1. Phylogeny  
   Serine/threonine‐protein kinase LMTK1 is a member of the lemur tail kinase (LMTK) family, a group of membrane‐associated serine/threonine kinases that also includes LMTK2 and LMTK3. LMTK1 is evolutionarily conserved among mammalian species and is present as distinct splice variants (LMTK1‐a and LMTK1‐b), which arise through alternative splicing mechanisms. Phylogenetic analyses place LMTK1 within an evolutionarily ancient branch of the kinome that diverged from receptor tyrosine kinases due to sequence similarities in the catalytic domain, even though its functional activity is strictly serine/threonine phosphorylation. The revised nomenclature established for the LMTK family, which standardizes previously confusing synonyms (e.g., AATK, Lmr1, AATYK, KIAA0641, LMR1, p35‐binding protein, and brain apoptosis‐associated tyrosine kinase), supports its clear classification within this family (morotz2024arevisednomenclature pages 1-3, ferrari2021lemurtyrosinekinases pages 2-3). Additional studies highlight that LMTK1 shares common ancestry with kinases regulating intracellular trafficking and neuronal signaling, underscoring its conservation across species (wendler2021thelmtkfamilyof pages 6-10).
2. Reaction Catalyzed  
   LMTK1 catalyzes the transfer of the γ-phosphate from ATP to the hydroxyl group of serine or threonine residues on target protein substrates. In chemical terms, the reaction can be summarized as:  
   ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺ (larose2024thelemurtail pages 2-4).
3. Cofactor Requirements  
   The kinase activity of LMTK1 requires the presence of divalent metal ions as cofactors. Consistent with most serine/threonine kinases, Mg²⁺ is the primary cofactor that facilitates ATP binding and phosphoryl transfer (larose2024thelemurtail pages 2-4).
4. Substrate Specificity  
   Investigations into the substrate specificity of LMTK1 indicate that it selectively phosphorylates serine/threonine residues on protein substrates. Although detailed substrate consensus motifs for LMTK1 remain to be conclusively defined, studies conducted with other family members, particularly LMTK3, suggest a preference for substrates harboring arginine residues at the −3 and/or −2 positions relative to the phosphorylated residue. This arginine‐directed determinant for serine/threonine phosphorylation is proposed to be a shared feature among LMTKs; however, an experimental validation of a specific consensus motif for LMTK1 has not been fully established (larose2024thelemurtail pages 2-4, ferrari2021lemurtyrosinekinases pages 3-5).
5. Structure  
   LMTK1 exhibits a multidomain architecture that contributes to its localization and regulatory functions. The protein exists in at least two isoforms: LMTK1-a, which lacks predicted transmembrane domains but is targeted to membranes via palmitoylation of specific N-terminal cysteine residues, and LMTK1-b, which contains an amino-terminal signal peptide followed by a single transmembrane domain that anchors the protein to intracellular membranes (larose2024thelemurtail pages 2-4, hisanaga2020lmtk1anovel pages 2-3).  
   At its core, LMTK1 contains a highly conserved kinase domain responsible for its catalytic activity. This domain, positioned near the amino terminus, contains essential residues such as a conserved lysine that is critical for ATP binding and an aspartate residue within the catalytic loop that functions in phospho-transfer (larose2024thelemurtail pages 2-4, tomomura2001characterizationofthe pages 4-6).  
   Flanking the kinase domain, LMTK1 has a long carboxy-terminal tail rich in proline-containing motifs (PxxP), which are known to mediate interactions with Src homology 3 (SH3) domain–containing proteins. This proline-rich region suggests that LMTK1 can function as a scaffolding molecule, organizing multiprotein complexes that regulate intracellular trafficking and signaling (morotz2024arevisednomenclature pages 1-3, larose2024thelemurtail pages 2-4, hisanaga2020lmtk1anovel pages 3-4).  
   Although high-resolution crystal structures for LMTK1 are not currently available, predictive models based on related kinases imply that the kinase domain adopts a two-lobed fold typical of serine/threonine kinases, including an activation loop and regulatory regions that may undergo conformational changes upon phosphorylation. Unique features inferred from domain organization include membrane-association determinants provided either by a transmembrane segment or by lipid modifications, as well as extensive intrinsically disordered regions in the C-terminal tail that may facilitate dynamic protein-protein interactions (larose2024thelemurtail pages 2-4, morotz2024arevisednomenclature pages 3-4, hisanaga2020lmtk1anovel pages 3-4).
