

# Csk

## Key References

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## Overview

The C-terminal c-Src kinase (Csk) is a 50-kDa cytosolic tyrosine kinase expressed in all examined cell types. Structurally, it resembles the Src family kinases in having SH3, SH2 and kinase domains, but it differs from Src kinases in lacking an N-terminal extension with a myristylation sequence motif, a tyrosine autophosphorylation site, and a C-terminal regulatory tyrosine phosphorylation site.

The physiological function of Csk is to phosphorylate the negative regulatory tyrosine residue in the C-terminus of all Src family kinases. In fact, Csk is probably the only kinase that efficiently phosphorylates this site *in vivo*, making Csk the general negative regulator of all Src family kinase-mediated events in cells. It is unclear if Csk has any other substrates.

Csk is encoded by an essential gene, the deletion of which is early embryonic lethal in mice due to defects in closure of the neural tube. Transformed embryonic fibroblasts from these animals display a near complete loss of phosphorylation of the C-terminal negative regulatory site in Src family kinases, significantly elevated catalytic activity of all Src like kinases, and constitutive hyperphosphorylation of their substrates.

In contrast to other tyrosine kinases, Csk is apparently not regulated by tyrosine phosphorylation. In fact, the activation loop is shorter than in other kinases and it does not contain any tyrosine residues. Instead, Csk is regulated by phosphorylation of a serine residue, S364, within the larger lobe of its catalytic domain. This site is phosphorylated by cAMP-dependent kinase and results in a several fold activation of Csk. In T cells, agents that elevate cAMP levels (e.g.

prostaglandin E<sub>2</sub> or membrane-permeable cAMP analogs) caused the phosphorylation of Csk at S364, activated Csk, suppressed Src family kinases, and prevented T cell activation. A phosphorylation site mutant of Csk prevented these responses, suggesting that Csk may be a critical target for cAMP-induced immune suppression.

An important regulator of Csk function is a transmembrane molecule, termed PAG or Cbp, which specifically binds the Csk SH2 domain when phosphorylated. PAG/Cbp is anchored to lipid rafts and is phosphorylated on tyrosine in resting cells, thus anchoring Csk in the subcellular compartment that is enriched in Src family kinases. Upon T cell antigen-receptor triggering, PAG/Cbp is transiently dephosphorylated leading to the dissociation of Csk. This allows lipid raft-located Src family kinases (Lck and Fyn in T cells) to remain active and phosphorylate receptor subunits and other molecules. After a few minutes, PAG/Cbp is again phosphorylated and Csk returns to the lipid rafts. This coincides with the downturn of tyrosine phosphorylation of Src family kinase substrates.

Csk also associates through its SH3 domain with the protein tyrosine phosphatases PTP-PEST and LYP (mouse ortholog is called PEP). As these phosphatases dephosphorylate the positive regulatory tyrosine residue in Src family kinases, it is thought that they synergize with Csk by jointly targeting and suppressing these kinases. Csk has also been shown to bind paxillin and other adapter proteins.

The Csk-homologous kinase (Chk) is 53% identical to Csk and shares the same overall structure of SH3-SH2-kinase domains, but has somewhat longer N- and C-terminal

extensions. There are two splice variants of Chk, 52 and 57 kDa, expressed predominantly in brain and hematopoietic cells. Chk expression can be upregulated by several growth factors and mitogen in leukocytes. Chk can phosphorylate Src family kinases *in vitro* and in breast cancer cells upon recruitment and binding to the ErbB-2/neu receptor kinase.

<b>FAMILY MEMBERS</b>	Csk	Ctk
<b>OTHER NAMES</b>	Cyl, c-Src tyrosine kinase	lsk, matk, ntk, hyl, batk, Chk, megakaryocyte-associated tyrosine protein kinase
<b>MOLECULAR WEIGHT/ STRUCTURAL DATA</b>	50 kDa 450 aa (human, mouse, and rat)	52 kDa and 57 kDa 466/507 aa (human), 465/505 aa (mouse)
<b>ISOFORMS</b>	Not known	Not known
<b>SPECIES</b>	Yeast, human, mouse, rat, chicken	Human, mouse, rat
<b>DOMAIN ORGANIZATION</b>	1 SH2 domain, 1 SH3 domain, 1 protein kinase domain	1 SH2 domain, 1 SH3 domain, 1 protein kinase domain
<b>PHOSPHORYLATION SITES</b>	Tyr <sup>184</sup> , Tyr <sup>304</sup> , Tyr <sup>416</sup> , Ser <sup>364</sup>	Ser <sup>501</sup>
<b>TISSUE DISTRIBUTION</b>	Ubiquitous	Brain and leukocytes
<b>SUBCELLULAR LOCALIZATION</b>	Cytosolic	Cytosolic
<b>BINDING PARTNERS/ ASSOCIATED PROTEIN</b>	PAG, PEP, PTP-PEST, Paxillin	Paxillin, TrkA
<b>UPSTREAM ACTIVATORS</b>	PKA	Not found
<b>DOWNSTREAM ACTIVATION</b>	Src, Lyn, Fyn, Lck	Src, Lyn, Fyn, Lck?
<b>ACTIVATORS</b>	Not known	Not known
<b>IN VIVO SUBSTRATES</b>	C-terminus of Src PTKs (Y527 in Src)	Not known
<b>IN VITRO SUBSTRATES</b>	polyGlu/Tyr	C-terminus of Src PTKs
<b>INHIBITORS</b>	Not known	Not known
<b>SELECTIVE INHIBITORS</b>	Not known	Not known
<b>PHYSIOLOGICAL FUNCTION</b>	Suppression of Src PTKs	May play inhibitory role in control of T-cell proliferation
<b>DISEASE RELEVANCE</b>	Not known	Not known

## FOOTNOTES