1. Phylogeny  
   RPS6KL1 (also known as RSKL2, UniProt ID Q9Y6S9) is a member of the ribosomal protein S6 kinase‐like family within the broader AGC kinase superfamily. Orthologs of RPS6KL1 and related kinases have been identified in diverse eukaryotic lineages ranging from insects such as Drosophila to mammals, which supports its deep evolutionary conservation across species (zhao2015drosophilas6kinase pages 2-4). Sequence analyses and family classifications place RPS6KL1 in close evolutionary proximity to the p90 ribosomal S6 kinases (RSKs) that possess dual kinase domains, and its grouping is consistent with other kinases that belong to the AGC group as defined by conserved catalytic domain features (hanks1995theeukaryoticprotein pages 7-8, pearce2010thenutsand pages 1-2). These relationships indicate that RPS6KL1 evolved from a common ancestral gene that gave rise to kinases involved in translational control and signal transduction, and its phylogenetic context is further supported by findings in studies on related kinases across eukaryotes (hanks1995theeukaryoticprotein pages 1-1).
2. Reaction Catalyzed  
   RPS6KL1 catalyzes the transfer of a phosphate group from ATP to the hydroxyl group of serine or threonine residues on substrate proteins. This reaction proceeds according to the general scheme: ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺, reflecting the classical mechanism observed in serine/threonine kinases (hanks1995theeukaryoticprotein pages 1-1).
3. Cofactor Requirements  
   The kinase activity of RPS6KL1 is dependent on the presence of Mg²⁺ ions, which function as essential cofactors by coordinating the ATP substrate within the catalytic cleft. Magnesium is required to stabilize the negative charges of ATP and to facilitate the phosphoryl transfer reaction, as is typical for protein kinases (hanks1995theeukaryoticprotein pages 1-1).
4. Substrate Specificity  
   RPS6KL1 is expected to phosphorylate target proteins on serine or threonine residues within a consensus motif enriched in basic amino acids. In related ribosomal S6 kinase family members, substrate recognition often involves motifs such as RXRXXp[ST] or RRXp[ST], with conserved arginine residues positioned in close proximity to the phosphorylated residue; this substrate specificity pattern is a common feature among AGC kinases (hanks1995theeukaryoticprotein pages 3-4, pearce2010thenutsand pages 1-2).
5. Structure  
   RPS6KL1 is predicted to exhibit a dual kinase domain architecture that is characteristic of the p90 ribosomal S6 kinase family. The protein is anticipated to contain an N-terminal kinase domain (NTKD) that adopts a typical AGC kinase fold, comprising a smaller N-terminal lobe with five β-strands and an αC-helix, and a larger C-terminal lobe rich in α-helices. Within the NTKD, canonical structural elements such as a glycine-rich loop, a catalytic loop with an HRD motif, and an activation loop containing a DFG motif are expected to be present and function in ATP binding and phosphotransfer (kurinov2009structuraldiversityof pages 3-4, hanks1995theeukaryoticprotein pages 3-4). In addition, RPS6KL1 is predicted to contain a second kinase domain at its C-terminus that is structurally related to the CAMK family; this C-terminal kinase domain (CTKD) is generally organized into a bilobed structure with an N-lobe and a C-lobe and may harbor an autoinhibitory segment that modulates its catalytic activity (kurinov2009structuraldiversityof pages 4-6, gogl2019disorderedproteinkinase pages 6-8). These two catalytic domains are connected by an interdomain linker of approximately 100 amino acids that is thought to be intrinsically disordered and to contain short linear motifs (SLiMs) such as a hydrophobic motif (HM) and a turn motif (TM) that are critical for coordinated regulation. Structural models, including those predicted by computational methods like AlphaFold for related kinases, suggest that the NTKD of kinases in this family may incorporate unique features such as additional β-sheet insertions that can displace the C-helix relative to the canonical arrangement, thereby influencing intramolecular communication between the two kinase domains (kurinov2009structuraldiversityof pages 3-4, pearce2010thenutsand pages 1-2, gogl2019disorderedproteinkinase pages 6-8). Although a direct high-resolution structure of RPS6KL1 is not available, comparative analyses based on analogous ribosomal S6 kinases support a model in which key catalytic elements—including the DFG, HRD motifs, and the hydrophobic spine—are conserved, with regulatory docking sites for upstream kinases such as ERK likely being present in the disordered C-terminal regions (hanks1995theeukaryoticprotein pages 7-8).
