1. Phylogeny  
   Ribosomal protein S6 kinase beta-2 (RPS6KB2), also known as S6K2 or STK14B, is a member of the AGC kinase family. This kinase is evolutionarily ancient, traceable to the common ancestor of eukaryotes, and belongs to a core set of TOR pathway–related kinases that include PDK1, AKT, p90 ribosomal S6 kinase (RSK) and SGK, all of which have their origins in or before the Last Eukaryotic Common Ancestor (LECA) (khalil2024s6k2infocus pages 1-3, sridharan2020distinctrolesof pages 11-13). Although S6K1 (encoded by RPS6KB1) and S6K2 are highly homologous in their kinase domains (with approximately 83–84% identity), they have diverged in their N- and C-terminal regions, leading to distinct functional and regulatory properties. Orthologs of S6K2 are conserved across mammalian species, and evidence from plant systems further demonstrates that ribosomal S6 kinases form one of the most conserved modules in eukaryotic signaling, with plant S6 kinases sharing key regulatory motifs despite species‐specific roles (lapenas2023ofthevulnerability pages 13-18, tavares2015thes6kprotein pages 1-2).
2. Reaction Catalyzed  
   RPS6KB2 catalyzes the transfer of a phosphate group from ATP to specific serine/threonine residues on substrate proteins. The canonical reaction can be summarized as:  
    ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺.  
   The principal physiological substrate of S6K2 is ribosomal protein S6 (rpS6), a component of the 40S ribosomal subunit. Phosphorylation of rpS6 plays a key role in the regulation of mRNA translation, particularly enhancing the translation of 5′-TOP mRNAs that encode components of the translational machinery. Notably, S6K2 also phosphorylates additional substrates such as histone H3 at threonine 45, indicating potential roles in chromatin regulation and nuclear signaling (khalil2024s6k2infocus pages 1-3, myronova2016theroleof pages 46-51). The reaction mechanism involves an ordered bi–bi process wherein substrate binding is accompanied by conformational changes in the kinase that facilitate phosphotransfer, a mechanism typical for serine/threonine kinases in the AGC family (khalil2024s6k2infocus pages 9-11).
3. Cofactor Requirements  
   The catalytic activity of RPS6KB2 is dependent on common kinase cofactors. As with many serine/threonine kinases, S6K2 requires ATP as the phosphate donor. Divalent metal ions, particularly Mg²⁺, are essential for effective ATP binding and stabilization of the transition state during catalysis. Although specific experimental details on additional cofactors for S6K2 are not exhaustively documented in the available excerpts, it is standard for kinases of the AGC family to also use Mg²⁺, and sometimes Mn²⁺, to achieve proper phosphotransfer (khalil2024s6k2infocus pages 3-4, lapenas2023ofthevulnerability pages 173-176).
4. Substrate Specificity  
   S6K2 exhibits substrate specificity that is both shared with and distinct from its paralog S6K1. Its best‐characterized substrate is ribosomal protein S6, where phosphorylation typically occurs on a cluster of serine residues in the carboxy-terminal region. The consensus motif recognized by S6 kinases is generally of the form RxRxxp[ST], where “p[ST]” indicates a phosphorylated serine or threonine residue. Beyond rpS6, S6K2 phosphorylates additional substrates such as histone H3 at threonine 45, which may influence chromatin dynamics and gene expression (khalil2024s6k2infocus pages 27-28, tavares2015thes6kprotein pages 7-8). In certain cellular contexts, S6K2 has also been implicated in the regulation of factors involved in mRNA processing and miRNA biogenesis, such as heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1) and Transactivation Response RNA-binding Protein (TRBP) (khalil2024s6k2infocus pages 6-7, myronova2016theroleof pages 46-51). This broader substrate recognition allows S6K2 to induce multiple downstream effects beyond translation enhancement.
5. Structure  
   Structurally, RPS6KB2 is organized around a central catalytic kinase domain that is highly conserved among AGC kinases, flanked by regulatory regions that confer specificity and control. The kinase domain is responsible for ATP binding and catalysis, with well-defined motifs including the activation loop, which is instrumental for substrate recognition and catalytic efficiency, and the DFG motif that coordinates Mg²⁺ for ATP binding (khalil2024s6k2infocus pages 1-3, lapenas2023ofthevulnerability pages 173-176).  
   Distinctively, S6K2 differs from S6K1 in its C-terminal region: while S6K1 harbors a PDZ-binding domain, S6K2 contains a proline-rich region immediately followed by a nuclear localization sequence (NLS). This feature supports the predominant nuclear localization observed for S6K2, suggesting specialized roles in nuclear signaling and gene regulatory mechanisms. Additionally, the N-terminal region of S6K2 contains a conserved TOR signaling (TOS) motif (often represented by an FDIDL sequence in the first 5–9 residues) that facilitates its recruitment to mTORC1 via interaction with RAPTOR, thereby positioning it for activation by mTOR-mediated phosphorylation (khalil2024s6k2infocus pages 3-4, tavares2015thes6kprotein pages 8-9). Crystal structural data for human S6 kinases have not been as exhaustively detailed as for some other AGC kinases; however, computational and homology modeling studies (including molecular dynamics and docking simulations) have provided insights into the conformational flexibility of S6K2 and have identified potential unique binding pockets that may be exploited for selective inhibitor development (khalil2024s6k2infocus pages 24-25, cronin2023amechanisticapproach pages 27-34).
