## Phylogeny

Serine/arginine-protein kinase 1 (SRPK1) belongs to the CMGC group of the human kinome and, more specifically, to the SRPK family (Manning et al., 2002; Pastor et al., 2021). Orthologues are present throughout eukaryotes—from yeast and Drosophila to plants and vertebrates—highlighting deep evolutionary conservation (Zhou & Fu, 2013; Hogg & Findlay, 2023). In mammals, three paralogues exist: SRPK1 (ubiquitously expressed), SRPK2 (brain-enriched) and SRPK3 (skeletal and cardiac muscle-specific) (Nikas et al., 2019; Pastor et al., 2021).

## Reaction Catalyzed

ATP + protein-Ser → ADP + protein-phospho-Ser (Aubol et al., 2013; Hogg & Findlay, 2023).

## Cofactor Requirements

Catalysis requires Mg²⁺ for ATP coordination (Aubol et al., 2018) and ATP as phosphate donor (Hatcher et al., 2018; Pastor et al., 2021).

## Substrate Specificity

SRPK1 selectively phosphorylates serine residues within arginine/serine-rich (RS) domains. Preferred motifs include Arg-Ser dipeptide repeats typified by RxxRSRS or RxxSPxR, favouring Arg at the −3/−2 positions and Arg or Pro at +1 (Aubol et al., 2013; Hogg & Findlay, 2023). A separate docking sequence, R-x-R/K-x(3)-R, engages an acidic groove on the kinase surface to orient substrates (Lesgidou et al., 2025). SRPK1 shows little activity toward Ser-Pro dipeptides (Aubol et al., 2013). High-throughput peptide array data exist, but detailed PSSM values were not provided (Johnson et al., 2023).

## Structure

SRPK1 adopts the canonical bilobal protein-kinase fold. A large intrinsically disordered spacer-insert domain (SID) splits the N- and C-lobes and mediates cytoplasmic anchoring via chaperones (Plocinik et al., 2011; Zheng et al., 2023). Key catalytic features include the C-helix and activation loop, which is pre-configured for activity (Aubol et al., 2013). A distinctive deep electronegative groove on the C-lobe serves as the RS-domain docking site, guiding directional, processive phosphorylation (Aubol et al., 2021; Hogg & Findlay, 2023). Disulfide bonds contribute to structural stability and nuclear localisation (Koutroumani et al., 2017).

## Regulation

SRPK1 is constitutively active; no activation-loop phosphorylation is required (Hogg & Findlay, 2023). Regulation occurs through:  
• Autophosphorylation at Thr326 and Ser587 downstream of EGF–AKT signalling, influencing localisation (Hogg & Findlay, 2023).  
• Redox-dependent disulfide bond formation (Koutroumani et al., 2017).  
• Cytoplasmic sequestration by Hsp70/Hsp90 binding to the SID and growth-factor-induced nuclear import (Pastor et al., 2021; Zheng et al., 2023).  
• Nuclear inhibition via binding to SAFB1/2, TAF15 and PIM-1L (Aubol et al., 2021; Lesgidou et al., 2025).  
Catalytic mechanism varies with substrate length: semi-processive for long RS repeats (rate-limited by ADP release) and distributive for shorter repeats (Aubol et al., 2013).

## Function

SRPK1 phosphorylates SR-proteins (e.g., SRSF1, SRSF2) and SR-like proteins (LBR, PRM1), thereby controlling their nuclear import, speckle dynamics and spliceosome assembly; consequently, it is a central regulator of alternative pre-mRNA splicing (Duggan et al., 2022; Zheng et al., 2023). Upstream, PI3K/AKT drives SRPK1 activation (Nikas et al., 2019); downstream, SRPK1 cooperates with the nuclear kinase CLK1 to enhance SR-protein phosphorylation (Aubol et al., 2018). The kinase participates in broader PI3K/AKT, MAPK, Wnt and NF-κB signalling pathways (Nikas et al., 2019). Expression: SRPK1 is ubiquitous, whereas paralogues show tissue-restricted patterns (Nikas et al., 2019).

## Inhibitors

Experimental ATP-competitive or covalent inhibitors include SRPIN340, SPHINX, SPHINX31 and the irreversible compound SRPKIN-1; these agents modulate VEGF splicing from pro-angiogenic to anti-angiogenic isoforms (Hatcher et al., 2018; Duggan et al., 2022; Nikas et al., 2019).

## Other Comments

SRPK1 is frequently overexpressed in colorectal, prostate, breast, lung, pancreatic and gastric cancers. High levels correlate with advanced stage, poor prognosis and resistance to therapy (Duggan et al., 2022; Nikas et al., 2019). Oncogenic effects stem from altered splicing of VEGF, MCL-1, insulin receptor and other genes that promote proliferation, migration and angiogenesis. Dysregulation is also linked to certain human developmental disorders (Hogg & Findlay, 2023).

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