## Phylogeny

Tyrosine-protein kinase Lck is a Src-family, non-receptor tyrosine kinase largely confined to lymphoid lineages. Sequence analyses place Lck in the Src-module subgroup that emerged early in metazoan evolution and retains the characteristic SH3-SH2-kinase domain architecture seen in paralogs such as Src, Fyn and Lyn (Korade-Mirnics & Corey, 2000; Kwon, 2019). Orthologues span invertebrate chordates through mammals; the presence of Lck in amphioxus (Branchiostoma belcheri) underscores its deep conservation in immune-related signalling (Zhou et al., 2021).

## Reaction Catalyzed

ATP + [protein]-tyrosine ⇌ ADP + [protein]-O-phosphotyrosine + H⁺ (Chylek et al., 2014).

## Cofactor Requirements

Requires Mg²⁺ to coordinate ATP during phosphoryl transfer (Chylek et al., 2014; Loris, 2007).

## Substrate Specificity

Lck phosphorylates tyrosine residues within immunoreceptor tyrosine-based activation motifs (ITAMs) on CD3 and ζ-chain subunits of the T-cell receptor complex. Substrate docking is assisted by its SH2 domain (phosphotyrosine binding) and SH3 domain (proline-rich motif binding). Membrane recruitment via CD4/CD8 and other partners further restricts phosphorylation to appropriately clustered ITAMs, thereby creating ZAP-70 docking sites (Samraj, 2005; Chylek et al., 2014; Korade-Mirnics & Corey, 2000).

## Structure

Canonical Src-family layout:  
• N-terminal unique region bearing myristoylation (and often palmitoylation) for membrane attachment.  
• SH3 → SH2 → catalytic (SH1) kinase domain.  
• C-terminal tail with regulatory Tyr505.  
Phosphorylation of Tyr505 promotes an SH2-tail intramolecular interaction that locks an autoinhibited conformation, whereas phosphorylation of Tyr394 in the activation loop stabilises the active state. Structural studies highlight a hydrophobic regulatory spine and C-helix repositioning as key elements of this switch (Majeti, 2000; Posevitz, 2007; Loris, 2007; Kwon, 2019).

## Regulation

Activity is controlled by two opposing phosphorylation sites: autophosphorylation at Tyr394 activates Lck, while C-terminal Src kinase (Csk) phosphorylates Tyr505 to inactivate it. CD45 phosphatase removes the Tyr505 phosphate, maintaining Lck in a primed state for rapid activation after T-cell receptor engagement. Reversible myristoylation/palmitoylation regulates membrane localisation and microdomain targeting, adding an additional layer of control (Majeti, 2000; Okada, 2012; Korade-Mirnics & Corey, 2000; Posevitz, 2007; Samraj, 2005).

## Function

Expressed throughout thymocyte maturation and in peripheral T cells, Lck initiates T-cell receptor signalling by phosphorylating ITAMs on CD3/ζ-chain subunits, thereby recruiting and activating ZAP-70. Subsequent cascades drive cytokine production, proliferation and differentiation. Lck also participates in signalling by CD2, IL-2 receptor and other surface receptors, and phosphorylates additional substrates (RUNX3, PTK2B/PYK2, MAPT, RHOH, TYROBP) linking it to adhesion, migration and apoptosis pathways (Chylek et al., 2014; Samraj, 2005; Posevitz, 2007).

## Inhibitors

Multiple experimental ATP-competitive inhibitors that broadly target Src-family kinases have been evaluated for immunomodulation and anti-cancer therapy, but their selectivity for Lck versus other Src-family members remains limited (Posevitz, 2007; Okada, 2012).

## Other Comments

Dysregulated Lck activity contributes to T-cell leukaemias and thymic tumours, whereas loss or mis-regulation impairs T-cell development and causes immunodeficiency. The evolutionary conservation of Lck across vertebrates and invertebrate chordates highlights its pivotal role in immune signalling (Samraj, 2005; Majeti, 2000; Zhou et al., 2021; Kwon, 2019).

## 9. References

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