## Phylogeny

Based on sequence similarity of the kinase domain, SRPK1 is classified within the CMGC group of the human kinome, a group which also includes Cyclin-dependent kinases (CDKs), Mitogen-activated protein kinases (MAPKs), Glycogen synthase kinases (GSKs), and Cdc2-like kinases (CLKs) (manning2002theproteinkinase pages 1-1, manning2002theproteinkinase pages 7-8, pastor2021interplaybetweencmgc pages 3-5, zhou2013regulationofsplicing pages 4-5). Within this group, it is a member of the Serine/arginine Protein Kinase (SRPK) family (manning2002theproteinkinase pages 1-1, manning2002theproteinkinase pages 2-3, pastor2021interplaybetweencmgc pages 3-5). The SRPK family is conserved across all eukaryotic organisms, with orthologs identified in species from yeast and Drosophila to plants and animals (zhou2013regulationofsplicing pages 4-5, hogg2023functionsofsrpkclkanddyrkkinasesin pages 2-4). In mammals, the family comprises three paralogs: SRPK1, which is ubiquitously expressed; SRPK2, which is found predominantly in the brain; and SRPK3, which is specific to skeletal and cardiac muscle (nikas2019serinearginineproteinkinase pages 12-14, pastor2021interplaybetweencmgc pages 3-5).

## Reaction Catalyzed

SRPK1 catalyzes the transfer of the γ-phosphate group from an ATP molecule to the hydroxyl group of serine residues within its protein substrates (hogg2023functionsofsrpkclkanddyrkkinasesin pages 2-4, pastor2021interplaybetweencmgc pages 3-5, zhou2013regulationofsplicing pages 4-5). The reaction is: ATP + substrate protein → ADP + phospho-substrate protein (aubol2013splicingkinasesrpk1 pages 1-2).

## Cofactor Requirements

The catalytic activity of SRPK1 requires ATP as the phosphate donor cofactor (hatcher2018srpkin1acovalent pages 21-23, hogg2023functionsofsrpkclkanddyrkkinasesin pages 2-4, pastor2021interplaybetweencmgc pages 3-5). Its kinase activity is also dependent on the presence of Mg²⁺ ions, which are necessary for ATP binding and catalysis (aubol2018mobilizationofa pages 9-11).

## Substrate Specificity

An extensive analysis of the human kinome generated normalized position-specific scoring matrices (PSSMs) for 283 human kinases, including SRPK1; however, the explicit consensus motif and PSSM details derived from this analysis are not available in the provided context (johnson2023anatlasof pages 9-10).

Other studies report that SRPK1 specifically phosphorylates serine residues within arginine/serine-rich (RS) domains (aubol2013splicingkinasesrpk1 pages 1-2, zhou2013regulationofsplicing pages 4-5). Its substrate specificity centers on Arg-Ser (RS) dipeptide repeats, with a strong preference for serine residues flanked by arginines (aubol2013partitioningrsdomain pages 1-2, aubol2013splicingkinasesrpk1 pages 1-2). The optimal consensus sequences are reported to follow motifs such as RxxRSRS or RxxSPxR, which indicates a preference for arginine at positions P-3 and P-2, and either arginine or proline at P+1 relative to the phosphoacceptor serine (hogg2023functionsofsrpkclkanddyrkkinasesin pages 2-4, hogg2023functionsofsrpkclkanddyrkkinasesin pages 2-4). Substrate recognition is also mediated by a separate docking motif, R-x-R/K-x(3)-R, which binds to an acidic groove on the kinase distinct from the active site (lesgidou2025pim‐1lkinasebinds pages 1-2). SRPK1 does not significantly phosphorylate Ser-Pro dipeptides (aubol2013partitioningrsdomain pages 1-2).

## Structure

SRPK1 has a canonical bilobal kinase fold, consisting of a small N-terminal lobe and a large C-terminal lobe (aubol2013splicingkinasesrpk1 pages 1-2, koutroumani2017evidencefordisulfide pages 1-2). The two lobes of the kinase domain are bifurcated by a large, non-conserved, and intrinsically disordered spacer insert domain (SID) (plocinik2011regulatingsrprotein pages 1-2, zheng2023serinearginineproteinkinases pages 1-2). The SID influences subcellular localization by anchoring the kinase in the cytoplasm through interactions with chaperone proteins (plocinik2011regulatingsrprotein pages 1-2, zheng2023serinearginineproteinkinases pages 1-2).

Key catalytic elements include the activation loop and the C-helix (aubol2013splicingkinasesrpk1 pages 8-10, aubol2021aconservedsequence pages 1-2). A unique structural feature is a conserved, deep, electronegative (acidic) substrate docking groove located in the large C-lobe, outside the ATP-binding site (aubol2013splicingkinasesrpk1 pages 1-2, aubol2021aconservedsequence pages 1-2, hogg2023functionsofsrpkclkanddyrkkinasesin pages 2-4). This groove is essential for recognizing the RS domains of substrates and facilitating their translocation into the active site for directional phosphorylation (aubol2013splicingkinasesrpk1 pages 1-2, plocinik2011regulatingsrprotein pages 1-2).

## Regulation

SRPK1 is considered a constitutively active kinase, as its activation loop is stably maintained in an active conformation without requiring regulatory phosphorylation (hogg2023functionsofsrpkclkanddyrkkinasesin pages 2-4, koutroumani2017evidencefordisulfide pages 1-2). Its function is regulated through multiple mechanisms, including post-translational modifications, subcellular localization, and allostery. SRPK1 undergoes autophosphorylation, which can be triggered by the EGF-AKT pathway and affects its subcellular localization (hogg2023functionsofsrpkclkanddyrkkinasesin pages 2-4, pastor2021interplaybetweencmgc pages 3-5). Specific autophosphorylation sites influenced by AKT include T326 and S587 (hogg2023functionsofsrpkclkanddyrkkinasesin pages 2-4). Formation of disulfide bonds is also required for SRPK1 activity and nuclear localization (duggan2022serinearginineproteinkinase pages 15-16).

