## Phylogeny

CSNK1A1 (CK1α) belongs to the Casein Kinase 1 (CK1) group, a distinct branch of the human kinome that is separate from the AGC, CAMK, CMGC, STE, TK and TKL groups (Manning et al., 2002).  
Within the CK1 clade it clusters with tau-tubulin (TTBK) and vaccinia-related (VRK) kinases, reflecting an ancient serine/threonine lineage (Venerando et al., 2014).  
Orthologs are present in fungi (Saccharomyces cerevisiae HRR25, YCK1-3; Schizosaccharomyces pombe Cki1/2, Hhp1/2), indicating an early eukaryotic origin (Gross & Anderson, 1998).  
Lineage-specific expansion is evident: Dictyostelium discoideum encodes two CK1 genes, Caenorhabditis elegans ~85, and Drosophila melanogaster ~10 (Goldberg et al., 2006; Manning et al., 2002).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr ⇌ ADP + protein-L-Ser/Thr-phosphate (Cullati et al., 2024).

## Cofactor Requirements

Catalysis is Mg²⁺-dependent; GTP is not used as an alternative phosphate donor (Venerando et al., 2014).

## Substrate Specificity

CK1α prefers Ser/Thr residues located three to four positions C-terminal to a pre-existing phospho-Ser/Thr or an acidic residue, yielding the consensus pS/pT-X-X-S/T with a strong Asp/Glu bias at −3 (Xu et al., 2019).  
High-density peptide arrays confirm maximal activity when Asp or phospho-Ser occupies the −3 position (Cullati et al., 2024).  
An SLS (Ser-Leu-Ser) motif followed by acidic residues, as in β-catenin and NFAT, is a recognised variant (Xu et al., 2019).

## Structure

CK1α contains an N-terminal ~300-residue kinase domain followed by a variable autoinhibitory C-terminal tail (Venerando et al., 2014).  
Paralog structures CK1δ (PDB 1CKI) and CK1γ (PDB 2CMW) reveal the canonical bilobal fold and serve as templates for CK1α modelling (Xu et al., 2019).  
Key catalytic residues: Lys46 (ATP anchoring), Asp133 (HRD motif catalytic base) and Asp149 (DFG motif, Mg²⁺ coordination) (Xu et al., 2019).  
Subdomain VIII carries the CK1-signature SIN triad replacing the usual APE sequence (Venerando et al., 2014).  
Met82 functions as the gatekeeper residue controlling inhibitor access (Xu et al., 2019).  
The activation loop adopts an open conformation for catalysis, whereas a multi-phosphorylated C-tail can fold across the active site to impose autoinhibition (Knippschild et al., 2014; Cullati et al., 2024).

## Regulation

• Autophosphorylation at Ser318/321/326 creates a pseudo-substrate segment that suppresses activity (Jiang et al., 2018).  
• PKA phosphorylation at Ser370 further reduces catalytic efficiency (Knippschild et al., 2014).  
• SCF^FBXW7-mediated ubiquitination targets the kinase for proteasomal degradation, while SUMOylation affects localisation (Knippschild et al., 2014).  
• Proteolytic trimming or substrate-induced displacement of the C-tail relieves autoinhibition (Venerando et al., 2014; Cullati et al., 2024).  
• A dimer interface observed in CK1δ structures can occlude the ATP site, suggesting a transient inhibitory assembly for CK1α (Xu et al., 2019).  
• Phosphatidylinositol-4,5-bisphosphate binding diminishes activity in certain cell types (Venerando et al., 2014).

## Function

CK1α is ubiquitously expressed with high levels in intestinal epithelium, melanomas, multiple myeloma, lung and breast cancers, and hematopoietic progenitors (Jiang et al., 2018).  
Major roles include:  
– Initiation of β-catenin turnover in canonical Wnt signalling via phosphorylation at Ser45 (Janovská et al., 2020).  
– Regulation of the circadian clock through PER1/2 phosphorylation (Jiang et al., 2018).  
– Activation of mTORC1/2 by phosphorylating DEPTOR at Ser286/287/291 under nutrient-rich conditions (Jiang et al., 2018).  
– Support of mitotic spindle dynamics and chromosome segregation (Gross & Anderson, 1998).  
– Modulation of cytoskeletal remodelling through keratin filament phosphorylation, aiding epithelial migration (Unknown Authors, 2020).  
– Restriction of NLRP3 inflammasome activation via direct phosphorylation (Knippschild et al., 2014).

## Inhibitors

• D4476: ATP-competitive; IC₅₀ ≈ 0.2–0.3 µM for CK1 isoforms; >20-fold selectivity over unrelated kinases (Pérez et al., 2011).  
• PF-670462: Imidazol-pyrazol-pyrimidine; IC₅₀ ≈ 0.013 µM for CK1δ with partial cross-activity on CK1α (Cozza & Pinna, 2016).  
• SR-3029: Nanomolar inhibitor, selective for CK1δ yet active on CK1α (Knippschild et al., 2014).  
• IC261: Indolinone; IC₅₀ ≈ 1 µM for CK1δ/ε and ~10 µM for CK1α; also binds tubulin (Cozza & Pinna, 2016).  
• CK1α shows relative resistance to staurosporine, requiring ≥100 µM for inhibition (Venerando et al., 2014).

## Other Comments

Haploinsufficiency of CSNK1A1 due to chromosome 5q deletion activates β-catenin and expands hematopoietic stem cells in myelodysplastic syndrome (Unknown Authors, 2017).  
Missense mutations E98K, H134L and D140A occur in ~5–7 % of del(5q) MDS cases and impair kinase function (Bello et al., 2015).  
Combined CSNK1A1 haploinsufficiency and mutant TP53 elevate MYC expression and accelerate leukemic transformation (Fuchs et al., 2024).  
Low CK1α expression correlates with poor prognosis in colorectal cancer (Jiang et al., 2018).  
CK1α activity modulates resistance to EGFR inhibitors and chemotherapeutics in solid tumours and multiple myeloma (Jiang et al., 2018).  
Phosphorylation of tau and α-synuclein by CK1 family members links the kinase to Alzheimer-related pathology (Qiao et al., 2019).

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