1. Phylogeny  
   STK38L (also known as NDR2 or Nuclear Dbf2-related kinase 2) is a member of the NDR kinase subfamily within the AGC group of serine/threonine kinases that is highly conserved across eukaryotic species, with orthologs identified in yeast (e.g., Dbf2, Dbf20, Cbk1p), invertebrates (e.g., Drosophila Tricornered) and mammals (including the closely related NDR1) (bichsel2005mechanismofactivation pages 101-105, fukasawa2023theroleof pages 1-2). STK38L is embedded within an evolutionary core set of kinases that have been maintained since the common ancestor of eukaryotes, which underscores its conserved regulatory roles in cell division and morphological regulation (hergovich2008mammalianndrprotein pages 1-2, hergovich2016therolesof pages 1-3). The phylogenetic relationships among NDR kinases reveal that STK38L shares significant sequence and functional similarity with its paralog NDR1, and both exhibit conserved regulatory mechanisms mediated by upstream kinases and adaptor proteins (martin2019thestk38kinase pages 35-39).
2. Reaction Catalyzed  
   STK38L catalyzes the transfer of a phosphate group from ATP to L-serine or L-threonine residues on specific protein substrates, thereby converting ATP into ADP and phosphorylated protein along with the release of a proton (bichsel2005mechanismofactivation pages 101-105, fukasawa2023theroleof pages 1-2).
3. Cofactor Requirements  
   The catalytic activity of STK38L is dependent on the presence of divalent metal ions, with Mg²⁺ serving as the essential cofactor required for effective ATP binding and phosphate transfer during the phosphorylation reaction (bichsel2005mechanismofactivation pages 101-105).
4. Substrate Specificity  
   STK38L phosphorylates serine/threonine residues within target substrates that frequently display consensus motifs enriched in basic amino acids, with evidence suggesting a preference for sequences resembling the HXRXXS/T motif characteristic of other NDR kinases (hergovich2016therolesof pages 3-5, fukasawa2023theroleof pages 2-4). Identified substrates for the kinase include regulatory proteins involved in cell cycle control—such as CDC25A and p21—and components associated with the Hippo signaling pathway, including effectors like YAP, although the complete substrate repertoire remains to be fully delineated (fukasawa2023theroleof pages 8-10, martin2021thestk38–xpo1axis pages 2-4).
5. Structure  
   STK38L is organized into a modular architecture that includes an N-terminal regulatory domain (NTR) responsible for binding MOB adaptor proteins and calcium-binding modulators, followed by a central catalytic kinase domain and a C-terminal hydrophobic motif (HM) essential for full kinase activation (fukasawa2023theroleof pages 1-2, hergovich2008mammalianndrprotein pages 1-2). The central kinase domain comprises the conventional 12 subdomains found in serine/threonine kinases and features an atypically long activation segment; this segment is characterized by an autoinhibitory basic insertion that can hinder substrate binding and is relieved upon phosphorylation (xiong2018structuralbasisfor pages 1-3, hergovich2016therolesof pages 3-5). Key structural elements within the catalytic core include a conserved DFG motif, an essential C-helix involved in ATP coordination, and a regulatory hydrophobic spine that contributes to catalytic competency (bichsel2005mechanismofactivation pages 101-105, xiong2018structuralbasisfor pages 4-5). Structural models predict that STK38L adopts a bilobal kinase fold typical of AGC kinases, with the smaller N-lobe dedicated to ATP binding and the larger C-lobe specialized for substrate recognition (martin2019thestk38kinase pages 39-42, xiong2018structuralbasisfor pages 12-13).
6. Regulation  
   STK38L is regulated by multisite phosphorylation events that play critical roles in switching the kinase from an inactive to an active conformation. Autophosphorylation at the activation loop is required for its initial activation, and phosphorylation of the hydrophobic motif (for example, at a residue equivalent to Thr442) by upstream MST-type kinases (such as MST3) further enhances its catalytic activity (bichsel2005mechanismofactivation pages 101-105, stegert2005regulationofndr pages 1-2). The binding of MOB adaptor proteins, particularly MOB1, to the NTR relieves the autoinhibitory constraints imposed by the basic insertion region, thereby promoting autophosphorylation and full activation of the kinase (hergovich2016therolesof pages 11-12, martin2021thestk38–xpo1axis pages 1-2). In addition, STK38L activity is modulated by calcium-binding proteins such as S100B and by inhibitory phosphorylation events—such as those mediated by GSK-3 at residues located in the NTR—that can attenuate kinase function; dephosphorylation by protein phosphatase PP2A also plays a role in downregulating activity (fukasawa2023theroleof pages 2-4, stegert2005regulationofndr pages 2-3).
7. Function  
   STK38L is involved in the regulation of structural processes in differentiating and mature neuronal cells, contributing to the organization of the cytoskeleton and neuronal polarity (fukasawa2023theroleof pages 1-2, hergovich2016therolesof pages 1-3). In neurons, the kinase is implicated in the control of dendritic branching and neurite outgrowth, thereby influencing cell shape and connectivity (fukasawa2023theroleof pages 1-2, hergovich2016therolesof pages 5-7). Beyond its roles in neuronal cells, STK38L participates in broader cellular processes such as cell cycle progression, centrosome duplication, and the DNA damage response through its phosphorylation of substrates including CDC25A and p21, which are critical regulators of cell cycle checkpoints (fukasawa2023theroleof pages 8-10, martin2021thestk38–xpo1axis pages 11-12). Additionally, the kinase functions within the Hippo signaling pathway, where it phosphorylates downstream effectors such as YAP to modulate cellular proliferation and apoptosis (hergovich2016therolesof pages 3-5, martin2019thestk38kinase pages 42-45).
8. Other Comments  
   Although no inhibitors have been designed specifically for STK38L, modulation of its activity has been achieved indirectly through agents such as HSP90 inhibitors that affect its stability and downstream signaling cascades (fukasawa2023theroleof pages 8-10, martin2021thestk38–xpo1axis pages 2-4). Alterations in STK38L expression or activity have been linked to various disease states; for example, dysregulation of this kinase has been associated with oncogenic processes in B-cell and T-cell lymphomas, as well as in lung and pancreatic cancers, while its role in neuronal differentiation suggests potential implications in neurodegenerative conditions (flax2024illuminationofunderstudied pages 6-7, fukasawa2023theroleof pages 11-12). Its involvement in regulating endomembrane trafficking and autophagy further positions STK38L as a candidate target for therapeutic strategies aimed at enhancing radiosensitivity in cancer treatment (fukasawa2023theroleof pages 8-10, martin2021thestk38–xpo1axis pages 4-6).
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