## Phylogeny

Ribosomal protein S6 kinase beta-1 (RPS6KB1), also known as p70S6K, is classified within the AGC group of protein kinases, specifically belonging to the RSK (ribosomal S6 kinase) family (manning2002theproteinkinase pages 3-3, manning2002theproteinkinase pages 7-8). The RSK family shares a close evolutionary relationship with other AGC kinase families, including protein kinase A (PKA), protein kinase G (PKG), and protein kinase C (PKC) (manning2002theproteinkinase pages 7-8). The kinase has clear orthologs in key model organisms including yeast, the nematode worm (*Caenorhabditis elegans*), and the fruit fly (*Drosophila melanogaster*), demonstrating deep evolutionary roots and conservation of the signaling pathway across eukaryotes (manning2002evolutionofprotein pages 1-2, manning2002theproteinkinase pages 7-8).

## Reaction Catalyzed

RPS6KB1 is a serine/threonine protein kinase that catalyzes the transfer of a gamma-phosphate from ATP to the hydroxyl groups of serine or threonine residues on substrate proteins (magnuson2012regulationandfunction pages 1-2, magnuson2012regulationandfunction pages 3-4, pende2014ribosomalproteins6 pages 1-3). The catalytic chemical reaction is described as: ATP + protein-serine/threonine → ADP + protein-serine/threonine-phosphate (pende2014ribosomalproteins6 pages 1-3, tchevkina2012proteinphosphorylationas pages 41-44).

## Cofactor Requirements

The kinase activity of RPS6KB1 requires ATP as the phosphate donor cofactor (bahramib2014p70ribosomalprotein pages 1-2, johnson2023anatlasof pages 4-4, pende2014ribosomalproteins6 pages 1-3). The reaction also requires Mg²⁺ ions as an essential cofactor, which coordinates and stabilizes ATP binding to facilitate the phosphate transfer (magnuson2012regulationandfunction pages 1-2, fenton2011functionsandregulation pages 13-13, sridhar2022targetingrps6k1for pages 16-16, tchevkina2012proteinphosphorylationas pages 41-44).

## Substrate Specificity

RPS6KB1 is a basophilic kinase whose substrate recognition is strongly influenced by basic amino acids at upstream positions relative to the phosphorylation site (johnson2023anatlasof pages 3-4). Analysis of its substrate specificity shows strong preferences for the basic residues Arginine (R) and Lysine (K) at positions -3 and -5 N-terminal to the phosphorylated serine or threonine residue (johnson2023anatlasof pages 3-4, johnson2023anatlasof pages 1-2). This defined substrate motif allows for the accurate prediction of kinase-substrate relationships (johnson2023anatlasof pages 6-7).

## Structure

The structure of RPS6KB1 includes a bilobal kinase domain typical of the AGC family, featuring a small N-terminal lobe and a larger C-terminal lobe that coordinates ATP binding (magnuson2012regulationandfunction pages 3-4, magnuson2012regulationandfunction pages 2-3). The crystal structure of the catalytic domain (PDB ID: 3A62) reveals key structural features: the N-terminal lobe contains the ATP-binding site and a conserved C-helix, while the larger C-terminal lobe contains the activation loop (johnson2023anatlasof pages 6-7). The hydrophobic spine, formed by aligned hydrophobic residues, provides structural integrity and stabilizes the active conformation (johnson2023anatlasof pages 6-7). Domain organization includes: - An N-terminal TOS (TOR signaling) motif, with the sequence FDIDL, which is required for binding to the Raptor component of mTORC1 (magnuson2012regulationandfunction pages 4-5, unknownauthors2011investigationofthe pages 34-39). - A central kinase domain containing the activation loop (T-loop) and the critical phosphorylation site Thr229 (magnuson2012regulationandfunction pages 3-4, magnuson2012regulationandfunction pages 4-5). - A C-terminal region containing a hydrophobic motif (HM) with the phosphorylation site Thr389 and an autoinhibitory pseudosubstrate region (magnuson2012regulationandfunction pages 2-3, magnuson2012regulationandfunction pages 3-4). - Alternative translational start sites produce isoforms like p85-S6K1, which has an N-terminal nuclear localization signal, and the predominantly cytoplasmic p70-S6K1, which lacks it (fenton2011functionsandregulation pages 2-2, magnuson2012regulationandfunction pages 3-4).

