1. Phylogeny  
   Tyrosine‐protein kinase Lck (LCK) is a member of the Src family kinases (SFKs), a group of non‐receptor tyrosine kinases that are evolutionarily conserved across metazoans and central to the regulation of immune cell signaling. Lck shares homology with other SFK members such as Fyn, Src, and Lyn, and orthologs of Lck are found in mammals where its function in T‐cell signaling is essential; its conservation reflects its critical role in thymocyte development and T‐cell activation (hans1996srcfamilykinases pages 14-18, posevitz2007functionalelucidationof pages 34-37). As outlined in kinome-wide classifications, Lck is part of an evolutionary core set of cytoplasmic tyrosine kinases that emerged early in eukaryotic evolution and has been maintained as a key regulator of antigen receptor signaling in lymphocytes (hans1996srcfamilykinases pages 25-29, ubau2013functionalcharacterizationof pages 12-15).
2. Reaction Catalyzed  
   Lck catalyzes the phosphorylation reaction in which a phosphate group from adenosine triphosphate (ATP) is transferred to a tyrosine residue on a substrate protein. The chemical reaction can be represented schematically as follows: ATP + [protein]-tyrosine → ADP + [protein]-phosphotyrosine + H⁺ (chylek2014phosphorylationsitedynamics pages 16-16).
3. Cofactor Requirements  
   The enzymatic activity of Lck is dependent on the presence of divalent metal ions, with Mg²⁺ serving as the essential cofactor required for ATP binding and the subsequent transfer of the phosphate group to the substrate (banerjee2013phosphorylationubiquitylationand pages 26-29).
4. Substrate Specificity  
   Lck exhibits a substrate specificity that is defined by its ability to recognize and phosphorylate specific tyrosine residues predominantly present within immunoreceptor tyrosine-based activation motifs (ITAMs) on T-cell receptor (TCR) complex proteins. In the context of TCR signaling, Lck specifically phosphorylates tyrosine residues on CD3 subunits and the TCR-ζ chains, thereby creating docking sites for the tandem SH2 domains of the kinase ZAP70 (chylek2014phosphorylationsitedynamics pages 5-7, posevitz2007functionalelucidationof pages 37-40). In addition, Lck has been shown to phosphorylate a range of substrates including components of the costimulatory pathways such as the cytoplasmic tail of CD2 and even non-TCR substrates like RUNX3 and PTK2B/PYK2, with amino acid preferences that often include basic or hydrophobic residues in a local sequence context that facilitates SH2 and SH3 domain-mediated interactions (banerjee2013phosphorylationubiquitylationand pages 20-26).
5. Structure  
   Lck possesses a modular domain organization characteristic of Src family kinases. It has an N-terminal SH4 (unique) domain, which contains a myristoylation signal critical for its membrane targeting and association with the inner leaflet of the plasma membrane; this is followed by a unique region that mediates selective protein–protein interactions, especially with the cytoplasmic tails of co-receptors such as CD4 and CD8. Adjacent to the unique region are the SH3 and SH2 domains, with the SH3 domain recognizing proline-rich motifs and the SH2 domain binding phosphorylated tyrosine residues, thus contributing to autoinhibitory interactions and substrate selection. Lck’s catalytic (kinase) domain follows, which contains the conserved activation loop (T-loop) and exhibits regulatory phosphorylation sites, including the activating autophosphorylation site Tyr-394 and the inhibitory C-terminal tyrosine (commonly designated as Tyr-505 in analogous SFKs), that control its conformational state and catalytic activity (hans1996srcfamilykinases pages 25-29, chylek2014phosphorylationsitedynamics pages 16-16). This arrangement allows Lck to adopt distinct structural conformations: an open, active form when dephosphorylated at the inhibitory tyrosine and phosphorylated at the activation loop, and a closed, autoinhibited form when the SH2 domain binds to the phosphorylated C-terminal tail (posevitz2007functionalelucidationof pages 43-46).
6. Regulation  
   Lck activity is tightly regulated by a combination of post-translational modifications, protein–protein interactions, and subcellular localization dynamics. Phosphorylation of Tyr-394 within the activation loop enhances Lck’s kinase activity, whereas phosphorylation of the C-terminal inhibitory tyrosine (comparable to Tyr-505 in other SFKs) induces an intramolecular interaction with the SH2 domain that results in a closed, less active conformation. Enzymes such as C-terminal Src kinase (Csk) phosphorylate the inhibitory tyrosine to maintain Lck in an inactive state, while phosphatases like CD45 dephosphorylate this residue to prime Lck for activation. Additional regulatory modulation is achieved via reversible lipid modifications, including N-terminal myristoylation and potential palmitoylation, which facilitate membrane localization, and interactions with adaptor proteins such as PAG and costimulatory molecules like CD2, all of which contribute to compartmentalizing Lck’s activity within specialized microdomains (chylek2014phosphorylationsitedynamics pages 14-14, posevitz2007functionalelucidationof pages 95-97, hans1996srcfamilykinases pages 195-200).
7. Function  
   Lck plays a central role in T-cell biology, being expressed at all stages of thymocyte development and essential for both the selection and maturation of T-cells within the thymus. It is constitutively associated with the cytoplasmic portions of CD4 and CD8 co-receptors, and upon engagement of the T-cell receptor (TCR) with a peptide–MHC complex, Lck phosphorylates ITAMs on the CD3 and TCR-ζ chains, thereby initiating a signaling cascade that leads to the recruitment and activation of the tyrosine kinase ZAP70. This event triggers downstream signaling pathways that ultimately result in lymphokine synthesis, T-cell proliferation, and differentiation. In addition to its established role in TCR signaling, Lck is also involved in signaling initiated by other receptors such as CD2 and the interleukin-2 (IL2) receptor, contributing to multiple aspects of T-cell function including adhesion, migration, and proliferation. Lck phosphorylates substrates including RUNX3, PTK2B/PYK2, the microtubule-associated protein MAPT, RHOH, and TYROBP, thereby integrating signals from diverse receptors to fine-tune immune responses (chylek2014phosphorylationsitedynamics pages 15-16, posevitz2007functionalelucidationof pages 43-46, ubau2013functionalcharacterizationof pages 91-92).
8. Other Comments  
   A range of selective inhibitors targeting Src family kinases, including Lck, have been developed for experimental and therapeutic purposes; abnormal Lck activity has been implicated in immune deficiencies, autoimmune disorders, and oncogenic transformations such as T-cell leukemia. Mutational analyses have underscored the importance of specific phosphorylation sites, with alterations in the regulatory tyrosine residues leading to dysregulated kinase activity. Although detailed inhibitor profiles specific to Lck are not provided in the available context, the development and application of ATP-competitive inhibitors remain a prominent strategy for modulating its activity in pathological conditions (banerjee2013phosphorylationubiquitylationand pages 26-29, posevitz2007functionalelucidationof pages 43-46).
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