## Phylogeny

STRADα is a member of the STE20 group of the human kinome and contains a pseudokinase domain related to SPAK and ILPIP (Baas et al., 2003; Smith et al., 2021). A single vertebrate duplication generated the paralogue STRADβ, leaving STRADα as the ancestral branch (Veleva-Rotse et al., 2014). Verified orthologues are present in Mus musculus (Strada), Drosophila melanogaster (Strad) and Caenorhabditis elegans (strd-1) (Baas et al., 2003; Narbonne et al., 2010). No homologue is detected in Saccharomyces cerevisiae, consistent with co-evolution alongside LKB1 in metazoans (Narbonne et al., 2010).

## Reaction Catalyzed

ATP + protein-Ser/Thr ⇌ ADP + protein-Ser/Thr-P.  
(Note: no phosphotransfer activity has been detected; STRADα behaves as a catalytically inactive pseudokinase) (Zeqiraj et al., 2009; Baas et al., 2003).

## Cofactor Requirements

ATP binds in the absence of Mg²⁺ or other divalent cations (Zeqiraj et al., 2009).

## Substrate Specificity

Radioactive, in-gel and large-scale profiling assays detect no phosphorylation of generic Ser/Thr substrates; consequently, no consensus motif is assigned (Baas et al., 2003; Zeqiraj et al., 2009; Smith et al., 2021).

## Structure

• Single ~430-residue pseudokinase adopting the canonical bilobal fold (Zeqiraj et al., 2009).  
• Crystal structures of the LKB1–STRADα–MO25α heterotrimer (2.65 Å) show STRADα in a closed, “active-like” conformation with bound AMP-PNP (Zeqiraj et al., 2009).  
• Catalytic motifs are degenerate: HRD Asp → Ser232; DFG → GLR240-242, rationalising loss of activity (Zeqiraj et al., 2009).  
• αC-helix, WEF motif, p+1 loop and αEF/αF loop create the docking surface for LKB1, while MO25α clamps the ordered LKB1 activation loop (Zeqiraj et al., 2009).  
• Solution studies reveal interchangeable “GLR-in” (closed) and “GLR-out” (open) nucleotide-binding states (Smith et al., 2021).

## Regulation

• LKB1 phosphorylates STRADα on Thr329 and Thr419 (Baas et al., 2003).  
• In LKB1-null cancer cells, STRADα is poly-ubiquitinated and degraded via Hsp90- and proteasome-dependent pathways (Eggers et al., 2012).  
• Multiple leucine-rich NESs drive CRM1/Exportin-7-dependent cytoplasmic localisation of the STRADα–LKB1 complex (Smith et al., 2021).  
• Cooperative binding of ATP and MO25α locks STRADα in the closed conformation required for full LKB1 activation; loss of either interaction abolishes activation (Zeqiraj et al., 2009).

## Function

STRADα is broadly expressed, with enrichment in brain, skeletal muscle and diverse epithelia (Veleva-Rotse et al., 2014). It forms a 1:1:1 complex with STK11/LKB1 and CAB39/MO25, stabilising LKB1 and greatly enhancing its kinase activity (Zeqiraj et al., 2009). Activated LKB1 phosphorylates AMPK and twelve related kinases, promoting catabolic metabolism and suppressing mTOR-dependent anabolism (Trelford & Shepherd, 2024). STRADα-mediated nuclear export of LKB1 is essential for epithelial and neuronal polarity (Trelford & Shepherd, 2024). In LKB1-deficient tumour cells, STRADα independently restrains Rac1–PAK1 signalling, limiting motility and invasion (Eggers et al., 2012).

## Inhibitors

Fragment screens identified compound 11 and related scaffolds that bind the “GLR-out” pocket, thermally stabilising STRADα and providing chemical probes for pseudokinase pharmacology (Smith et al., 2021).

## Other Comments

• A homozygous truncation at residue 251 disrupts LKB1 binding and causes polyhydramnios-megalencephaly-symptomatic epilepsy (PMSE) syndrome (Zeqiraj et al., 2009).  
• STRADα-null mice die perinatally and display cortical axogenesis defects, recapitulating the human PMSE phenotype (Veleva-Rotse et al., 2014).  
• Many tumour-derived LKB1 mutants fail to engage the STRADα–MO25 scaffold, underscoring the complex’s role in tumour suppression (Eggers et al., 2012).

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