Regulation is largely controlled by its cellular location. SRPK1 is sequestered in the cytoplasm by binding to Hsp70/Hsp90 chaperone complexes via its spacer domain (pastor2021interplaybetweencmgc pages 3-5, zheng2023serinearginineproteinkinases pages 1-2). Upon growth factor stimulation, it is released and translocates to the nucleus (aubol2021aconservedsequence pages 1-2, pastor2021interplaybetweencmgc pages 3-5). In the nucleus, its activity can be inhibited by binding to proteins like SAFB1/2, TAF15, and the kinase PIM-1L (lesgidou2025pim‐1lkinasebinds pages 1-2, zheng2023serinearginineproteinkinases pages 1-2).

The kinetic mechanism of SRPK1 adapts to its substrate. For substrates with long RS repeats like SRSF1, it uses a directional, semi-processive mechanism where ADP release is the rate-limiting step (aubol2013splicingkinasesrpk1 pages 1-2). For substrates with shorter RS repeats, it uses a distributive mechanism where substrate dissociation is rate-limiting (aubol2013splicingkinasesrpk1 pages 1-2). There is conflicting information regarding the direction of processive phosphorylation, with some sources stating it proceeds in an N-terminal direction (C-to-N) (aubol2013splicingkinasesrpk1 pages 1-2, plocinik2011regulatingsrprotein pages 1-2), while another indicates an N-terminal to C-terminal direction (aubol2013splicingkinasesrpk1 pages 8-10).

## Function

SRPK1 is a key regulator of pre-mRNA splicing (duggan2022serinearginineproteinkinase pages 15-16, hatcher2018srpkin1acovalent pages 21-23). Its primary function is the phosphorylation of the arginine/serine-rich (RS) domains of SR proteins, such as SRSF1 and SRSF2, as well as other SR-like proteins like the Lamin B Receptor (LBR) and protamine 1 (PRM1) (aubol2013splicingkinasesrpk1 pages 1-2, hogg2023functionsofsrpkclkanddyrkkinasesin pages 2-4, pastor2021interplaybetweencmgc pages 3-5). This phosphorylation controls the nuclear import and subnuclear distribution of SR proteins, thereby modulating spliceosome assembly and alternative splicing (zheng2023serinearginineproteinkinases pages 1-2).

The AKT signaling pathway acts upstream of SRPK1 (nikas2019serinearginineproteinkinase pages 6-7, pastor2021interplaybetweencmgc pages 3-5). Downstream, SRPK1 interacts with and forms a functional complex with the nuclear kinase CLK1, which enhances the phosphorylation of SR proteins and mobilizes them from nuclear speckles (aubol2018mobilizationofa pages 9-11, aubol2021aconservedsequence pages 1-2, zheng2023serinearginineproteinkinases pages 1-2). SRPK1 is involved in several major signaling pathways, including PI3K/AKT, MAPK, Wnt, and NF-κB (nikas2019serinearginineproteinkinase pages 6-7, nikas2019serinearginineproteinkinase pages 7-9).

## Inhibitors

Several experimental inhibitors targeting SRPK1 have been developed. These include SRPIN340, which targets SRPK1 and SRPK2; SPHINX and SPHINX31, which show selectivity for SRPK1; and SRPKIN-1, which is an irreversible, covalent inhibitor of SRPK1 and SRPK2 (duggan2022serinearginineproteinkinase pages 15-16, hatcher2018srpkin1acovalent pages 21-23, nikas2019serinearginineproteinkinase pages 12-14). These compounds have been shown in preclinical studies to modulate alternative splicing of key targets like VEGF, shifting its expression from pro-angiogenic to anti-angiogenic isoforms (duggan2022serinearginineproteinkinase pages 15-16, hatcher2018srpkin1acovalent pages 21-23).

## Other Comments

SRPK1 is frequently overexpressed in a wide range of human cancers, including colorectal, prostate, breast, lung, pancreatic, and gastric cancers (duggan2022serinearginineproteinkinase pages 15-16, nikas2019serinearginineproteinkinase pages 3-4, nikas2019serinearginineproteinkinase pages 9-12). Elevated SRPK1 expression often serves as a prognostic biomarker, correlating with higher tumor grade, advanced stage, and shorter patient survival (duggan2022serinearginineproteinkinase pages 15-16, nikas2019serinearginineproteinkinase pages 3-4).

Its role in oncogenesis is linked to the regulation of alternative splicing of genes critical for angiogenesis (VEGF), apoptosis (MCL-1, IR), and proliferation (nikas2019serinearginineproteinkinase pages 12-14, nikas2019serinearginineproteinkinase pages 6-7). The SRPK1/SRSF1 axis, for example, controls VEGF-A splicing to promote pro-angiogenic isoforms (duggan2022serinearginineproteinkinase pages 15-16, nikas2019serinearginineproteinkinase pages 6-7). This activity implicates SRPK1 in promoting cell proliferation, migration, invasion, metastasis, and resistance to chemotherapy (nikas2019serinearginineproteinkinase pages 7-9, nikas2019serinearginineproteinkinase pages 12-14). Dysregulation of SRPK1 is also implicated in human developmental disorders, including intellectual disabilities (hogg2023functionsofsrpkclkanddyrkkinasesin pages 2-4).

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