1. Phylogeny  
   Tyrosine‐protein kinase SRMS (gene SRMS, also known as Srm or C20orf148, UniProt Q9H3Y6) belongs to a group of non‐receptor tyrosine kinases that are closely related to the Src family. It is assigned to the BRK family kinases, a subgroup that includes BRK (PTK6) and FRK, and its gene is localized adjacent to that of BRK on human chromosome 20q13.33, indicating an evolutionarily conserved gene cluster among vertebrates (OpenTargets Search: -SRMS, mcclendon2020structurefunctionand pages 1-3, robinson2000theproteintyrosine pages 6-8). Comparative phylogenetic analyses based on kinase domain sequences classify SRMS within the broader Src‐related kinase branch, and its evolutionary history is marked by gene duplication events that gave rise to distinct regulatory families within the non‐receptor tyrosine kinases (robinson2000theproteintyrosine pages 6-8, yaronbarir2024theintrinsicsubstrate pages 5-6). Orthologs of SRMS have been identified in mammalian species, signifying its conservation across evolution, while its domain composition and regulatory motifs distinguish it from classical Src kinases (mcclendon2020structurefunctionand pages 1-3, yaronbarir2024theintrinsicsubstrate pages 5-6).
2. Reaction Catalyzed  
   SRMS catalyzes the transfer of a phosphate group from adenosine triphosphate (ATP) to the hydroxyl group of a tyrosine residue on a protein substrate, thereby converting the substrate into its phosphorylated form and releasing adenosine diphosphate (ADP) along with a proton (robinson2000theproteintyrosine pages 6-8). The generic chemical reaction can be summarized as: ATP + [protein]-tyrosine → ADP + [protein]-tyrosine-phosphate + H⁺, which is characteristic of protein tyrosine kinases involved in signal transduction (robinson2000theproteintyrosine pages 6-8).
3. Cofactor Requirements  
   The enzymatic activity of SRMS, similar to other protein kinases, is dependent on divalent metal ions, with magnesium (Mg²⁺) being the essential cofactor for the coordination of ATP in the active site (mcclendon2020structurefunctionand pages 1-3). The presence of Mg²⁺ is critical for optimal kinase activity, as it facilitates the proper positioning of ATP during the phosphoryl transfer reaction (mcclendon2020structurefunctionand pages 1-3).
4. Substrate Specificity  
   SRMS exhibits a defined substrate specificity that is determined by its intrinsic preference for certain sequence motifs surrounding the phosphoacceptor tyrosine residue. Experimentally derived data indicate that SRMS phosphorylates multiple substrates, including DOK1, KHDRBS1/SAM68, vimentin (VIM), and OTUB1; the phosphorylation of SAM68 is especially notable for its dependence on epidermal growth factor (EGF) stimulation (OpenTargets Search: -SRMS, goel2023seekingabetter pages 7-8). High-throughput peptide array analyses and mass spectrometry–based phosphoproteomic studies have revealed that SRMS preferentially targets motifs enriched in lysine residues immediately preceding the tyrosine (e.g., KxY) and motifs containing arginine residues (e.g., RxY), which govern substrate recognition (yaronbarir2024theintrinsicsubstrate pages 12-15, mcclendon2020structurefunctionand pages 3-5). In addition, the phosphorylation event on OTUB1 by SRMS functions to promote the deubiquitination of RPTOR, further expanding the range of its substrate interactions (OpenTargets Search: -SRMS, goel2023seekingabetter pages 7-8).
5. Structure  
   SRMS is organized into multiple functional domains that collectively orchestrate its catalytic and regulatory functions. The structure of SRMS comprises a unique extended N-terminal region – approximately 50 amino acids long – that is indispensable for its kinase activity; deletion of this region abolishes enzymatic function (goel2023seekingabetter pages 2-4, mcclendon2020structurefunctionand pages 7-10). This is followed by an SH3 domain, which typically mediates interactions with proline-rich sequences, and an SH2 domain that recognizes phosphotyrosine-containing motifs, thereby guiding substrate targeting and subcellular localization (mcclendon2020structurefunctionand pages 1-3, goel2023seekingabetter pages 2-4). The central catalytic kinase domain of SRMS harbors the ATP-binding pocket and key catalytic residues; notably, residue K258 is critical for ATP coordination, and the activation loop contains an autophosphorylation site, Y380, which is essential for full catalytic activation (mcclendon2020structurefunctionand pages 3-5, goel2023seekingabetter pages 1-2). Unlike canonical Src family kinases, SRMS lacks the N-terminal myristoylation signal and the C-terminal regulatory tyrosine residue that normally contribute to auto-inhibition and membrane localization, resulting in a distinct intracellular distribution often observed as cytoplasmic punctae (goel2023seekingabetter pages 7-8, mcclendon2020structurefunctionand pages 7-10). These structural attributes collectively define its three-dimensional organization, which, although not yet resolved by high-resolution crystallography, has been modeled using homology with related kinases and AlphaFold predictions (mcclendon2020structurefunctionand pages 1-3, yaronbarir2024theintrinsicsubstrate pages 5-6).
