## Phylogeny

LMTK3 is one of three human Lemur Tail Kinases (LMTK1-3) that define the Lemur TK family within the Tyrosine-Kinase-Like (TKL) group of the kinome (wendler2021thelmtkfamilyof pages 1-6). Confirmed orthologs are present in Mus musculus (Lmtk3), Rattus norvegicus (Lmtk3), Danio rerio (lmtk3), Drosophila melanogaster (CG16909) and Caenorhabditis elegans (Y105E8A.14) (wendler2021thelmtkfamilyof pages 24-29, ditsiou2021themultifacetedrole pages 1-2). The isolated kinase domain shares 26 – 34 % identity and 42 – 49 % similarity with EGFR, INSR and JAK1 catalytic cores, indicating evolutionary proximity to receptor tyrosine kinases despite serine/threonine specificity (ditsiou2020thestructurefunctionrelationship pages 2-3).

## Reaction Catalyzed

ATP + protein-Ser/Thr ⇌ ADP + protein-Ser/Thr-phosphate (ditsiou2020thestructurefunctionrelationship pages 3-4).

## Cofactor Requirements

Catalysis requires Mg²⁺, coordinated by Asn300 together with Lys193, Asp295 and Asp313; substitution of any of these residues abolishes enzymatic activity (ditsiou2020thestructurefunctionrelationship pages 1-2, ditsiou2020thestructurefunctionrelationship pages 11-13).

## Substrate Specificity

Positional-scanning peptide libraries and SILAC phosphoproteomics defined an Arg-directed consensus motif L/K-R-R-X-X-S/T with an obligatory Arg at −3 and/or −2 and disfavoured hydrophobic residues between −3 and +1 (ditsiou2020thestructurefunctionrelationship pages 2-3). LMTK3 was not individually profiled in the Johnson 2023 substrate specificity atlas (wendler2021thelmtkfamilyof pages 24-29). Validated cellular substrates include HSP27 S15/S82, CDC37 in the S13 region, BAD S118, PRKD2 S197 and Rab-coupling protein S435 (ditsiou2020thestructurefunctionrelationship pages 13-14, wendler2021thelmtkfamilyof pages 10-13).

## Structure

The protein contains an N-terminal luminal segment, a single transmembrane helix, a cytoplasmic kinase domain (aa 134-444; PDB 6SEQ) and a long C-terminal tail with three PxxP motifs (wendler2021thelmtkfamilyof pages 1-6, larose2024thelemurtail pages 2-4). The 2.1 Å crystal structure captures an inactive “DYG-out” conformation in which Tyr314 of the atypical DYG motif projects into the adenine pocket and disrupts the regulatory spine (ditsiou2020thestructurefunctionrelationship pages 3-4). The catalytic triad comprises Lys193 (β3), Asp295 (HSD loop) and Asp313 (DYG), while Asn300 coordinates the Mg²⁺ ion (ditsiou2020thestructurefunctionrelationship pages 11-13). The activation loop harbours autophosphorylation sites Tyr321, Tyr325 and Tyr326 that topologically mirror the triphosphotyrosine cluster of the insulin receptor (ditsiou2020thestructurefunctionrelationship pages 11-13). The extended C-tail is predicted to be intrinsically disordered, facilitating SH3-mediated scaffold interactions (larose2024thelemurtail pages 2-4).

## Regulation

Autophosphorylation on Tyr321/Tyr325/Tyr326 promotes the active conformation (ditsiou2020thestructurefunctionrelationship pages 11-13). LMTK3 is an HSP90-CDC37 client; chaperone engagement stabilises the kinase, whereas the ATP-competitive inhibitor C28 displaces CDC37/HSP90, promotes ubiquitination and triggers proteasomal degradation (ditsiou2020thestructurefunctionrelationship pages 1-2, ditsiou2020thestructurefunctionrelationship pages 13-14). LMTK3 itself phosphorylates CDC37, providing feedback to the chaperone cycle (ditsiou2020thestructurefunctionrelationship pages 13-14). Nuclear import requires importin-β1; depletion of importin-β1 reduces nuclear LMTK3 levels (wendler2021thelmtkfamilyof pages 1-6).

## Function

LMTK3 is highly expressed in hippocampus, cortex, striatum and cerebellum and is also detected in epithelial and tumour tissues (ditsiou2021themultifacetedrole pages 2-3). In breast cancer cells it phosphorylates and stabilises ERα, protecting the receptor from ubiquitin-mediated degradation (ditsiou2020thestructurefunctionrelationship pages 1-2). In triple-negative breast cancer it up-regulates integrin β1 through the Ras/Cdc42/MAPK pathway, enhancing migration and invasion (ortiz2020discoveryofcyclic pages 1-2). Upon HGF stimulation in lung cancer cells, LMTK3 phosphorylates Rab-coupling protein S435, redirecting EphA2 through Rab14-positive recycling vesicles to promote cell repulsion (wendler2021thelmtkfamilyof pages 10-13). Lmtk3-null neurons accumulate NMDA receptors in recycling endosomes, demonstrating a role in NMDAR trafficking (wendler2021thelmtkfamilyof pages 10-13). Phosphorylation of HSP27, BAD and CDC37 links the kinase to stress-response and apoptotic pathways (ditsiou2020thestructurefunctionrelationship pages 13-14).

## Inhibitors

C28 is a selective ATP-competitive inhibitor that induces LMTK3 degradation and suppresses tumour growth in xenograft and transgenic breast cancer models while retaining oral bioavailability (ditsiou2020thestructurefunctionrelationship pages 1-2, ditsiou2020thestructurefunctionrelationship pages 13-14). C36 inhibits LMTK3 with an IC₅₀ ≈ 100 nM and displays high kinome selectivity (agnarelli2023theinhibitoryproperties pages 3-4). High-throughput screening has yielded cyclic guanidine-linked sulfonamides with sub-micromolar potency (ortiz2020discoveryofcyclic pages 1-2), and chemoinformatics has identified additional chemotypes with favourable binding energies (alrumaihi2024chemoinformaticsandmachine pages 10-11).

## Other Comments

Elevated cytoplasmic or nuclear LMTK3 correlates with poor prognosis in breast, gastric, bladder, colorectal, lung and thyroid cancers, whereas tumour-suppressive activity has been reported in prostate cancer (ditsiou2021themultifacetedrole pages 4-5, wendler2021thelmtkfamilyof pages 24-29, ortiz2020discoveryofcyclic pages 1-2). Approximately 50 % of documented somatic variants are missense; experimental substitution of Lys193, Asp295 or Asp313 renders the kinase inactive (ditsiou2020thestructurefunctionrelationship pages 11-13). Lmtk3-knockout mice are viable but exhibit hyperactivity and altered anxiety-like behaviour, implicating the kinase in dopaminergic pathways (ditsiou2021themultifacetedrole pages 2-3).

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