## Phylogeny

LIM domain kinase 2 (LIMK2) is retained throughout vertebrate evolution—including mammals, birds, amphibians—and is also detected in some invertebrates that require advanced cytoskeletal control (Ribba et al., 2022; Scott, 2010). The kinase shares ~50 % overall sequence identity with its paralogue LIMK1 and forms the closest branch to TESK kinases, which likewise regulate cofilin (Goyal, 2005; Scott, 2010). Phylogenetic analyses indicate that LIMK2 arose from an early vertebrate gene-duplication event and belongs to the conserved “core” kinome set governing actin dynamics (Ribba et al., 2022).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr ⇌ ADP + protein-L-Ser/Thr-P + H⁺  
A physiological example is Ser3 phosphorylation of ADF/cofilin, which suppresses its actin-severing activity (Brion et al., 2021).

## Cofactor Requirements

Catalysis requires Mg²⁺ for ATP binding and phosphotransfer (Brion et al., 2021; Goyal, 2005).

## Substrate Specificity

The kinase shows pronounced selectivity for ADF/cofilin family members, phosphorylating Ser3 and thereby blocking actin-filament severing. Although a strict consensus motif is undefined, efficient recognition depends on presentation of the cofilin N-terminus in a phosphorylation-competent conformation (Chatterjee et al., 2022; Ribba et al., 2022).

## Structure

LIMK2 comprises two N-terminal LIM zinc-finger domains that mediate protein interactions, a central PDZ domain influencing localisation, a Ser/Pro-rich linker region, and a C-terminal protein-kinase domain with the canonical bilobal fold (Goyal, 2005; Villalonga et al., 2023). The kinase domain possesses an unusual catalytic-loop sequence (DLNSHN) in sub-domain VIB and an activation loop that toggles between DFG-out (inactive) and DFG-in (active) states (Chatterjee et al., 2022; Manetti, 2012). Homodimerisation through LIM domains facilitates auto-phosphorylation and stabilisation of the active conformation (Chatterjee et al., 2022). Autoinhibitory contacts between the LIM/PDZ modules and the kinase domain have also been described (Goyal, 2005; Casanova-Sepúlveda et al., 2023).

## Regulation

• Activation-loop phosphorylation on Thr505 by ROCK, PAKs and MRCKα markedly increases catalytic activity (Brion et al., 2021; Chatterjee et al., 2022).  
• Aurora-A can further stimulate LIMK2 via multi-site phosphorylation (Rak et al., 2014).  
• Intramolecular LIM- and PDZ-mediated autoinhibition is relieved upon appropriate upstream signals (Goyal, 2005; Casanova-Sepúlveda et al., 2023).  
• Dimerisation and Hsp90 chaperone binding stabilise the active enzyme, whereas Hsp90 inhibition lowers LIMK2 levels (Chatterjee et al., 2022; Manetti, 2012).  
• Phosphatases PP1 and PP2A counteract activation by de-phosphorylating LIMK2 and/or its substrates (Brion et al., 2021).

## Function

Principal role is regulation of actin dynamics: Ser3 phosphorylation of cofilin stabilises filamentous actin, influencing cell morphology, adhesion and migration (Brion et al., 2021; Chatterjee et al., 2022). LIMK2 also modulates microtubule organisation through TPPP phosphorylation to steer spindle orientation during mitosis (Podkowa, 2010). Operating downstream of Rho-family GTPases, the kinase integrates extracellular cues that drive migration, proliferation and differentiation, and its hyper-activation is connected to tumour invasion and metastasis (Rak et al., 2014; Ribba et al., 2022; Shah & Cook, 2023). LIMK2 further suppresses ciliogenesis by phosphorylating CFL1 and promoting nuclear YAP1 accumulation. Expression is ubiquitous and broader than LIMK1, encompassing neuronal, muscle and epithelial tissues (Villalonga et al., 2023; Shah & Cook, 2023).

## Inhibitors

Selective small-molecule inhibitors have been described. T56-LIMKi and several type I–III chemical probes potently and preferentially inhibit LIMK2, decrease cofilin phosphorylation and impair tumour cell migration or proliferation (Rak et al., 2014; Hanke et al., 2022; Berabez et al., 2022; Manetti, 2012).

## Other Comments

Aberrant LIMK2 activity is linked to diverse cancers, chemoresistance, ciliopathies and developmental defects, yet disease-causing point mutations remain uncommon (Brion et al., 2021; Shah & Cook, 2023).

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