## Phylogeny

SRPK3 is a member of the serine arginine protein kinase (SRPK) family, which also includes SRPK1 and SRPK2 (hanke2025thedevelopmentof pages 1-2, hanke2025thedevelopmentof pages 4-5). It is phylogenetically classified within the CMGC group of serine/threonine protein kinases (johnson2023anatlasof pages 7-7, manning2002theproteinkinase pages 7-8). However, one analysis places SRPK3 within the AGC kinase group (johnson2023anatlasof pages 4-4). Based on substrate preference, it is also categorized as a basophilic kinase in Cluster 1 (johnson2023anatlasof pages 12-18).

## Reaction Catalyzed

SRPK3 catalyzes the transfer of the γ-phosphate from ATP to phosphorylate serine residues located within arginine/serine-rich (RS) domains of substrate proteins (johnson2023anatlasof pages 7-7, johnson2023anatlasof pages 4-4, hanke2025thedevelopmentof pages 1-2).

## Cofactor Requirements

The catalytic activity of SRPK3 requires Mg²⁺ ions as a cofactor (johnson2023anatlasof pages 7-7, manning2002theproteinkinase pages 7-8). Mn²⁺ may also serve as a cofactor (johnson2023anatlasof pages 4-4).

## Substrate Specificity

SRPK3 is a basophilic kinase that preferentially phosphorylates serine residues within arginine/serine (RS) dipeptide repeats (johnson2023anatlasof pages 12-18, johnson2023anatlasof pages 7-7). The kinase substrate motif is characterized by a preference for arginine at positions -3 to -1 relative to the phosphoacceptor serine/threonine, with identified motifs including R-x-x-S/T and R-x-S/T (johnson2023anatlasof pages 12-18).

## Structure

A crystal structure of SRPK3 is not available; however, a high-confidence AlphaFold 3D model of the kinase domain exists and shows strong structural similarity to SRPK1 and SRPK2 crystal structures, with RMSDs between 0.438 and 0.563 Å (hanke2025thedevelopmentof pages 4-5). SRPK3 contains conserved kinase domains and distinct non-conserved regions, including an N-terminal extension (residues 1–79) and a large insert domain within the kinase domain (residues 228–401) (hanke2025thedevelopmentof pages 4-5). The structure comprises a bilobed kinase fold that facilitates substrate and ATP binding (johnson2023anatlasof pages 7-7). Key active site residues implicated in ligand interactions include Leu167, His169, Glu165, Arg83, and Leu85 (hanke2025thedevelopmentof pages 4-5). The non-conserved N-terminal and insert domains are involved in regulating cellular localization but do not influence catalytic activity (hanke2025thedevelopmentof pages 4-5). There are conflicting reports on the domain architecture; one source describes an N-terminal kinase domain with an extended insertion domain (johnson2023anatlasof pages 7-7), while another indicates conserved dual kinase domains arranged non-contiguously (manning2002theproteinkinase pages 7-8). Specific structural details for the activation loop, C-helix, or hydrophobic spine are not described in the provided context (hanke2025thedevelopmentof pages 8-9, hanke2025thedevelopmentof pages 9-10).

## Regulation

SRPK3 activity is regulated by phosphorylation at specific sites and by subcellular localization, which is influenced by modifying enzymes (johnson2023anatlasof pages 7-7, manning2002theproteinkinase pages 7-8). These post-translational modifications modulate kinase activity and interactions with substrates (johnson2023anatlasof pages 7-7). However, the specific phosphorylation sites, upstream modifying enzymes, and direct functional consequences of these modifications are not described in the provided sources (hanke2025thedevelopmentof pages 4-5, hanke2025thedevelopmentof pages 8-9, hanke2025thedevelopmentof pages 9-10).

## Function

SRPK3 is a muscle-specific kinase highly expressed in skeletal muscle, where it plays a critical role in muscle development and differentiation (johnson2023anatlasof pages 7-7, manning2002theproteinkinase pages 7-8). It phosphorylates serine/arginine-rich splicing factors (SRSFs), such as its substrate SRSF1, to regulate the alternative splicing of muscle-related genes (johnson2023anatlasof pages 7-7, johnson2023anatlasof pages 12-18, manning2002theproteinkinase pages 7-8). SRPK3 has also been implicated in breast cancer progression, particularly in aggressive subtypes (hanke2025thedevelopmentof pages 1-2).

## Inhibitors

A series of selective chemical probes for SRPK3 have been developed (hanke2025thedevelopmentof pages 9-10). Six compounds exhibited high selectivity for SRPK3 over SRPK1 and SRPK2 with low micromolar IC50 values. Of these, compounds BP152, BP310, and BP311 demonstrated dose-dependent, cancer-selective cytotoxicity in breast cancer cell lines while sparing non-malignant cells (hanke2025thedevelopmentof pages 8-9).

## Other Comments

Dysregulation and mutations of SRPK3 are associated with muscle myopathies, and altered phosphorylation patterns are implicated in disease contexts (johnson2023anatlasof pages 7-7). The kinase is also implicated in breast cancer (hanke2025thedevelopmentof pages 1-2).

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