 and SH3 domains may also be required to disrupt intramolecular interactions and to localize the kinases in signaling complexes.

Although Tec kinases are activated by many receptors, their functions are best understood downstream of lymphocyte antigen receptors. Notably, mutations affecting Btk cause the human primary immunodeficiency, X-linked agammaglobulinemia, as well as the mouse mutant x-linked immunodeficiency, *xid*, characterized by impaired B cell development and function. Similarly, mutations disrupting Itk or Itk and Rlk in mice cause defective T lymphocyte development and function associated with reduced antigen receptor induced proliferation, cytokine production, adhesion and migration. Btk and Itk are required for the phosphorylation and full activation of PLC-γ and downstream readouts including mobilization of calcium and activation of MAP kinases and downstream transcription factors, including NFATs, AP-1 and NFκB. Btk also interacts with and is cross-regulated by PKC-β. Additional roles for Tec kinases in T cells include regulation of the actin cytoskeleton, adhesion and migration. Upon antigen receptor activation, Rlk, Itk and Btk can translocate to the nucleus, suggesting direct effects on transcription.

In T cells, mutation of the Tec kinases neither prevents T cell development nor signaling but instead alters the efficiency or type of T cells responses. In particular, Itk-deficiency impairs TH2 responses associated with allergy and asthma, making Itk an attractive therapeutic target for such diseases. Several inhibitors of Itk have been

recently described--data from three highly selective Itk antagonists demonstrate putative therapeutic use for allergic-induced asthma.

In other cell types, Bmx/Etk and Tec participate in the regulation of Rho and serum response factor in response to Gα₁₂. Tec is activated in response to multiple cytokine and growth factor receptors and has also been linked to the actin cytoskeleton via interactions with Vav. Bmx/Etk also participates in signaling from integrins and roles in wound healing and cardioprotection were also recently described. Bmx Etk is also required for phosphorylation of STAT-3 in cellular transformation by Src, suggesting potential therapeutic uses for Tec kinase inhibitors in cancer.

FAMILY MEMBERS	Tec	Btk	Itk
OTHER NAMES	Cytoplasmic tyrosine kinase, PSCTK4, Dsrc28C	ATK, BPK, PSCTK1, XLA Bruton's tyrosine kinase, Xid	Emt, Tsk, LYK, PSCTK2
MOLECULAR WEIGHT/ STRUCTURAL DATA	73 kDa ^a 631 aa ^b	76.2 kDa 659 aa	71.8 kDa 620 aa
ISOFORMS	Multiple splice variants	Not known	2 Forms in mouse that differ by 6 aa
SPECIES	Human, mouse, rat, dog, chimpanzee, <i>Drosophila</i>	Human, mouse, rat, dog, chimpanzee, chicken, <i>Drosophila</i>	Human, mouse, rat, dog, chicken, zebrafish, skate
DOMAIN ORGANIZATION	PH domain, Btk homology domain, Tec homology domain, SH3 domain, SH2 domain, kinase domain	PH domain, Btk homology domain, Tec homology domain, SH3 domain, SH2 domain, kinase domain	PH domain, Btk homology domain, Tec homology region, SH3 domain, SH2 domain, kinase domain
PHOSPHORYLATION SITES	Tyr ²⁰⁶ (auto), Tyr ⁵¹⁹	Tyr ²²³ (auto), Tyr ⁵⁵¹	Tyr ¹⁸⁰ (auto), Tyr ⁵¹¹
TISSUE DISTRIBUTION	Embryonic limb, adult liver, myeloid, B and T cells, melanocytes; overexpression of Tec I isoform is associated with cellular transformation	B cells, myeloid cells, mast cells	T cells, NK cells, NK-T cells, myeloid cells, mast cells, elevated in atopic dermatitis
SUBCELLULAR LOCALIZATION	Cytoplasm, membrane-associated	Cytoplasm, moves to plasma membrane, nucleus	Cytoplasm, moves to plasma membrane, nucleus
BINDING PARTNERS/ ASSOCIATED PROTEINS	Vav1, Gα _q , Gα ₁₂ , Kit, Dok-1, -2, CD28, BRDG1, Sak, Lyn, Fyn, Hck, Grb10, PI3Kp85	PKC, Gβγ, Gα _q , Gα ₁₂ , Hck, Lyn, Fyn, WASp, Fas, Sab, Sam68, EWS, Cbl, TFII-I, Vav, F-actin, Syk, BLNK, PLCγ, Caveolin, IBtk	CD28, SLP-76, Vav1, WASp, Grb2, Lyn, Fyn, Hck, PI3Kp85
UPSTREAM ACTIVATORS	TCR/CD3, CD28, SCF/c-Kit, BCR, IL-3R, IL-6R, ErythropoietinR, PI3K, Src family kinases	BCR, TNFR, VEGFR, Integrin, IL-3, IL-5, IL-6, FcεRI, CD19, CD38, CD72, collagen, CXCR4, Gβγ, gp130, PKC, PI3K, Src family kinases	TCR, CD2, CD28, CXCR4, Src family kinases, PI3K, Peptidyl prolyl isomerase, CypA
DOWNSTREAM ACTIVATION	PLK-4, BRDG1, Grb10/GrbLR, PI3K,	PLCγ1, PLCγ2, Fas, TFII-I, Bright	PLCγ1, CD28, LAT, WASP, T-bet
SUBSTRATES	Dok-1, -2, Vav, LARG, CD28, Sak	WASP, Gβγ, Vav, Caveolin, PKCθ	Not known
ACTIVATORS	Not known	Not known	Not known
SELECTIVE INHIBITORS	Not known	LFM-A13 (L8789)	BMS-28507, BMS-488516, BMS-509744
NON-SELECTIVE INHIBITORS	Herbamycin A, Wortmanin (W1628), LY-294002 (L9908)	Herbamycin A, Wortmanin (W1628), LY-294002 (L9908)	Rosamarinic acid, Cyclophilin A, Herbamycin A, Wortmanin (W1628), LY-294002 (L9908)
SELECTIVE ACTIVATORS	Not known	Not known	Not known
PHYSIOLOGICAL FUNCTION	Activates AP1 and NFAT transcription, IL2-promoter	BCR driven: PLCγ1,γ2 activation, PKC activation, transcription factor activation, adhesion, apoptosis, B cell maturation	TCR driven: Transcription factor activation, PLCγ1 activation, Th2 responses, actin reorganization, adhesion, thymic selection
DISEASE RELEVANCE	Cancer?	XLA (h), xid (m)	Allergies?, contact hypersensitivity, asthma (mice)