## Regulation

RPS6KB1 activation is governed by an allosteric mechanism and a hierarchical multi-site phosphorylation cascade (magnuson2012regulationandfunction pages 4-5, tchevkina2012proteinphosphorylationas pages 26-29). The TOS motif of S6K1 binds to the RAPTOR component of mTORC1, an essential allosteric interaction that brings the kinase into proximity for phosphorylation by mTORC1 (tchevkina2012proteinphosphorylationas pages 26-29, xu2020targetingmtorfor pages 1-2). This priming event is followed by subsequent phosphorylation steps: - **Thr389 (T389):** This hydrophobic motif residue is phosphorylated by mTORC1 as a prerequisite for further activation (tchevkina2012proteinphosphorylationas pages 26-29, magnuson2012regulationandfunction pages 4-5). This phosphorylation creates a docking site for PDK1 (magnuson2012regulationandfunction pages 4-5, folajimi2024themultifacetedrole pages 7-8). - **Thr229 (T229):** Following Thr389 phosphorylation, PDK1 phosphorylates this residue in the activation loop, leading to full kinase activation (fenton2011functionsandregulation pages 1-2, tchevkina2012proteinphosphorylationas pages 19-21, pende2014ribosomalproteins6 pages 5-7). - Additional phosphorylation at sites including Ser411, Ser418, Thr421, and Ser424 by kinases like ERK1/2 and p38-MAPK further regulates activity (folajimi2024themultifacetedrole pages 7-8). - The C-terminal domain has an autoinhibitory role that is relieved by mitogen-induced phosphorylation, allowing access for mTORC1 and PDK1 (magnuson2012regulationandfunction pages 4-5). - Regulation also occurs via miRNAs like miR-506-3p, which suppress expression by targeting its mRNA, and competing acetylation and ubiquitination modifications that influence protein stability (folajimi2024themultifacetedrole pages 7-8).

## Function

RPS6KB1 is a key downstream effector of the mTORC1 signaling pathway, integrating signals from growth factors, cytokines, and nutrients to regulate fundamental cellular processes (fenton2011functionsandregulation pages 1-2, magnuson2012regulationandfunction pages 1-2). - **Upstream regulators:** The kinase is activated by mTORC1 and PDK1 (fenton2011functionsandregulation pages 1-2). Its activity is also influenced by PI3K, Akt, and small G-proteins like Cdc42 and Rac (magnuson2012regulationandfunction pages 4-5). - **Downstream substrates:** Activated RPS6KB1 phosphorylates multiple substrates to promote protein synthesis, cell growth, and proliferation (fenton2011functionsandregulation pages 1-2). Key substrates include: - Ribosomal protein S6 (RPS6), promoting the translation of mRNAs with a 5’ terminal oligopyrimidine (TOP) motif (fenton2011functionsandregulation pages 1-2, bahramib2014p70ribosomalprotein pages 1-2). - Eukaryotic initiation factor 4B (EIF4B) at Ser422, which enhances translation initiation (fenton2011functionsandregulation pages 1-2, tchevkina2012proteinphosphorylationas pages 19-21). - Programmed cell death 4 (PDCD4) at Ser67, leading to its ubiquitination and degradation and promoting translation (pende2014ribosomalproteins6 pages 5-7, tchevkina2012proteinphosphorylationas pages 19-21). - Eukaryotic elongation factor 2 kinase (eEF2K), relieving inhibition of translation elongation (pende2014ribosomalproteins6 pages 5-7). - **Biological roles:** RPS6KB1 also regulates mRNA processing, glucose homeostasis, cell survival, cell cycle progression, and participates in negative feedback loops controlling the PI3K pathway (fenton2011functionsandregulation pages 1-2).

## Inhibitors

Direct inhibitors of RPS6KB1 are in development by pharmaceutical companies, but pharmacological inhibition is most commonly achieved indirectly by targeting its upstream activator, mTORC1 (fenton2011functionsandregulation pages 1-2, tchevkina2012proteinphosphorylationas pages 26-29). mTOR inhibitors like rapamycin and its analogs (rapalogs) form a complex with FKBP12 that binds to the FRB domain of mTOR, preventing mTORC1-mediated phosphorylation of RPS6KB1 at Thr389 and thereby blocking its activation (magnuson2012regulationandfunction pages 1-2, magnuson2012regulationandfunction pages 2-3, roux2018signalingpathwaysinvolved pages 3-5).

## Other Comments

Dysregulation of RPS6KB1 activity, including overexpression and hyperactivation, is implicated in numerous pathologies such as cancer, obesity, diabetes, and aging (fenton2011functionsandregulation pages 1-2). Gene amplification of its chromosomal region (17q23) is correlated with proliferation in breast cancer (folajimi2024themultifacetedrole pages 7-8). Due to its central role in these diseases, RPS6KB1 has become a target for therapeutic intervention (fenton2011functionsandregulation pages 1-2).

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