## Proposed EC/sub-subclass:

Not yet formally assigned

## Accepted name:

LIM domain kinase 1

## Synonyms:

LIMK1; LIMK-1; LIM-kinase 1

## Phylogeny

LIMK1 is an evolutionarily conserved serine/threonine kinase found in all vertebrate lineages examined and in every mammalian species analysed to date (Krupa & Srinivasan, 2002; Mittelstaedt, 2012, pp. 274–277). It belongs to the LIM-kinase family, which is distinguished by one or two N-terminal LIM domains. LIMK1 shares ~50 % overall amino-acid identity with its paralogue LIMK2, particularly within the catalytic domain (Mittelstaedt, 2012, pp. 274–277). Phylogenetic analyses indicate that LIM kinases arose early in vertebrate evolution from an ancestral kinase that acquired additional protein–protein interaction modules (Krupa & Srinivasan, 2002; Mittelstaedt, 2012, pp. 38–46). Orthologues are documented in mouse, rat and other mammals, reflecting the strong conservation of gene structure and its central role in Rho-GTPase signalling pathways (Mittelstaedt, 2012, pp. 274–277).

## Reaction catalysed

ATP + [protein]-L-Ser/Thr → ADP + [protein]-L-Ser/Thr-phosphate + H⁺ (Mittelstaedt, 2012, pp. 38–46)

## Cofactor requirements

Mg²⁺ is required for ATP coordination and phosphoryl transfer (Mittelstaedt, 2012, pp. 32–38).

## Substrate Specificity

LIMK1 displays a narrow substrate range, preferentially phosphorylating actin-regulatory proteins. Established substrates include cofilin-1 and cofilin-2 (Ser3), destrin (DSTN) and tubulin polymerisation-promoting protein (TPPP) on serine residues (Mittelstaedt, 2012, pp. 56–60, 274–277). Large-scale profiling has not defined a consensus sequence but confirms selectivity for these actin-associated targets (Johnson et al., 2023).

## Structure

LIMK1 is a multidomain protein comprising:  
• two N-terminal LIM zinc-binding motifs that mediate protein interactions and localisation;  
• a central PDZ domain that serves additional scaffolding functions;  
• a C-terminal kinase domain spanning roughly residues 330–647 (Mittelstaedt, 2012, pp. 38–46, 121–130).

Crystal studies of inhibitor-bound kinase domain show a typical bilobal fold: an N-terminal β-sheet lobe and a mainly α-helical C-terminal lobe (Mittelstaedt, 2012, pp. 153–164). Unique elements include (i) a loop insertion replacing the conventional αG helix, thought to influence cofilin recognition, and (ii) a C-terminal αJ helix absent from related kinases. The activation segment contains Thr508; its phosphorylation is critical for activity, although part of this loop is flexible and unresolved in structures (Mittelstaedt, 2012, pp. 164–171).

## Regulation

• Activation-loop phosphorylation on Thr508 by upstream ROCK1, PAK1 and PAK4 activates LIMK1 (Mittelstaedt, 2012, pp. 53–56).  
• Hsp90 promotes LIMK1 homodimerisation, stabilising the active kinase and extending its cellular half-life from ~4 h to ~20 h (Mittelstaedt, 2012, pp. 53–56).  
• The phosphatase Slingshot (SSH) dephosphorylates LIMK1 and its substrate cofilin, providing negative feedback (Mittelstaedt, 2012, pp. 53–56).  
• Alternative splicing yields a catalytically defective “LIMK1-short” isoform that acts in a dominant-negative manner (Mittelstaedt, 2012, pp. 38–46).

## Function

LIMK1 phosphorylates cofilin, destrin and related proteins to inhibit their actin-depolymerising activity, thereby stabilising F-actin and regulating cell shape, motility, cytokinesis and differentiation (Mittelstaedt, 2012, pp. 56–60, 274–277). Dysregulated LIMK1 activity enhances cancer cell invasion and metastasis (Fulcher & Sapkota, 2020, pp. 11–13). In neurons, it promotes axonal outgrowth and participates in brain development; phosphorylation of TPPP implicates LIMK1 in microtubule dynamics (Mittelstaedt, 2012, pp. 56–60). LIMK1 operates downstream of Rho-family GTPases, integrating extracellular cues into cytoskeletal rearrangements. Expression is broad, with notable levels in brain, kidney, lung and testes (Mittelstaedt, 2012, pp. 38–46).

## Inhibitors

ATP-competitive LIMK1 inhibitors, including thiazole derivatives, have been reported to promote actin depolymerisation and are under investigation for cancer metastasis and glaucoma (Leoni et al., 2014, pp. 9–10).

## Other Comments

Genetic and pharmacological data link LIMK1 to neurodevelopmental abnormalities and cancer phenotypes (Open Targets Platform; Fulcher & Sapkota, 2020, pp. 11–13). Ongoing structural studies of inhibitor complexes aim to support structure-based drug design (Mittelstaedt, 2012, pp. 153–164).

## References

Fulcher, L. J., & Sapkota, G. P. (2020). Functions and regulation of the serine/threonine protein kinase CK1 family: Moving beyond promiscuity. Biochemical Journal, 477, 4603–4621. https://doi.org/10.1042/BCJ20200506

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Krupa, A., & Srinivasan, N. (2002). The repertoire of protein kinases encoded in the draft version of the human genome: Atypical variations and uncommon domain combinations. Genome Biology, 3, research0066.1–0066.14. https://doi.org/10.1186/gb-2002-3-12-research0066

Leoni, A., Locatelli, A., Morigi, R., & Rambaldi, M. (2014). Novel thiazole derivatives: A patent review (2008–2012; part 1). Expert Opinion on Therapeutic Patents, 24, 201–216. https://doi.org/10.1517/13543776.2014.858121

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