Protein: STE20-related kinase adaptor protein α (STRADα) Gene: STRADA UniProt: Q7RTN6

## Phylogeny

STRADα is classified within the STE20 group of the human kinome on the basis of sequence similarity to SPAK and ILPIP and the presence of a kinase-like domain that lacks catalytic residues (baas2003activationofthe pages 2-3, smith2021typeiibinders pages 3-4).  
A single vertebrate duplication produced the paralog STRADβ, leaving STRADα as the ancestral branch member (velevarotse2014stradpseudokinasesregulate pages 1-4).  
Verified orthologs include Mus musculus Strada (baas2003activationofthe pages 2-3), Drosophila melanogaster Strad (baas2003activationofthe pages 2-3), and Caenorhabditis elegans strd-1 (narbonne2010differentialrequirementsfor pages 1-2).  
No STRAD homologue is detected in Saccharomyces cerevisiae, consistent with co-evolution alongside STK11/LKB1 in metazoans (narbonne2010differentialrequirementsfor pages 1-2).

## Reaction Catalyzed

ATP + protein-Ser/Thr → ADP + protein-Ser/Thr-P.  
No phosphotransfer catalysis has been observed; STRADα is a catalytically inactive pseudokinase (zeqiraj2009atpandmo25α pages 1-2, baas2003activationofthe pages 2-3).

## Cofactor Requirements

ATP binds to STRADα without a requirement for Mg²⁺ or other divalent cations (zeqiraj2009atpandmo25α pages 9-12).

## Substrate Specificity

Radioactive and in-gel assays show no detectable phosphorylation of generic Ser/Thr substrates; consequently no consensus motif is assigned (baas2003activationofthe pages 2-3, zeqiraj2009structureofthe pages 1-2).  
Large-scale kinase-substrate profiling further failed to attribute a motif to STRADα, confirming the absence of intrinsic specificity (smith2021typeiibinders pages 6-8).

## Structure

STRADα is a single ~430-residue pseudokinase domain that adopts the canonical bilobal fold (zeqiraj2009structureofthe pages 1-2).  
Crystal structures of the heterotrimeric LKB1–STRADα–MO25α complex at 2.65 Å reveal STRADα in a closed, ‘active-like’ conformation with AMP-PNP bound (zeqiraj2009structureofthe pages 5-8).  
Key catalytic motifs are degenerate: the HRD Asp is replaced by Ser232, and the DFG motif is substituted by GLR240-242, rationalising loss of catalysis (zeqiraj2009atpandmo25α pages 1-2).  
The αC-helix, WEF motif, p+1 loop and αEF/αF loop form an extensive interface that docks LKB1 as a pseudosubstrate, while MO25α clamps the ordered activation loop of LKB1 (zeqiraj2009structureofthe pages 4-5, zeqiraj2009atpandmo25α pages 8-9).  
Solution studies and thermal-shift screens demonstrate interchangeable “GLR-in” (closed) and “GLR-out” (open) nucleotide-binding states that can be targeted by small molecules (smith2021typeiibinders pages 22-25).

## Regulation

LKB1 phosphorylates STRADα on Thr329 and Thr419 both in vitro and in cells (baas2003activationofthe pages 2-3).  
In LKB1-null cancer cells STRADα is poly-ubiquitinated and degraded in an Hsp90- and proteasome-dependent manner (eggers2012ste20relatedkinaseadaptor pages 1-2).  
Multiple leucine-rich nuclear-export signals confer CRM1/Exportin-7-dependent cytoplasmic localization of the STRADα–LKB1 complex (smith2021typeiibinders pages 6-8).  
ATP and MO25α bind cooperatively to lock STRADα in the closed conformation required for high-activity LKB1; loss of both interactions abrogates activation (zeqiraj2009atpandmo25α pages 9-12).

## Function

STRADα is broadly expressed, with enrichment in brain, skeletal muscle and diverse epithelial tissues (velevarotse2014stradpseudokinasesregulate pages 8-9).  
It forms a 1:1:1 complex with STK11/LKB1 and CAB39/MO25 that stabilises LKB1 and increases its kinase activity (zeqiraj2009structureofthe pages 1-2).  
Activated LKB1 phosphorylates AMPK and twelve related kinases, thereby promoting catabolic metabolism and inhibiting mTOR-dependent anabolism (trelford2024lkb1biologyassessing pages 4-5).  
STRADα-directed nuclear export of LKB1 is essential for epithelial and neuronal polarity programmes (trelford2024lkb1biologyassessing pages 2-4).  
In LKB1-deficient tumour cells STRADα independently limits Rac1–PAK1 signalling, constraining motility and invasion (eggers2012ste20relatedkinaseadaptor pages 1-2).

## Inhibitors

Fragment screens identified compound 11 and related scaffolds that bind the “GLR-out” pocket of STRADα and thermally stabilise the protein, providing tool compounds for pseudokinase pharmacology (smith2021typeiibinders pages 22-25).

## Other Comments

A homozygous truncation at residue 251 abolishes LKB1 binding and causes polyhydramnios-megalencephaly-symptomatic epilepsy (PMSE) syndrome (zeqiraj2009atpandmo25α pages 9-12).  
STRADα-null mice exhibit perinatal lethality and cortical axogenesis defects, mirroring the human PMSE phenotype (velevarotse2014stradpseudokinasesregulate pages 8-9).  
In lung adenocarcinoma, numerous tumour-derived LKB1 mutants fail to engage the STRADα–MO25 scaffold, underscoring the complex’s importance in tumour suppression (eggers2012ste20relatedkinaseadaptor pages 1-2).

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