## Phylogeny

UHMK1 (U2AF-homology-motif kinase 1) is a serine/threonine protein kinase that belongs to the human kinome (Manning et al., 2002). It has been classified as an AGC-family member (Arfelli & Archangelo, 2018) and, based on its proline-directed activity, is also considered part of the CMGC group of cyclin-, MAP- and CDK-like kinases (Arfelli et al., 2023; Manning et al., 2002). The enzyme is highly conserved: > 99 % identity with other primates and mammals, 99.3 % with rodents, 88.2 % with chicken and 73.6 % with zebrafish (Arfelli & Archangelo, 2018). Its C-terminal U2AF homology motif (UHM) derives from RNA-recognition motifs and mediates protein–protein interactions (Arfelli et al., 2023).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Manning et al., 2002; Arfelli et al., 2023)

## Cofactor Requirements

Requires Mg²⁺ for catalytic activity (Arfelli & Archangelo, 2018; Arfelli et al., 2023; Francone et al., 2010).

## Substrate Specificity

UHMK1 is a proline-directed kinase that preferentially phosphorylates serine followed by Pro at +1 (Arfelli & Archangelo, 2018; Arfelli et al., 2023). pLogo analysis of phosphoproteomics defined a consensus [R]-X₀–₃-S-P-[E/D/Q]:  
• Pro at +1 present in 41.7 % of sites  
• Arg enriched at –3; Glu enriched at –4, +2, +3 (Arfelli et al., 2023).  
UHMK1 was included in a kinome-wide peptide array screen (Johnson et al., 2023), but no additional motif was reported in the present data set.

## Structure

The protein comprises an N-terminal kinase domain (~ aa 1–282) and a C-terminal 100-aa UHM protein-interaction module (Arfelli & Archangelo, 2018). Lys54 is essential for catalysis (Arfelli & Archangelo, 2018). No experimental crystal/NMR structures are available; AlphaFold models are referenced (Arfelli et al., 2023; Johnson et al., 2023). Structural elements such as activation loop or C-helix have not been experimentally defined in the cited literature.

## Regulation

Transcription: activated by GABP and FOXM1, with WDR5/KMT2A-mediated H3K4me3 at the promoter (Arfelli & Archangelo, 2018).  
Cell-cycle expression: accumulates in G1 and declines in S phase (Arfelli & Archangelo, 2018).  
Activation: mitogenic stimulation induces autophosphorylation (Unknown Authors, 2008).  
Post-translational modification: phosphorylation (Y197, S283, S290) and ubiquitination (K190, K282, K383, K387) reported; functional consequences not yet resolved (Arfelli & Archangelo, 2018).  
Upstream pathways: Akt, FGF-2, PI3K/Rac1 and ERK1/2 influence UHMK1 functions (Arfelli & Archangelo, 2018).

## Function

Localization & expression: nucleus and cytoplasm; ubiquitous with enrichment in nervous tissue (especially hippocampus) and hematopoietic cells (Arfelli & Archangelo, 2018; Francone et al., 2010).  
Major substrate pathways  
• RNA processing/splicing – phosphorylates SF1, SF3B1, SUGP1, hnRNP M, PRRC2B; controls > 270 alternative-splicing events (Arfelli & Archangelo, 2018; Arfelli et al., 2023).  
• Cell-cycle progression – phosphorylates p27^Kip1 (CDKN1B) on Ser10, promoting nuclear export and degradation during G1 (Arfelli & Archangelo, 2018; Barbutti et al., 2018; Arfelli et al., 2023).  
• Cytoskeletal dynamics – phosphorylates Stathmin on Ser38, leading to its degradation and reduced cell migration (Arfelli & Archangelo, 2018; Arfelli et al., 2023).  
• Secretory/neuronal roles – phosphorylates PAM on Ser949, modulating secretory-pathway trafficking; associates with KIF3A, NONO and regulates localized mRNA translation (Francone et al., 2010; Arfelli & Archangelo, 2018).  
Additional interactions: binds PIMREG and MYBL2; phosphorylates PIK3C3, WNK1, NUCKS1, PRPF4B and PPP4R2 (Arfelli & Archangelo, 2018; Arfelli et al., 2023).

## Inhibitors

No selective small-molecule inhibitors reported. Expression is down-regulated by the EGFR antibody trastuzumab and by clozapine (but not haloperidol); UHMK1 depletion sensitises EGFR-positive breast-cancer cells to erlotinib (Arfelli & Archangelo, 2018; Unknown Authors, 2008).

## Other Comments

Elevated UHMK1 transcripts in neurofibromatosis type 1 tumours and breast cancer; implicated in vascular remodelling and neointima formation (Arfelli & Archangelo, 2018). A GWAS SNP associates the UHMK1 locus with bone-mineral density (Arfelli & Archangelo, 2018). Possible, but controversial, link to schizophrenia (Unknown Authors, 2008). COSMIC lists > 160 somatic mutations across cancers; no recurrent mutations in MDS (Barbutti et al., 2018). Uhmk1-knockout mice show hyperactivity, impaired learning, altered SF1 phosphorylation and splicing defects (Arfelli & Archangelo, 2018).

## 9. References

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