## Phylogeny

Ribosomal protein S6 kinase β-1 (RPS6KB1, p70-S6K) belongs to the AGC super-family and is placed in the ribosomal S6 kinase (RSK) sub-family, which is evolutionarily related to PKA, PKG and PKC (Manning et al., 2002). Clear orthologues are present in yeast, nematode and fruit-fly, indicating strong conservation of the pathway across eukaryotes (Manning et al., 2002; Manning, Plowman, Hunter, & Sudarsanam, 2002).

## Reaction Catalyzed

ATP + protein-Ser/Thr ⇌ ADP + protein-Ser/Thr-P (Magnuson, Ekim, & Fingar, 2012; Pende & Treins, 2014; Tchevkina & Komelkov, 2012).

## Cofactor Requirements

Mg²⁺ is required to coordinate ATP during catalysis (Magnuson et al., 2012; Sridhar, Komati, & Kumar, 2022).

## Substrate Specificity

RPS6KB1 is a basophilic Ser/Thr kinase that prefers arginine or lysine at positions −3 and −5 relative to the phospho-acceptor site, enabling motif-based prediction of its targets (Johnson et al., 2023).

## Structure

The crystal structure of the catalytic domain (PDB 3A62) shows a canonical bilobal kinase fold with an N-terminal lobe harbouring the ATP-binding pocket and a C-terminal lobe containing the activation loop and hydrophobic spine (Johnson et al., 2023; Magnuson et al., 2012).  
Domain organisation:  
• N-terminal FDIDL TOS motif for RAPTOR binding  
• Central kinase domain with activation loop residue Thr229  
• C-terminal hydrophobic motif containing Thr389 and an autoinhibitory pseudosubstrate segment  
• Alternative start sites generate a nuclear p85-S6K1 isoform and a cytoplasmic p70-S6K1 isoform (Fenton & Gout, 2011; Magnuson et al., 2012).

## Regulation

Activation is hierarchical: the TOS motif docks S6K1 to mTORC1, which phosphorylates Thr389; phosphorylated Thr389 then recruits PDK1 to modify Thr229, producing full activity (Magnuson et al., 2012; Tchevkina & Komelkov, 2012). Additional sites (Ser411, Ser418, Thr421, Ser424) are targeted by ERK1/2 or p38-MAPK (Folajimi et al., 2024). Mitogen-dependent phosphorylation relieves C-terminal autoinhibition, while expression is tempered by miR-506-3p and by competing acetylation or ubiquitination events (Folajimi et al., 2024).

## Function

As a key effector of mTORC1, RPS6KB1 integrates growth-factor, cytokine and nutrient signals (Fenton & Gout, 2011; Magnuson et al., 2012).  
Upstream activators: mTORC1 and PDK1; signalling input from PI3K-Akt and small G-proteins (Magnuson et al., 2012).  
Principal substrates: ribosomal protein S6, eIF4B (Ser422), PDCD4 (Ser67) and eEF2K, promoting translation initiation/elongation, cell growth and proliferation (Fenton & Gout, 2011; Pende & Treins, 2014; Tchevkina & Komelkov, 2012). Additional roles include mRNA processing, glucose homeostasis, cell-cycle progression and feedback inhibition of PI3K signalling (Fenton & Gout, 2011).

## Inhibitors

Direct ATP-competitive inhibitors are under development, but pharmacological blockade is routinely achieved with rapamycin or rapalogs that inhibit mTORC1, preventing Thr389 phosphorylation and downstream activation of S6K1 (Magnuson et al., 2012; Roux & Topisirovic, 2018; Xu et al., 2020).

## Other Comments

Over-expression or hyperactivation of RPS6KB1 is linked to cancer, obesity, diabetes and ageing. Amplification of chromosome 17q23 (containing RPS6KB1) is frequent in breast cancer, underscoring its therapeutic relevance (Fenton & Gout, 2011; Folajimi et al., 2024).

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