## Phylogeny

• Member of the AGC kinase group, S6K sub-family (unknownauthors2016theroleof pages 25-30).  
• Paralog of RPS6KB1 (S6K1) sharing ≈83 % amino-acid identity within the catalytic domain (khalil2024s6k2infocus pages 7-9).  
• Orthologs are present in Mus musculus, Rattus norvegicus, Danio rerio, Drosophila melanogaster and unicellular eukaryotes, illustrating conservation from yeast to mammals (magnuson2012regulationandfunction pages 1-2, malanchuk2024investigatingtheregulation pages 1-2).  
• Utilises the hydrophobic-motif activation mechanism common to AGC kinases such as PKC, Akt, RSK and SGK (unknownauthors2016theroleof pages 36-41).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr ⇌ ADP + [protein]-O-phospho-Ser/Thr (magnuson2012regulationandfunction pages 1-2).

## Cofactor Requirements

Catalysis requires Mg²⁺ (Mn²⁺ can substitute) coordinated with ATP in the active site (fenton2011functionsandregulation pages 1-2).

## Substrate Specificity

• Prefers basic consensus motif R/K-X-R/K-X-X-S/T (unknownauthors2016theroleof pages 25-30).  
• Principal substrate: ribosomal protein S6 at Ser235/236 and Ser240/244 (pende2014ribosomalproteins6 pages 5-7).  
• Additional validated substrates: eIF4B, eEF2K and PDCD4, linking the kinase to translation initiation and elongation control (pende2014ribosomalproteins6 pages 5-7).  
• Phosphorylates TAR RNA-binding protein (TRBP) affecting miRNA biogenesis (khalil2024s6k2infocus pages 7-9).  
• Modulates expression of transcription factor YY1 downstream of its kinase activity (khalil2024s6k2infocus pages 7-9).

## Structure

• Domain organisation: N-terminal nuclear localisation signal, bilobal kinase domain, kinase extension, and C-terminal regulatory tail containing hydrophobic-motif Thr388 and an autoinhibitory pseudosubstrate sequence (unknownauthors2016theroleof pages 25-30).  
• AlphaFold model AF-Q9UBS0-F1 exhibits the canonical AGC fold with catalytic Lys100, DFG motif (Asp215-Phe216-Gly217) and activation loop Thr228 (khalil2024s6k2infocus pages 9-11).  
• Phosphorylation of Thr388 stabilises the αC-helix and creates the PDK1 docking surface, mirroring conformational changes seen in S6K1 crystal structure 3A60 (sunami2010structuralbasisof pages 1-2).  
• Activation-loop phosphorylation at Thr228 aligns catalytic and regulatory spines to complete the active conformation (khalil2024s6k2infocus pages 7-9).  
• Unique hinge-region Cys150 differentiates S6K2 from S6K1 (Tyr) and is exploitable for covalent inhibitor binding (gerstenecker2021discoveryofa pages 7-10).

## Regulation

• Sequential phosphorylation: Ser370 priming → mTORC1 at Thr388 → PDK1 at Thr228 for full activation (khalil2024s6k2infocus pages 7-9).  
• ERK pathway phosphorylates Ser410, Ser417 and Ser423, relieving autoinhibition (khalil2024s6k2infocus pages 7-9).  
• PKC phosphorylates Ser486, masking the NLS and causing cytoplasmic retention (khalil2024s6k2infocus pages 9-11).  
• Fyn phosphorylates Tyr45 in vivo, linking receptor tyrosine kinase signals (khalil2024s6k2infocus pages 9-11).  
• PRMT-mediated arginine methylation of C-terminal RXR motifs promotes nuclear localisation and survival signalling (khalil2024s6k2infocus pages 9-11).  
• Lysine acetylation by p300/PCAF enhances stability; deacetylation by HDACs and sirtuins reverses this modification (khalil2024s6k2infocus pages 9-11).  
• Polyubiquitination targets the kinase for proteasomal degradation (fenton2011functionsandregulation pages 13-13).  
• PP2A dephosphorylates activation sites, while PTEN and TSC1/2 limit upstream PI3K-mTOR signalling (unknownauthors2016theroleof pages 36-41).

## Function

• Predominantly nuclear due to intrinsic NLS; p54 and p56 isoforms accumulate in the nucleus (unknownauthors2016theroleof pages 25-30).  
• Gene amplification and elevated expression observed in multiple cancers (khalil2024s6k2infocus pages 24-25).  
• Acts downstream of mTORC1 to drive ribosome biogenesis and protein synthesis via rpS6 phosphorylation, integrating PI3K/AKT, ERK and PKC inputs (magnuson2012regulationandfunction pages 1-2).  
• Enhances translation initiation by phosphorylating eIF4B and promoting PDCD4 degradation; accelerates elongation through inhibitory phosphorylation of eEF2K (pende2014ribosomalproteins6 pages 5-7).  
• Regulates miRNA processing via TRBP and augments YY1 expression, linking kinase activity to transcriptional programs (khalil2024s6k2infocus pages 7-9).  
• Participates in negative feedback attenuation of PI3K signalling, impacting metabolic homeostasis (fenton2011functionsandregulation pages 1-2).  
• High S6K2 activity supports chemoresistance, survival and migration in small-cell lung cancer and NRAS-mutant melanoma (khalil2024s6k2infocus pages 24-25).  
• Double knockout of S6K1 and S6K2 results in perinatal lethality, demonstrating essential developmental roles (khalil2024s6k2infocus pages 11-12).

## Inhibitors

• LY2584702 – ATP-competitive pan-p70S6K inhibitor; limited clinical efficacy and tolerability (khalil2024s6k2infocus pages 11-12).  
• PF-4708671 – S6K1-biased tool compound with partial S6K2 activity; induces apoptosis in resistant breast cancer and suppresses non-small-cell lung cancer proliferation (khalil2024s6k2infocus pages 11-12).  
• Covalent inhibitor “compound 2” – exploits Cys150 to achieve high potency and isoform selectivity (gerstenecker2021discoveryofa pages 7-10).  
• Rapamycin and rapalogues – inhibit mTORC1, preventing Thr388 phosphorylation and indirectly suppressing S6K2 activation (magnuson2012regulationandfunction pages 1-2).

## Other Comments

• Over-expression or hyperactivation correlates with poor prognosis and therapeutic resistance in several cancer types (khalil2024s6k2infocus pages 24-25).  
• PRMT-dependent methylation-driven nuclear localisation underlies chemoresistance in small-cell lung cancer (khalil2024s6k2infocus pages 9-11).  
• Enhanced rpS6 phosphorylation downstream of S6Ks contributes to neurodevelopmental phenotypes in PPP2R5D variant disorders (unknownauthors2024regulationandfunction pages 127-130).

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