## Phylogeny

Vertebrate orthologs have been verified in Homo sapiens (SRMS), Mus musculus (Srm), Rattus norvegicus (Srm), Danio rerio (srm) and Gallus gallus (srm) (McClendon & Miller, 2020, pp. 10–11). Within the human kinome, SRMS is placed in the Tyrosine Kinase (TK) group, BRK family, together with PTK6/BRK and FRK/PTK5 (Goel, Kim, & Lukong, 2023, pp. 1–2). Although its overall SH3–SH2–kinase domain organisation resembles Src-family kinases, SRMS lacks N-terminal myristoylation as well as the C-terminal regulatory tail typical of Src-family members (McClendon & Miller, 2020, pp. 1–3).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine ⇌ ADP + [protein]-O-phospho-L-tyrosine (McClendon & Miller, 2020, pp. 1–3).

## Cofactor Requirements

Catalytic activity requires a divalent cation, either Mg²⁺ or Mn²⁺ (Brown, 2014, pp. 28–35).

## Substrate Specificity

Peptide studies identified preferential phosphorylation of Tyr within XIYX and YXXV motifs, with Lys or Arg frequently positioned −2 or −4 relative to the target tyrosine (McClendon & Miller, 2020, pp. 5–7).

## Structure

Domain organisation: unique N-terminal extension (~50 aa) → SH3 → SH2 → kinase catalytic domain (Goel, Miah, et al., 2013, pp. 1–2).  
Key catalytic elements: Lys258 (ATP binding), Tyr380 (activation-loop autophosphorylation), and Trp223 (intramolecular stabilisation) (McClendon & Miller, 2020, pp. 3–5).  
A homology model based on chicken Src (PDB 2H8H) predicts the canonical bilobed kinase fold but without the Src-type C-terminal tail (McClendon & Miller, 2020, pp. 3–5). The N-terminal region forms an amphipathic helix essential for enzymatic activity and punctate cytoplasmic localisation (Goel, Kim, & Lukong, 2023, pp. 2–4).

## Regulation

Activation is achieved through autophosphorylation of Tyr380 (McClendon & Miller, 2020, pp. 3–5). Mutating Trp223 to Ala or deleting the first 50 residues eliminates kinase activity and disrupts punctate localisation (McClendon & Miller, 2020, pp. 3–5; Goel, Miah, et al., 2013, pp. 1–2). Because SRMS lacks the C-terminal inhibitory tyrosine found in Src-family kinases, regulation relies on N-terminal intramolecular interactions (McClendon & Miller, 2020, pp. 1–3).

## Function

Expression: elevated in breast carcinoma and correlates with higher tumour grade; lower in normal mammary epithelium; detectable in lung, testis, liver, epidermis and keratinocytes (Goel, Miah, et al., 2013, pp. 12–14; McClendon & Miller, 2020, pp. 1–3, 7–10).  
Verified substrates: DOK1; Sam68/KHDRBS1 (EGF-dependent); Vimentin; OTUB1 Tyr26; FKBP51 Tyr54; PTK6/BRK Tyr447 (Goel, Miah, et al., 2013, pp. 12–14; McClendon & Miller, 2020, pp. 5–7; Goel, Kim, & Lukong, 2023, pp. 4–6).  
Pathway roles: modulates EGF signalling via Sam68 phosphorylation; inhibits autophagy upstream of autophagosome formation; stabilises mTORC1 through the OTUB1–RPTOR axis; suppresses MKK4–JNK signalling, contributing to platinum resistance in ovarian cancer (Goel, Kim, & Lukong, 2023, pp. 4–9; McClendon & Miller, 2020, pp. 5–7).

## Inhibitors

Dasatinib inhibits SRMS in vitro (McClendon & Miller, 2020, pp. 3–5).  
Ibrutinib reduces SRMS-mediated phosphorylation in breast-cancer cells (Goel, Kim, & Lukong, 2023, pp. 2–4).  
PLX4720 has been identified as an SRMS inhibitor that enhances platinum-based chemotherapy efficacy (Goel, Kim, & Lukong, 2023, pp. 8–9).

## Other Comments

The SRMS gene maps to chromosome 20q13.33, adjacent to PTK6; this locus is frequently amplified in breast and gastric cancers (Goel, Kim, & Lukong, 2023, pp. 1–2). Srms-null mice are viable and display no overt phenotype (McClendon & Miller, 2020, pp. 7–10).

## 9. References

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