## Phylogeny

Ribosomal protein S6 kinase α-1 (RPS6KA1; alternative names: RSK1, MAPKAPK1A, p90 RSK1) is a member of the AGC group of the human kinome and defines the p90 ribosomal S6 kinase (RSK) family (lee2007p90ribosomals6 pages 3-5).  
It shares 72–82 % amino-acid identity with the paralogues RSK2-4, but only ~40 % identity with the related MSK1/2 subfamily (lee2007p90ribosomals6 pages 3-5).  
Phylogenetic comparison places RSK1 as the most distant of the four human RSK isoforms (wright2023therapeutictargetingof pages 1-3).  
Orthologs are documented in mouse, rat, zebrafish, Drosophila, Caenorhabditis elegans and Xenopus laevis, reflecting conservation across metazoans (wright2023therapeutictargetingof pages 1-3, lee2007p90ribosomals6 pages 5-6).  
The RSK family emerged during metazoan evolution, expanding signalling capacity downstream of MAPK cascades (lee2007p90ribosomals6 pages 12-13).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr → ADP + [protein]-O-phospho-Ser/Thr (unknownauthors2015développementdenouvelles pages 208-211).

## Cofactor Requirements

Catalysis requires divalent metal ions, typically Mg²⁺ or Mn²⁺, to coordinate ATP in the active site (unknownauthors2015développementdenouvelles pages 208-211).

## Substrate Specificity

RSK1 preferentially phosphorylates basic motifs of the form Arg-X-Arg-X-X-Ser/Thr, a consensus that overlaps with recognition sites of AKT and S6K (wright2023therapeutictargetingof pages 3-4).  
Early biochemical data concur, describing a requirement for basic residues flanking the target residue within MAPK-activated kinase substrates (lee2007p90ribosomals6 pages 13-14).

## Structure

• Domain organisation: an N-terminal kinase domain (NTKD) with an AGC fold executes substrate phosphorylation; a C-terminal kinase domain (CTKD) with CaMK-like architecture regulates NTKD activity; a ~100-residue linker harbours regulatory phosphosites Thr359, Ser363 and Ser380 (lee2007p90ribosomals6 pages 3-5).  
• 3D data: crystal structures of the isolated human NTKD at 2.0 Å resolution with AMP-PCP, staurosporine or purvalanol A reveal a bilobal kinase core, a disordered activation loop and an outward-rotated αC helix, while the DFG motif adopts an active-like conformation (ikuta2007crystalstructuresof pages 1-2).  
• Unique feature: a three-stranded β-sheet replaces the canonical αC helix in several NTKD structures, implying a distinct catalytic conformational mechanism (utepbergenov2013theunusualmechanism pages 4-5).  
• Catalytic and regulatory residues: Ser221 in the NTKD activation loop is the PDK1 phospho-acceptor; Ser573 in the CTKD activation loop is the primary ERK1/2 target; linker Ser380 autophosphorylation generates the hydrophobic-motif PDK1 docking site (lee2007p90ribosomals6 pages 3-5).  
• Additional structures of isolated CTKDs are available for RSK1/2, supporting an ordered-activation model (utepbergenov2013theunusualmechanism pages 4-5).

## Regulation

Post-translational phosphorylation  
– ERK1/2 phosphorylates Ser573 (CTKD) and the linker residues Thr359 and Ser363, priming activation (lee2007p90ribosomals6 pages 3-5).  
– CTKD autophosphorylates Ser380, creating a PDK1 docking site (lee2007p90ribosomals6 pages 3-5).  
– PDK1 phosphorylates Ser221 in the NTKD, producing full catalytic activity (lee2007p90ribosomals6 pages 3-5).  
– mTOR phosphorylates the hydrophobic motif while RSK1 is bound to the eIF3 complex, promoting release for downstream EIF4B phosphorylation (lee2007p90ribosomals6 pages 9-10).