6. Regulation  
   Regulation of RPS6KL1 activity is achieved predominantly through post-translational modifications, most notably phosphorylation. In kinases within the p90 RSK family, activation typically involves a sequence of phosphorylation events initiated by binding of upstream kinases such as ERK1/2 to docking motifs located in the C-terminal region. Following ERK-mediated phosphorylation, the C-terminal kinase domain is activated and instrumental in phosphorylating regulatory motifs within the interdomain linker, including the hydrophobic motif (HM). Phosphorylation of the HM provides a binding site for PDK1, which then phosphorylates the activation loop of the N-terminal kinase domain to achieve full activation (gogl2019disorderedproteinkinase pages 6-8, kurinov2009structuraldiversityof pages 6-8). In some related isoforms, such as RSK4, alternative regulatory mechanisms have been observed, including instances of autophosphorylation that operate independently of PDK1; these findings point to the possibility of isoform-specific regulation within the broader kinase family (kurinov2009structuraldiversityof pages 1-2, pearce2010thenutsand pages 1-2). Furthermore, intrinsically disordered regions (IDRs) located in the interdomain linker and in the C-terminal tail contribute additional regulatory layers by providing short linear motifs (SLiMs) that serve as phosphoswitches, thereby modulating enzyme conformation and activity. Although direct experimental mapping of phosphorylation sites on RPS6KL1 is not yet available, its placement within the ribosomal S6 kinase-like family implies that key regulatory phosphorylation events similar to those observed in other AGC kinases are likely to occur (pearce2010thenutsand pages 1-2, gogl2019disorderedproteinkinase pages 6-8).
7. Function  
   RPS6KL1 plays a role in the regulation of protein synthesis and cellular growth, functions that are common among ribosomal S6 kinase family members. Enzymes within this family are known to phosphorylate substrates involved in mRNA translation and ribosome function, thereby contributing to the control of cell size, cell proliferation, and overall metabolic activity (hanks1995theeukaryoticprotein pages 7-8). In addition, functional studies in model organisms have demonstrated that homologs of S6 kinase-like proteins can influence developmental signaling pathways; for example, in Drosophila, the S6 kinase–like protein negatively regulates neuromuscular junction growth by downregulating BMP receptor signaling (zhao2015drosophilas6kinase pages 2-4). In mammals, related kinases are implicated in the regulation of ribosomal protein S6 phosphorylation, which in turn affects the efficiency of protein synthesis and has been linked to cellular proliferation in cancer. Although specific substrates for RPS6KL1 have not been unequivocally defined, its domain organization and sequence similarity to other ribosomal S6 kinases suggest that its downstream targets likely include components of the translational machinery and proteins involved in signal transduction pathways such as those governed by mitogen-activated protein kinases (MAPK) (yi2021ribosomalproteins6 pages 6-7, yi2021ribosomalproteins6 pages 19-21). Expression studies of related kinases have shown that these enzymes are often regulated by growth factors and mitogenic signals, and their activity is associated with processes such as cell cycle progression and metabolic regulation, which underlie their potential involvement in oncogenic signaling and therapy resistance (yi2021ribosomalproteins6 pages 41-43, yi2021ribosomalproteins6 pages 43-44).
8. Other Comments  
   Pharmacological inhibitors developed for kinases with related substrate specificities—such as PF-4708671, which inhibits S6 kinase activity—provide an experimental framework that may eventually be extended to RPS6KL1; however, to date no inhibitor has been specifically characterized for RPS6KL1 (pearce2010thenutsand pages 1-2). In addition, dysregulation of kinases within the ribosomal S6 kinase family has been associated with various pathological conditions, including metabolic disorders and cancer. Several studies in the literature have demonstrated that aberrant activation of related kinases can affect pathways such as androgen receptor signaling and contribute to therapy resistance in malignancies, particularly in prostate cancer (yi2021ribosomalproteins6 pages 17-18, yi2021ribosomalproteins6 pages 53-54). While detailed mutational analyses and disease association studies specific to RPS6KL1 are currently limited, its structural and functional similarity to other clinically significant kinases suggests that further investigation may elucidate its potential as a therapeutic target.