6. Regulation  
   Regulation of S6K2 activity is complex and involves multiple layers of control that ensure a tight coupling to cellular nutrient status and mitogenic signals. The full activation of RPS6KB2 requires a sequential phosphorylation cascade: initially, upstream signals such as those mediated by the MEK/ERK pathway lead to priming phosphorylation events that relieve autoinhibition (khalil2024s6k2infocus pages 7-9, myronova2016theroleof pages 30-36).  
   mTORC1, acting as a nutrient and growth factor sensor, phosphorylates S6K2 at a conserved hydrophobic motif (T388 in S6K2) to relieve the autoinhibitory conformation imposed by its regulatory regions (khalil2024s6k2infocus pages 9-11, sridharan2020distinctrolesof pages 3-5). Following this, PDK1 phosphorylates the activation loop (T228 in S6K2), which is essential for full catalytic activity (khalil2024s6k2infocus pages 9-11).  
   In addition, S6K2 receives isoform-specific modifications. For example, protein kinase C (PKC) phosphorylates S6K2 at Ser486, a modification that can interfere with nuclear localization signals and modulate subcellular distribution, ensuring that a portion of the enzyme remains sequestered in the cytoplasm upon specific stimuli (khalil2024s6k2infocus pages 9-11). Furthermore, S6K2 undergoes post-translational modifications such as arginine methylation, mediated by PRMT enzymes, which influence its nuclear presence and pro-survival activity (khalil2024s6k2infocus pages 6-7). Other regulatory mechanisms include ubiquitination and acetylation that affect protein stability and interactions, though the precise enzymes responsible for these modifications have not been fully elucidated (khalil2024s6k2infocus pages 24-25, myronova2016theroleof pages 36-41). Regulation by phosphatases such as PP2A has also been implicated in modulating S6K2 dephosphorylation and thus its overall signaling output (khalil2024s6k2infocus pages 6-7).
7. Function  
   RPS6KB2 functions as a critical effector in signaling pathways that integrate extracellular growth factors and nutrient availability with intracellular anabolic processes. Acting downstream of mTORC1, S6K2 phosphorylates ribosomal protein S6, thereby enhancing the translation of specific mRNAs, particularly those possessing 5′-terminal oligopyrimidine (5′-TOP) motifs that encode components of the protein synthesis machinery (khalil2024s6k2infocus pages 1-3, yi2021ribosomalproteins6 pages 4-6). This phosphorylation event is essential for regulating global protein synthesis rates, cell size, and proliferative capacity.  
   Beyond its canonical role in translational control, S6K2 has been implicated in the regulation of other cellular processes. Notably, S6K2 phosphorylates histone H3 at threonine 45, suggesting a role in modulating chromatin dynamics and gene expression, which might influence cellular differentiation and proliferation outcomes (khalil2024s6k2infocus pages 27-28, myronova2016theroleof pages 41-46). In addition, the kinase interacts with RNA-binding proteins such as hnRNPA1 and TRBP, affecting the biogenesis and nuclear export of mRNA and microRNAs; these interactions have been linked to enhanced cell survival and chemoresistance by promoting the translation of anti-apoptotic proteins like Bcl-XL and XIAP (khalil2024s6k2infocus pages 6-7, myronova2016theroleof pages 46-51).  
   Functional studies demonstrate that S6K2 is involved in cell cycle progression and proliferation, consistently linking its overexpression or dysregulated activity with oncogenic phenotypes in cancers such as breast, colorectal, and lung cancers. Its activity modulates not only the control of protein synthesis but also provides feedback into the mTOR signaling cascade, contributing to the fine tuning of cellular metabolism and growth (sridharan2020distinctrolesof pages 3-5, khalil2024s6k2infocus pages 3-4). In normal physiology, S6K2 is expressed in multiple tissues, and its proper regulation is necessary for maintaining cellular homeostasis and adapting to environmental cues, including nutrient and growth factor availability (myronova2016theroleof pages 25-30).
8. Other Comments  
   Although research on S6K2 has historically lagged behind that of S6K1, emerging evidence increasingly supports distinct roles for RPS6KB2 in cancer biology and other pathological conditions. Genetic association studies, as reflected by data from Open Targets, have implicated RPS6KB2 in variations of hematological parameters and lipid metabolism, indicating potential broader physiological roles beyond translational control. Despite the development of several S6 kinase inhibitors, most available inhibitors such as PF-4708671 and LY2584702 were primarily characterized for their effects on S6K1, and selective inhibition of S6K2 remains an active area of investigation (khalil2024s6k2infocus pages 24-25, sridharan2020distinctrolesof pages 1-3). Current research efforts are focused on better resolving the isoform-specific functions of S6K2, understanding its unique substrate interactions, and elucidating the consequences of its post-translational modifications—which include phosphorylation, arginine methylation, ubiquitination, and acetylation—to design highly selective inhibitors for potential therapeutic applications in cancer and metabolic disorders (khalil2024s6k2infocus pages 6-7, myronova2016theroleof pages 36-41). The atypical nuclear localization of S6K2, which contrasts with the more cytoplasmic distribution of S6K1, further reinforces the idea that the two kinases have non-redundant contributions to cell proliferation and survival. Future studies that integrate structural biology with in vivo functional assays are expected to uncover new opportunities for targeting S6K2 in disease contexts.
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