## Proposed EC/sub-subclass:

Not specified in the source material

## Accepted name:

Ribosomal protein S6 kinase β-1

## Synonyms:

70 kDa ribosomal protein S6 kinase 1; p70 ribosomal S6 kinase; S6K1; S6 kinase α

## Phylogeny

RPS6KB1 is an AGC-family serine/threonine kinase that arose early in eukaryotic evolution, with orthologues traceable to the Last Eukaryotic Common Ancestor (LECA). Gene-duplication events in the animal/fungal lineage generated the separate S6K and RSK branches (Karlsson, 2014, pp. 116-117; LaPenas, 2023, pp. 166-168; Domanova et al., 2016, pp. 12-13). In mammals the enzyme is ubiquitously expressed, forming part of the conserved TOR-signalling core.

## Reaction Catalyzed

ATP + [protein]-Ser/Thr → ADP + [protein]-Ser/Thr-phosphate + H⁺ (Beltman, 2022, pp. 318-322; Tchevkina, 2012, pp. 19-21).

## Cofactor Requirements

Requires Mg²⁺ for ATP binding and phosphotransfer (LaPenas, 2023, pp. 171-173; Tchevkina, 2012, pp. 19-21).

## Substrate Specificity

Prefers the consensus motif RxRxxp[Ser/Thr] with critical Arg residues at −5 and −3. Verified cellular substrates include ribosomal protein S6, eIF4B and EEF2K (Beltman, 2022, pp. 35-40; Tchevkina, 2012, pp. 19-21).

## Structure

S6K1 contains an N-terminal TOR-signalling (TOS) motif (FDIDL, residues 5–9) that engages RAPTOR of mTORC1, a bi-lobed catalytic domain with an activation loop (Thr229) and a hydrophobic motif (Thr389), and a C-terminal PDZ-binding segment that distinguishes it from the paralog S6K2. Full activity requires phosphorylation of Thr229 by PDK1 and Thr389 by mTORC1 (Gerstenecker et al., 2021, pp. 9-10; Jülich, 2008, pp. 15-19; Khalil et al., 2024, pp. 7-9; Pende & Fumagalli, 2014, pp. 1-3).

## Regulation

Under nutrient deprivation S6K1 is held inactive in an EIF3 complex. Mitogenic cues activate mTORC1, which phosphorylates Thr389, creating a docking site for PDK1 that phosphorylates Thr229 and fully activates the kinase. Active S6K1 feeds back on the pathway by phosphorylating SIN1, mTOR, RICTOR, DEPTOR and IRS1, the latter leading to proteasomal degradation and contributing to insulin-signalling attenuation. Additional control involves ubiquitination, acetylation and dephosphorylation of Thr412 via PPP1CC released from phosphorylated URI1 (Hsu, 2011, pp. 71-75; Majeed et al., 2019, pp. 17-21; Bdzhola et al., 2025, pp. 9-10; Murphy, 2021, pp. 111-114; Sridhar, 2022, pp. 11-16).

## Function

Principal mTORC1 effector that drives anabolic growth by phosphorylating components of the translational machinery (S6, eIF4B, EEF2K), translation regulators (PDCD4, POLDIP3/SKAR), metabolic enzymes (CAD, EPRS) and survival factor BAD. Through IRS1 phosphorylation it contributes to insulin resistance, and by targeting mTORC2 subunits it modulates AKT signalling (Cronin, 2023, pp. 27-34; Pende & Fumagalli, 2014, pp. 1-3; Murphy, 2021, pp. 11-15).

## Inhibitors

PF-4708671 selectively inhibits S6K1, reducing phosphorylation of S6 and IRS1 without affecting upstream mTORC1 or PDK1 events (Karlsson, 2014, pp. 42-45; Sridhar, 2022, pp. 14-16; Scott et al., 2020, pp. 24-29).

## Other Comments

Dysregulated S6K1 activity is linked to cancer, obesity, insulin resistance and other metabolic disorders. Suppressing S6K1 can mimic aspects of caloric restriction, making the kinase a promising therapeutic target; ongoing efforts aim to develop isoform-selective inhibitors (Karlsson, 2014, pp. 42-45; Sridhar, 2022, pp. 14-16).

## 9. References

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