## Phylogeny

– Member of the AGC kinase group; assigned to the p90 ribosomal S6 kinase (RSK) subfamily within the MAPK-activated protein kinase branch that also contains MSKs, MNKs and MK2/3/5 (cargnello2011activationandfunction pages 12-13).  
– Within the human RSK clade, RSK2 clusters most closely with RSK4, whereas RSK1 and RSK3 form a parallel branch (wright2023therapeutictargetingof pages 1-3).  
– Conserved orthologs are documented in mouse (Rps6ka3), rat, zebrafish, Xenopus, Drosophila S6KII and C. elegans rsks-1, illustrating deep conservation from invertebrates to vertebrates (romeo2012regulationandfunction pages 1-2, lara2013thep90rsk pages 1-2).

## Reaction Catalyzed

ATP + [protein]-L-Ser/Thr ⇌ ADP + [protein]-O-phospho-L-Ser/Thr (utepbergenov2016bacterialexpressionpurification pages 1-2).

## Cofactor Requirements

Catalytic turnover requires divalent cations; enzymatic activity is supported by Mg²⁺ or Mn²⁺, typical of AGC kinases (nishimoto2014thehistoricalcoffin–lowry pages 8-8).

## Substrate Specificity

– High-throughput profiling defined a basophilic consensus: R/K-X-R/K-X-X-S/T*, with strong enrichment for Arg/Lys at −3 and −5 relative to the phosphoacceptor (wright2023therapeutictargetingof pages 1-3).*  
*– Earlier peptide library work and verified substrates converge on Arg/Lys-X-Arg-X-X-Ser/Thr* and a marked preference for serine over threonine (cargnello2011activationandfunction pages 12-13, romeo2012regulationandfunction pages 7-8).

## Structure

Domain organisation  
1 C-terminal kinase domain (CTKD, CaMK-like) – contains the ERK-phosphorylated activation-loop residue Thr577 (human numbering) and initiates the activation cascade (cargnello2011activationandfunction pages 12-13, nishimoto2014thehistoricalcoffin–lowry pages 8-8).  
2 Regulatory linker – harbours Thr359/Ser363 and the hydrophobic-motif Ser386 that is autophosphorylated to create the PDK1 docking site (cargnello2011activationandfunction pages 12-13).  
3 N-terminal kinase domain (NTKD, AGC-like) – executes substrate phosphorylation; activated by PDK1 phosphorylation of Ser221 (nishimoto2014thehistoricalcoffin–lowry pages 8-8).  
4 Auxiliary elements – ERK docking (KIM), nuclear localisation signals, nuclear export signal (cargnello2011activationandfunction pages 12-13).

3D structural information  
– High-resolution NTKD crystal structures: apo/ATP-analogue (PDB 2Z7Q), inhibitor-bound (PDB 3G51, PDB 4NUS) reveal a canonical bilobal fold with an ordered activation loop and intact catalytic and regulatory spines (malakhova2009structuraldiversityof pages 10-10, utepbergenov2013theunusualmechanism pages 4-5).  
– Structural snapshots show the active DFG-in conformation and the conserved Lys100–Glu119 salt bridge stabilising the C-helix (malakhova2009structuraldiversityof pages 10-10).

## Regulation

Sequential phosphorylation cascade  
1 ERK1/2 docks on the KIM and phosphorylates CTKD Thr577 and linker Thr359/Ser363, activating the CTKD (cargnello2011activationandfunction pages 12-13).  
2 Activated CTKD autophosphorylates Ser386 in the hydrophobic motif (cargnello2011activationandfunction pages 12-13, nishimoto2014thehistoricalcoffin–lowry pages 8-8).  
3 Phospho-Ser386 recruits PDK1 which phosphorylates NTKD Ser221, yielding full catalytic activity (nishimoto2014thehistoricalcoffin–lowry pages 8-8).

Additional regulatory inputs  
– Tyrosine phosphorylation downstream of FGFR/Src enhances ERK binding and accelerates activation (cargnello2011activationandfunction pages 12-13).  
– 14-3-3 binding and ubiquitination events modulate stability and localisation; specific sites are under active investigation (wright2023therapeutictargetingof pages 14-15).  
– Dephosphorylation by PP2Cδ contributes to signal termination (romeo2012regulationandfunction pages 7-8).

## Function

Expression  
Highest expression in brain regions (hippocampal pyramidal neurons, cerebellar Purkinje cells), with notable levels in T-cells, lymph nodes and prostate (lee2007p90ribosomals6 pages 10-12, lara2013thep90rsk pages 1-2).

Upstream regulators  
RAS–RAF–MEK–ERK cascade, FGFR/Src signals and PDK1 (cargnello2011activationandfunction pages 12-13).

Principal substrates / interactors  
CREB1, histone H3, NR4A1, ETV1, CREBBP, RPS6, EIF4B, BAD, DAPK1, ATF4, c-Fos, TSC2, SOS, p27^Kip1, L1-CAM, nNOS, RanBP3, Gab2 (romeo2012regulationandfunction pages 9-10, wright2023therapeutictargetingof pages 15-15, lee2007p90ribosomals6 pages 10-12).

Pathway roles  
– Drives mitogen-induced immediate-early gene expression via CREB1 and c-Fos phosphorylation (cargnello2011activationandfunction pages 12-13).  
– Enhances mTORC1 signalling through TSC2 phosphorylation (romeo2012regulationandfunction pages 11-12).  
– Represses apoptosis by inactivating BAD and DAPK1 (romeo2012regulationandfunction pages 11-12).  
– Provides negative feedback to ERK signalling by phosphorylating SOS (anjum2008therskfamily pages 4-4).  
– Regulates neuronal development, cytoskeletal dynamics and epithelial–mesenchymal transition (romeo2012regulationandfunction pages 12-13).

## Inhibitors

– ATP-competitive NTKD inhibitors: SL-0101 and BI-D1870 (lara2013thep90rsk pages 7-8, cargnello2011activationandfunction pages 12-13).  
– Irreversible CTKD inhibitor: FMK (cargnello2011activationandfunction pages 12-13).  
– Additional selective inhibitors: LJH685 (lara2013thep90rsk pages 7-8) and the covalent pan-RSK inhibitor PMD-026, currently in early-phase clinical evaluation (wright2023therapeutictargetingof pages 1-3).  
– Natural product modulators such as kaempferol and CX-F9 attenuate oncogenic RSK2 signalling (wright2023therapeutictargetingof pages 15-15).

## Other Comments

Loss-of-function mutations in RPS6KA3 cause X-linked Coffin–Lowry syndrome, characterised by severe intellectual disability and skeletal dysplasia; most alleles encode truncated or kinase-dead proteins (cargnello2011activationandfunction pages 12-13, nishimoto2014thehistoricalcoffin–lowry pages 8-8).  
Rsk2-null mice replicate the human neurocognitive and motor deficits, validating the pathogenic mechanism (cargnello2011activationandfunction pages 12-13).  
Elevated RSK2 activity or expression is reported in breast, prostate, lung and cutaneous melanoma, positioning the kinase as a potential therapeutic target in oncology (utepbergenov2016bacterialexpressionpurification pages 1-2, wright2023therapeutictargetingof pages 15-15).

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