Tec

FAMILY MEMBERS	Rlk	Bmx
OTHER NAMES	Txk, PSCTK5	Etk, PSCTK3
MOLECULAR WEIGHT/ STRUCTURAL DATA	58 kDa, 55kDa 527 aa, 502 aa ^a	78 kDa 675 aa
ISOFORMS	2 alternate start sites	2 alternate splice variants
SPECIES	Human, mouse, chimpanzee, dog, rat	Human, mouse, dog, rat, chicken, <i>Drosophila</i>
DOMAIN ORGANIZATION	Cysteine repeat, proline rich region, SH3 domain, SH2 domain, kinase domain	PH domain, Btk homology domain, SH3-like domain, SH2 domain, kinase domain
PHOSPHORYLATION SITES	Tyr ⁹¹ (auto) Tyr ⁴²⁰	Tyr ²¹⁵ (auto), Tyr ²²³ , Tyr ⁵⁶⁶
TISSUE DISTRIBUTION	T cells, mast cells	Granulocytes, monocytes, endothelial cells, epithelial cells, prostate cancer and breast cancer cell lines, keratinocytes, specialized epithelial cells of thymus, elevated in metastatic carcinoma cell lines
SUBCELLULAR LOCALIZATION	Cytoplasm, translocates to nucleus and plasma membrane	Cytoplasm, nucleus
BINDING PARTNERS/ ASSOCIATED PROTEINS	Fyn, Hck, Lyn, Grb2, SLP-76	FAK, caveolin, Pak1, STAT3, PTPD1, Gα ₁₂
UPSTREAM ACTIVATORS	TCR, CXCR4, Src family kinases	Tie-2, VEGFR-1, TNFR, integrin, Src family kinases, FAK, nitric oxide, Gα _q , Gα ₁₂ , Gα ₁₃
DOWNSTREAM ACTIVATION SUBSTRATES	PLCγ1, SLP-76, CTLA-4?	FAK, caveolin, Pak1, STAT3, p53
SUBSTRATES	PLC-γ1, SLP-76, CTLA-4?	FAK, Caveolin
ACTIVATORS	Not found	Not found
SELECTIVE INHIBITORS	Not found	Not found
NON-SELECTIVE INHIBITORS	Herbamycin A	Herbamycin A, Wortmanin (W1628), LY-294002 (L9908)
SELECTIVE ACTIVATORS	Not found	Not found
PHYSIOLOGICAL FUNCTION	TCR driven: PLCγ1 activation, Th1 responses?, transcription activation of IFNγ promoter	Activate STAT3, inhibit p53 anti-apoptotic, contributes to transformation, cardioprotection?, activation of SRE?
DISEASE RELEVANCE	Behcet's syndrome	Wound repair?, cancer?

Abbreviations

a Multiple isoforms exist due to alternate initiation start sites or splicing variants.

b Isoform Tec IV noted here, Tec isoforms I-IV have been reported for both human and mouse.

FOOTNOTES