## Phylogeny

Tyrosine-protein kinase CSK (gene CSK, UniProt P41240) is a cytosolic non-receptor tyrosine kinase that forms a distinct, evolutionarily conserved branch within the cytoplasmic tyrosine kinase clade. Clear orthologs occur throughout vertebrates (e.g., human, mouse, rat) and in lower metazoans. CSK and its Src-family kinase (SFK) substrates have co-evolved: CSK appeared early in metazoan evolution as an intrinsic inhibitory counterpart that restrains SFK activity, and its domain architecture has remained highly conserved (Fortner et al., 2022; Ia et al., 2010).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine ⇌ ADP + H⁺ + [protein]-L-tyrosine-phosphate  
CSK specifically phosphorylates the conserved C-terminal tail tyrosine of SFKs (e.g., Tyr-527 of c-Src), thereby imposing autoinhibition on the target kinase (Fortner et al., 2022; Ia et al., 2010).

## Cofactor Requirements

Mg²⁺ is required for ATP coordination and efficient phosphoryl transfer (Ia et al., 2010).

## Substrate Specificity

CSK displays high specificity for the inhibitory C-terminal tyrosine of SFKs. Combinatorial peptide studies indicate a preference for acidic determinants combined with hydrophobic residues flanking the target tyrosine, features that reinforce selectivity toward SFK tail motifs and minimize off-target phosphorylation (Ia et al., 2010; Yaron-Barir et al., 2024).

## Structure

CSK is a modular protein composed of:  
• N-terminal SH3 domain – β-barrel fold binding proline-rich motifs; can mediate homodimerization.  
• Central SH2 domain – binds phosphotyrosine motifs, directing membrane recruitment via adaptors such as Cbp/PAG.  
• C-terminal kinase domain – classical bi-lobed fold; Lys-222 in the β3-strand coordinates ATP, and the DFG motif binds Mg²⁺. CSK lacks an activation-loop autophosphorylation site typical of many tyrosine kinases, consistent with its inhibitory role. Linker regions enable allosteric communication among the three domains (Ia et al., 2010; Superti-Furga & Courtneidge, 1995; Kan et al., 2023).

## Regulation

• Localization: SH2-mediated binding to phosphotyrosine adaptors (e.g., Cbp/PAG) recruits CSK to the plasma membrane, placing it near membrane-anchored SFKs (Fortner et al., 2022; Hunter & Manning, 2015).  
• Post-translational modification: PKA-dependent phosphorylation at Ser364 modulates catalytic efficiency and substrate interactions (Sun & Ayrapetov, 2023).  
• Allostery: Inter-domain rearrangements triggered by SH2 ligand binding or possible redox-sensitive disulfide formation adjust kinase activity (Sun & Ayrapetov, 2023; Shah et al., 2018).

## Function

CSK enforces negative regulation of SFKs by phosphorylating their C-terminal inhibitory tyrosine, stabilizing an autoinhibited conformation. This control:  
• Sets activation thresholds in T-cell and B-cell receptor signaling by restraining LCK and FYN.  
• Modulates cell adhesion and migration through downstream effectors such as FAK and paxillin.  
• Acts as a barrier against oncogenic transformation driven by hyperactive SFKs (Fortner et al., 2022; Hunter & Manning, 2015).

## Inhibitors

No highly selective CSK inhibitors are currently available; existing small-molecule probes target broader components of the Src pathway. The absence of CSK-specific inhibitors highlights an active area of therapeutic interest (Fortner et al., 2022; Sun & Ayrapetov, 2023; Superti-Furga & Courtneidge, 1995).

## Other Comments

Loss of CSK function via mutation, altered expression, or mislocalization is linked to cancers and cardiovascular or neurological disorders characterized by excessive SFK signaling, underscoring the importance of developing CSK-targeted modulators (Fortner et al., 2022).

## References

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