## Phylogeny

• Orthologs are documented in Mus musculus, Rattus norvegicus, Danio rerio, Drosophila melanogaster (gene Drak) and Caenorhabditis elegans, indicating conservation from invertebrates to vertebrates (capra2006frequentalterationsin pages 2-3, chen2019drakstk17adrivesneoplastic pages 1-6).  
• STK17A clusters with STK17B in the DRAK sub-family, which belongs to the Death-Associated Protein Kinase (DAPK) family inside the Ca²⁺/Calmodulin-dependent kinase (CAMK) group of the human kinome as defined by Manning et al. 2002 (serafim2021chemicalprobesfor pages 10-14, picado2020achemicalprobe pages 18-19).  
• The catalytic domains of STK17A and STK17B share 67.1 % identity, whereas STK17A is ≈48 % identical to prototypic DAPK1, reflecting divergence within the family (farag2019death‐associatedproteinkinase pages 2-4, kogel2001thedapkinase pages 2-4).  
• Phylogenetic analyses of the DMT branch place DRAK1 apart from MLCK and TRIO kinases, underscoring a distinct evolutionary path within CAMK (temmerman2013structuralandfunctional pages 5-6).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr → ADP + protein-L-Ser/Thr-phosphate (sanjo1998draksnovelserinethreonine pages 1-2).

## Cofactor Requirements

Catalytic activity is Mg²⁺-dependent; biochemical assays employ 10 mM magnesium acetate for phosphate transfer (picado2020achemicalprobe pages 17-18).

## Substrate Specificity

• The Johnson 2023 kinome‐wide specificity atlas does not list STK17A; a consensus phosphorylation motif remains undefined (unknownauthors2019substrateidentificationof pages 37-42).  
• Verified substrates include:  
– Non-muscle myosin regulatory light chain (MRLC) and its Drosophila ortholog Spaghetti Squash (Sqh) (chen2019drakstk17adrivesneoplastic pages 6-9).  
– Myosin light chain in human colorectal cancer cells (short2019serinethreoninekinase pages 8-9).  
– β-Catenin, linking the kinase to cancer stemness pathways (chaudhry2024potentselectiveand pages 5-5).  
• STK17A undergoes Ser/Thr auto-phosphorylation, typical of DAPK family members (sanjo1998draksnovelserinethreonine pages 4-5).

## Structure

• Full-length protein: 414 aa, ≈46 kDa, composed of an N-terminal catalytic domain (≈261 aa) and a C-terminal tail lacking recognizable motifs (sanjo1998draksnovelserinethreonine pages 2-3, farag2019death‐associatedproteinkinase pages 2-4).  
• Crystal structure of the kinase domain bound to inhibitor CKJB68 reveals:  
– Canonical bilobed fold; VAIK motif Lys90 forms a salt bridge with Glu108 in helix αC.  
– Hinge hydrogen bonds to Ala141 and Glu139.  
– Hydrophobic spine residues Leu67, Val75, Leu138, Tyr140, Leu193 and Val206 line the ATP pocket (liu2022mechanisticinsightsinto pages 2-4).  
• Activation loop spans Asn216–Ser241 and, together with the C-lobe segment Ile260–Leu290, shows pronounced flexibility (RMSD ≈ 5 Å over 100 ns MD) (liu2022mechanisticinsightsinto pages 4-7).  
• Homology modelling using the STK17B/11s template (PDB 6Y6H) highlights an Arg16 substitution at the ATP-site entrance and lack of inhibitor contact by Arg69, differentiating STK17A from its paralogue (picado2020achemicalprobe pages 8-10).  
• Conserved catalytic motifs: VAIK (β3, Lys90), HRD (His115-Arg116-Asp117) and DFG (Asp200-Phe201-Gly202) are intact (liu2022mechanisticinsightsinto pages 2-4).  
• No full-length crystal structure has been reported; only kinase-domain structures or models are available (farag2019death‐associatedproteinkinase pages 2-4).

## Regulation

• Autophosphorylation and an intact C-terminal region are required for apoptosis induction (sanjo1998draksnovelserinethreonine pages 4-5).  
• Transcription is directly up-regulated by p53 following DNA damage, coupling STK17A to stress-response pathways (chaudhry2024potentselectiveand pages 5-5).  
• The protein localises predominantly to the nucleus, in contrast to cytoskeletal DAPK1, indicating compartment-specific regulation (kogel2001thedapkinase pages 2-4).  
• A Ca²⁺/Calmodulin-regulated autoregulatory domain is present, consistent with CAMK-group kinases (temmerman2013structuralandfunctional pages 5-6).  
• P-loop conformational switching governed by Arg16 modulates nucleotide and inhibitor binding (picado2020achemicalprobe pages 8-10).  
• Activation-loop mobility provides an intrinsic allosteric element influencing catalytic competence (liu2022mechanisticinsightsinto pages 4-7).

## Function

• Acts as a positive regulator of apoptosis (sanjo1998draksnovelserinethreonine pages 3-4).  
• Regulates cellular reactive oxygen species and enhances cisplatin sensitivity in testicular carcinoma models (chaudhry2024potentselectiveand pages 5-5).  
• Drives neoplastic glial proliferation downstream of EGFR and PI3K by phosphorylating MRLC, thereby controlling cytokinesis and actin dynamics (chen2019drakstk17adrivesneoplastic pages 1-6).  
• Maintains the epithelial state in colorectal cancer cells; knock-down induces EMT-like morphology, reduces E-cadherin/α-catenin and increases invasion (short2019serinethreoninekinase pages 8-9, short2019serinethreoninekinase pages 9-10).  
• Phosphorylation of β-catenin links STK17A to cancer stemness and tumour proliferation (chaudhry2024potentselectiveand pages 5-5).  
• Expression pattern: ubiquitous with highest mRNA levels in placenta (sanjo1998draksnovelserinethreonine pages 2-3); down-regulated in colorectal cancer and non-Hodgkin lymphoma (capra2006frequentalterationsin pages 3-5, short2019serinethreoninekinase pages 5-5); copy-number gain and overexpression in low-grade glioma and glioblastoma (chen2019drakstk17adrivesneoplastic pages 22-28).  
• Upstream regulators: p53, EGFR, PI3K (chaudhry2024potentselectiveand pages 5-5, chen2019drakstk17adrivesneoplastic pages 1-6).  
• Downstream substrates/interactors: MRLC, β-catenin, E-cadherin, α-catenin (chen2019drakstk17adrivesneoplastic pages 6-9, chaudhry2024potentselectiveand pages 5-5, short2019serinethreoninekinase pages 8-9).

## Inhibitors

• Quinazoline-based dual STK17A/17B inhibitors exhibit nanomolar biochemical potency and oral bioavailability (chaudhry2024potentselectiveand pages 5-5).  
• PKIS43 is an ATP-competitive inhibitor that binds the STK17A hinge via Ala141 and Glu139 (liu2022mechanisticinsightsinto pages 2-4).  
• CKJB68 co-crystallises with the kinase domain and defines key pocket interactions (liu2022mechanisticinsightsinto pages 2-4).  
• Chemical probe 11s, highly selective for STK17B, provides a structural template exploited for STK17A modelling (picado2020achemicalprobe pages 17-18).

## Other Comments

• Copy-number gain of STK17A on chromosome 7 is frequent in glioma and correlates with tumour proliferation (chen2019drakstk17adrivesneoplastic pages 22-28).  
• Reduced expression associates with metastatic progression in colorectal cancer and adverse outcome in non-Hodgkin lymphoma (short2019serinethreoninekinase pages 5-5, capra2006frequentalterationsin pages 3-5).

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