Allosteric and conformational control  
– Direct ERK docking to the CTKD is required for ordered multisite phosphorylation (lee2007p90ribosomals6 pages 3-5).  
– The extreme C-terminal tail exerts autoinhibition on the CTKD; its deletion yields constitutive kinase activity (wright2023therapeutictargetingof pages 1-3).

Protein–protein interactions  
– 14-3-3 proteins bind phosphorylated RSK substrates, contributing to complex stability and localisation (lee2007p90ribosomals6 pages 8-9, lee2007p90ribosomals6 pages 12-13).

## Function

Expression  
RSK1 is ubiquitously expressed, with elevated levels in proliferating tissues and neurons exhibiting high synaptic activity (lee2007p90ribosomals6 pages 10-12).

Upstream regulators  
MEK-ERK signalling activates RSK1; PDK1 and mTOR provide sequential phosphorylation inputs, and MOS can substitute for MEK in oocyte meiosis (lee2007p90ribosomals6 pages 3-5, lee2007p90ribosomals6 pages 5-6, lee2007p90ribosomals6 pages 9-10).

Downstream substrates and processes  
– Translation: EIF4B Ser422 and ribosomal protein S6 phosphorylation enhance cap-dependent translation (lee2007p90ribosomals6 pages 9-10).  
– mTOR axis: TSC2 Ser1798 phosphorylation up-regulates S6K1 activity (lee2007p90ribosomals6 pages 9-10).  
– Cell cycle: Myt1 inhibition, Bub1 phosphorylation and p27^Kip1 sequestration facilitate G2/M and S-phase progression (lee2007p90ribosomals6 pages 5-6, lee2007p90ribosomals6 pages 10-12).  
– Survival: BAD Ser155, GSK3α/β and DAPK1 phosphorylation repress apoptosis (lee2007p90ribosomals6 pages 8-9, lee2007p90ribosomals6 pages 10-12).  
– NF-κB pathway: association with IKK-2 promotes IκBα Ser32 phosphorylation and NF-κB activation (lee2007p90ribosomals6 pages 8-9).  
– Transcription: phosphorylates CREB, CBP/p300, NR4A1 and ETV1, driving immediate-early gene expression (lee2007p90ribosomals6 pages 8-9, lee2007p90ribosomals6 pages 10-12).  
– Neuronal signalling: interaction with PDZ-domain proteins modulates AMPA receptor transmission and constitutive activation stimulates neurite outgrowth in PC12 cells (lee2007p90ribosomals6 pages 9-10, lee2007p90ribosomals6 pages 14-15).  
Feedback modulation  
RSK1 negatively regulates upstream ERK1/2 signalling, adding an additional layer of pathway control (wright2023therapeutictargetingof pages 3-4).

## Inhibitors

• SL0101, a flavonol rhamnoside, selectively inhibits the NTKD and blocks proliferation of RSK-dependent cancer cells (lee2007p90ribosomals6 pages 9-10, utepbergenov2013theunusualmechanism pages 4-5).  
• BI-D1870 is a selective pan-RSK inhibitor, structurally characterised in complex with the NTKD (ikuta2007crystalstructuresof pages 10-10).  
• PMD-026 is a clinical-stage pan-RSK inhibitor under evaluation for metastatic breast cancer (wright2023therapeutictargetingof pages 1-3).  
• LJH685 is a tool inhibitor cited for RSK targeting (wright2023therapeutictargetingof pages 1-3).  
• Staurosporine and purvalanol A are broad-spectrum kinase antagonists crystallised with the NTKD and used as structural probes (ikuta2007crystalstructuresof pages 1-2).

## Other Comments

RSK1 activity is elevated in several tumour types, including breast and lung cancers, where it supports proliferation, metastasis and resistance to endocrine therapy (wright2023therapeutictargetingof pages 3-4, utepbergenov2013theunusualmechanism pages 4-5).  
Mouse knockout studies show that RSK1 deficiency is compatible with viability but leads to defects in fertility, lactation and immune responses, suggesting a therapeutic window for pharmacological inhibition (wright2023therapeutictargetingof pages 1-3).

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