6. Regulation  
   Regulation of SRMS activity involves multiple layers of control, including both autophosphorylation events and modulation by external stimuli. Autophosphorylation of the activation loop at tyrosine Y380 is a key regulatory mechanism required for initiating and maintaining its catalytic activity (mcclendon2020structurefunctionand pages 3-5, goel2023seekingabetter pages 1-2). The unique extended N-terminal region of SRMS plays a critical role in its autoregulation, with its integrity being essential for proper kinase function (goel2023seekingabetter pages 2-4, mcclendon2020structurefunctionand pages 7-10). In addition, extracellular signals such as EGF stimulation result in enhanced phosphorylation of substrates like SAM68, indicating that SRMS can be modulated in a stimulus-dependent manner (goel2023seekingabetter pages 7-8). SRMS has also been implicated in phosphorylating other kinases – for example, the phosphorylation of BRK at tyrosine Y447 serves as a regulatory interaction that may impact cross-talk between related kinases, although the precise regulatory dynamics of this event remain to be fully characterized (mcclendon2020structurefunctionand pages 11-13, goel2023seekingabetter pages 4-6). No specific phosphatases have been definitively assigned to dephosphorylate SRMS; thus, its regulation appears to rely predominantly on autophosphorylation and interactions with other kinases and signaling molecules (mcclendon2020structurefunctionand pages 7-10).
7. Function  
   SRMS functions as an intracellular signal transducer through its tyrosine kinase activity, and it is involved in several cellular processes. It phosphorylates DOK1 on tyrosine residues, a modification that is central to its role in modulating downstream signaling pathways (OpenTargets Search: -SRMS, mcclendon2020structurefunctionand pages 3-5). In addition, SRMS phosphorylates KHDRBS1/SAM68 and vimentin (VIM) on tyrosine residues, with the phosphorylation of SAM68 being dependent on EGF stimulation; these substrates are implicated in modulating RNA binding and cytoskeletal dynamics, respectively (goel2023seekingabetter pages 7-8, mcclendon2020structurefunctionand pages 5-7). SRMS also targets OTUB1, and its phosphorylation of OTUB1 is linked to the promotion of deubiquitination of RPTOR, suggesting a role in the modulation of mTOR signaling and protein turnover (OpenTargets Search: -SRMS, goel2023seekingabetter pages 7-8). Expression studies have observed elevated levels of SRMS in certain cancer cell lines and tumor tissues, particularly in breast carcinomas, indicating that it may participate in oncogenic signaling networks and could have potential utility as a diagnostic marker (goel2023seekingabetter pages 7-8, bhanumathy2021proteintyrosinekinases pages 7-9). The functional output of SRMS activity is integrated within broader cellular signaling cascades that regulate processes such as cell proliferation, apoptosis, and differentiation, which are fundamental to normal cell biology and pathogenesis (OpenTargets Search: -SRMS, bhanumathy2021proteintyrosinekinases pages 7-9).
8. Other Comments  
   Currently, no inhibitors have been developed that selectively target SRMS; however, small molecule tyrosine kinase inhibitors such as dasatinib—although originally optimized for Src family kinases—are known to affect the activity of related kinases and may exhibit activity towards SRMS (OpenTargets Search: -SRMS, bhanumathy2021proteintyrosinekinases pages 7-9). SRMS is associated with various disease states; data from the Open Targets platform indicate moderate to high evidence for associations with hematological malignancies, and further studies have implicated SRMS in other cancers such as breast, gastric, and colorectal tumors (OpenTargets Search: -SRMS, goel2023seekingabetter pages 7-8). Although the detailed mutational landscape and clinical impact of SRMS variants have not yet been fully characterized, its patterns of expression and substrate phosphorylation events underscore its potential as a therapeutic target in oncology (goel2023seekingabetter pages 7-8, bhanumathy2021proteintyrosinekinases pages 7-9). Additional research efforts, including high-resolution structural studies and comprehensive phosphoproteomic profiling, are expected to further define the regulatory mechanisms and functional implications of SRMS in both normal cellular physiology and disease (mcclendon2020structurefunctionand pages 7-10, yaronbarir2024theintrinsicsubstrate pages 12-15).

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