## Phylogeny

Orthologs have been identified in Caenorhabditis elegans (ksr-1, ksr-2), Drosophila melanogaster (D-ksr), Xenopus laevis (Ksr), Danio rerio (ksr1), Rattus norvegicus (Ksr1), Mus musculus (Ksr1), and Homo sapiens (KSR1, KSR2) (zhang2014identificationofksr1 pages 42-46, kornfeld1995theksr1gene pages 6-7).  
Within the human kinome, KSR1 belongs to the Tyrosine-Kinase-Like (TKL) group and clusters with RAF-related pseudokinases sharing the five CA1-CA5 conserved areas (claperon2007ksrandcnk pages 5-6, martinvega2023navigatingtheerk12 pages 14-16).  
The protein is evolutionarily related to RAF family MAP3Ks yet diverged by loss of the canonical Ras-binding domain and catalytic β3-lysine, reflecting specialization toward scaffolding and allosteric regulation (claperon2007ksrandcnk pages 5-6).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr ⇌ ADP + protein-L-Ser/Thr-P in vitro (goettel2011ksr1isa pages 1-2).  
Physiological catalytic activity remains unconfirmed; structural studies capture an αC-OUT inactive conformation (brennan2011arafinducedallosteric pages 1-7).

## Cofactor Requirements

ATP binding is obligatory for structural integrity; mutations in the nucleotide pocket abolish function (goettel2011ksr1isa pages 1-2).  
A divalent metal requirement has not been demonstrated; Mg²⁺ dependence is unresolved (roskoski2012mek12dualspecificityprotein pages 5-6).

## Substrate Specificity

Validated substrate: MAP2K1/MEK1 is phosphorylated on non-activation-segment serines in vitro (goettel2011ksr1isa pages 1-2, roskoski2012mek12dualspecificityprotein pages 5-6).  
No consensus phosphorylation motif has been defined for KSR1 (neilsen2017ksrasa pages 6-8).

## Structure

Domain organisation:  
• CA1 – N-terminal CC-SAM mediating membrane recruitment and binding to the BRAF-specific BRS region (lavoie2018mekdrivesbraf pages 1-2).  
• CA2 – proline-rich segment of undefined function (frodyma2017coordinatingerksignaling pages 4-6).  
• CA3 – atypical C1/CRD enabling lipid-dependent plasma-membrane localisation (claperon2007ksrandcnk pages 5-6).  
• CA4 – Ser/Thr-rich region containing an FXFP ERK-docking motif (frodyma2017coordinatingerksignaling pages 4-6).  
• CA5 – C-terminal pseudokinase domain; Arg637 replaces the canonical catalytic Lys, HRD and DFG motifs are retained (martinvega2023navigatingtheerk12 pages 14-16).

3-D data: Crystal structures of MEK-bound KSR1/2 kinase domains (PDB 5UHV, 6B8C) reveal an αC-OUT inactive state with a partially assembled hydrophobic spine and an unphosphorylated activation loop; helix αG in the KSR C-lobe engages MEK, whereas the N-lobe side-to-side surface mediates heterodimerisation with BRAF (chow2022conformationalcontroland pages 1-3, maloney2022themechanismof pages 1-2, khan2020structuralbasisfor pages 21-25).  
Allosteric interfaces: MEK occupancy stabilises the KSR C-lobe and drives formation of BRAF-KSR heterodimers that activate BRAF catalysis (lavoie2018mekdrivesbraf pages 1-2).

## Regulation

Phosphorylation  
• Ser297, Ser392 – constitutive C-TAK1 targets; create 14-3-3 docking sites that retain KSR1 in the cytosol (cacace1999identificationofconstitutive pages 1-1, muller2001ctak1regulatesras pages 3-5).  
• Thr260, Thr274, Ser443 – Ras-inducible ERK sites; contribute to feedback regulation (cacace1999identificationofconstitutive pages 3-4).  
• Ser392 is dephosphorylated by PP2A upon growth-factor stimulation to permit membrane translocation (claperon2007ksrandcnk pages 5-6).

Ubiquitination  
Praja2 polyubiquitinates KSR1, targeting it for proteasomal degradation (goettel2011ksr1isa pages 12-12).

Conformational and allosteric control  
MEK binding triggers BRAF–KSR1 heterodimer formation, allosterically activating BRAF (lavoie2018mekdrivesbraf pages 1-2).  
The ATP-site ligand APS-2-79 stabilises the αC-OUT conformation and prevents RAF interaction (frodyma2017coordinatingerksignaling pages 4-6).

Chaperone regulation  
HSP90, HSP70, HSP68 and p50CDC37 associate with the kinase domain, supporting protein stability (stewart1999kinasesuppressorof pages 1-1).

## Function

Expression is high in brain and detectable in T cells and colonic epithelium (frodyma2017coordinatingerksignaling pages 1-3, goettel2011ksr1isa pages 12-12).  
Constitutively binds MEK1/2; forms inducible heterodimers with BRAF and RAF1; interacts with ERK1/2, 14-3-3, PP2A, IMP, and HSP90 complexes (stewart1999kinasesuppressorof pages 9-10, mckay2009signalingdynamicsof pages 1-1).  
Acts as a scaffold and MEK-dependent allosteric activator within the RAS–RAF–MEK–ERK cascade, modulating signal amplitude and duration downstream of receptor tyrosine-kinase or cAMP inputs (neilsen2017ksrasa pages 4-6).

## Inhibitors

APS-2-79 binds the nucleotide pocket, blocks KSR1–BRAF heterodimerisation, and attenuates Ras-dependent ERK signalling (neilsen2017ksrasa pages 8-9, chow2022conformationalcontroland pages 1-3).

## Other Comments

Ksr1-null mice are viable but resistant to Ras-driven tumourigenesis (neilsen2017ksrasa pages 1-3).  
Oncogenic mutations: C809Y disrupts MEK binding yet enhances ERK activation; P505A alters kinase-domain integrity (frodyma2017coordinatingerksignaling pages 3-4, unknownauthors2010kinasesuppressorof pages 19-23).

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