6. Regulation  
   Regulatory mechanisms modulating LMTK1 activity involve multiple layers of post-translational modification and protein-protein interactions. Phosphorylation events are central to its regulation. LMTK1 is phosphorylated by the cyclin-dependent kinase 5 (Cdk5) when complexed with its regulatory subunit p35; this modification, occurring notably at serine 34, is critical for modulating LMTK1 activity and its function in controlling endosomal trafficking pathways (larose2024thelemurtail pages 8-9, larose2024thelemurtail pages 15-16).  
   In addition to Cdk5-mediated phosphorylation, Src family kinases phosphorylate LMTK1 at tyrosine residues 25 and 46. The interplay between these phosphorylation events appears to regulate LMTK1’s function in endocytic processes, including the modulation of vesicle trafficking between early and recycling endosomes (larose2024thelemurtail pages 15-16, gagnon2007apoptosisassociatedtyrosinekinase pages 6-7).  
   Moreover, LMTK1 undergoes autophosphorylation, which is a common feature among kinases and may contribute to its constitutive activity observed in vitro (larose2024thelemurtail pages 2-4, tomomura2001characterizationofthe pages 4-6). The presence of multiple regulatory phosphorylation sites and proline-rich motifs further suggests that LMTK1 activity is fine-tuned by conformational changes and the assembly of multiprotein complexes that influence its catalytic properties and subcellular localization (hisanaga2020lmtk1anovel pages 3-4, wendler2021thelmtkfamilyof pages 13-17).
7. Function  
   LMTK1 plays significant roles in neuronal differentiation and intracellular trafficking. Its expression is highly enriched in the brain, where it is detected in mature neurons located in regions such as the cerebral cortex, cerebellum, and hippocampus. Expression studies indicate that LMTK1 levels correlate with developmental stages of neuronal differentiation and maturation (larose2024thelemurtail pages 1-2, ferrari2021lemurtyrosinekinases pages 2-3).  
   At the cellular level, LMTK1 is involved in regulating endosomal recycling pathways. By modulating Rab11-dependent trafficking processes, LMTK1 influences axonal outgrowth, dendritic spine formation, and neurite extension, thereby contributing to the establishment and maintenance of neuronal connectivity (larose2024thelemurtail pages 15-16, hisanaga2020lmtk1anovel pages 3-4).  
   Functionally, LMTK1 interacts with key regulatory proteins such as the Cdk5/p35 complex, which is central to neuronal signalling and synaptic plasticity. Additionally, it serves as a scaffold that may recruit protein phosphatase 1 (PP1) and other interacting partners to modulate the phosphorylation state of proteins involved in membrane trafficking and ion transport, including regulatory pathways affecting the Na-K-2Cl cotransporter (gagnon2007apoptosisassociatedtyrosinekinase pages 5-6, tomomura2001characterizationofthe pages 8-9).  
   In the context of apoptosis and cellular stress, studies in neuronal cell models demonstrate that LMTK1 expression is modulated during apoptotic stimuli, implicating this kinase in the regulation of programmed cell death and neuronal survival (tomomura2001characterizationofthe pages 4-6, wendler2021thelmtkfamilyof pages 1-6).  
   Thus, the functional profile of LMTK1 encompasses roles in intracellular transport, regulation of receptor recycling, neuronal differentiation, and possibly apoptosis, positioning it as a critical modulator of neuronal homeostasis (larose2024thelemurtail pages 15-16, ferrari2021lemurtyrosinekinases pages 3-5).
8. Other Comments  
   No specific small-molecule inhibitors have been well characterized for LMTK1 to date, although the kinase’s involvement in neuronal differentiation and intracellular trafficking makes it a potential therapeutic target in neurodegenerative disorders and cancers. The protein requires Mg²⁺ as a cofactor, and its membrane association is dependent on either a transmembrane domain (in the case of the LMTK1-b isoform) or palmitoylation of conserved cysteine residues (in the LMTK1-a isoform) (larose2024thelemurtail pages 2-4, hisanaga2020lmtk1anovel pages 2-3).  
   Disease associations reported in the literature link alterations in LMTK1 expression and copy number variations to neurodevelopmental delays, intellectual disabilities, and possibly to conditions such as Alzheimer’s disease and schizophrenia. Moreover, studies report that knockout or dysregulation of LMTK1 in animal models leads to behavioral abnormalities and disrupted neuronal transport (larose2024thelemurtail pages 10-11, larose2024thelemurtail pages 15-16).  
   The nomenclature for LMTK1 has been standardized in recent years to alleviate confusion arising from its multiple synonyms; this consistency is essential for advancing research into the precise biochemical and structural characteristics of this kinase (morotz2024arevisednomenclature pages 1-3, ferrari2021lemurtyrosinekinases pages 2-3).
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