9. References  
   • Hanks, S. K. and Hunter, T. The eukaryotic protein kinase superfamily: kinase (catalytic) domain structure and classification. The FASEB Journal, May 1995, pages 1-1, pages 3-4, pages 7-8, pages 19-20.  
   • Gógl, G., Kornev, A. P., Reményi, A., & Taylor, S. S. Disordered protein kinase regions in regulation of kinase domain cores. Trends in Biochemical Sciences, 44:300-311, Apr 2019, pages 6-8.  
   • Kurinov, I. Structural diversity of the active conformation of the n-terminal kinase domain of p90 ribosomal s6 kinase 2. Worldwide Protein Data Bank, Feb 2009, pages 1-2, pages 3-4, pages 4-6, pages 6-8, pages 8-10, pages 10-10, pages 10-11, pages 6-6.  
   • Pearce, L. R., Komander, D., & Alessi, D. R. The nuts and bolts of AGC protein kinases. Nature Reviews Molecular Cell Biology, 11:9-22, Jan 2010, pages 1-2.  
   • Yi, Y. W., You, K. S., Park, J.-S., Lee, S.-G., & Seong, Y.-S. Ribosomal protein S6: a potential therapeutic target against cancer? International Journal of Molecular Sciences, 23:48, Dec 2021, pages 6-7, pages 8-10, pages 10-11, pages 12-13, pages 13-15, pages 17-18, pages 18-19, pages 19-21, pages 22-24, pages 27-28, pages 41-43, pages 43-44, pages 53-54.  
   • Zhao, G., Wu, Y., Du, L., Li, W., Xiong, Y., Yao, A., Wang, Q., & Zhang, Y. Q. Drosophila s6 kinase like inhibits neuromuscular junction growth by downregulating the BMP receptor Thickveins. PLoS Genetics, Mar 2015, pages 2-4.

References

1. (yi2021ribosomalproteins6 pages 17-18): Yong Weon Yi, Kyu Sic You, Jeong-Soo Park, Seok-Geun Lee, and Yeon-Sun Seong. Ribosomal protein s6: a potential therapeutic target against cancer? International Journal of Molecular Sciences, 23:48, Dec 2021. URL: https://doi.org/10.3390/ijms23010048, doi:10.3390/ijms23010048. This article has 96 citations and is from a peer-reviewed journal.
2. (yi2021ribosomalproteins6 pages 6-7): Yong Weon Yi, Kyu Sic You, Jeong-Soo Park, Seok-Geun Lee, and Yeon-Sun Seong. Ribosomal protein s6: a potential therapeutic target against cancer? International Journal of Molecular Sciences, 23:48, Dec 2021. URL: https://doi.org/10.3390/ijms23010048, doi:10.3390/ijms23010048. This article has 96 citations and is from a peer-reviewed journal.
3. (gogl2019disorderedproteinkinase pages 6-8): Gergő Gógl, Alexandr P. Kornev, Attila Reményi, and Susan S. Taylor. Disordered protein kinase regions in regulation of kinase domain cores. Trends in Biochemical Sciences, 44:300-311, Apr 2019. URL: https://doi.org/10.1016/j.tibs.2018.12.002, doi:10.1016/j.tibs.2018.12.002. This article has 74 citations and is from a domain leading peer-reviewed journal.
4. (kurinov2009structuraldiversityof pages 3-4): I. Kurinov. Structural diversity of the active conformation of the n-terminal kinase domain of p90 ribosomal s6 kinase 2. Worldwide Protein Data Bank, Feb 2009. URL: https://doi.org/10.2210/pdb3g51/pdb, doi:10.2210/pdb3g51/pdb. This article has 39 citations.
5. (kurinov2009structuraldiversityof pages 4-6): I. Kurinov. Structural diversity of the active conformation of the n-terminal kinase domain of p90 ribosomal s6 kinase 2. Worldwide Protein Data Bank, Feb 2009. URL: https://doi.org/10.2210/pdb3g51/pdb, doi:10.2210/pdb3g51/pdb. This article has 39 citations.
6. (kurinov2009structuraldiversityof pages 6-8): I. Kurinov. Structural diversity of the active conformation of the n-terminal kinase domain of p90 ribosomal s6 kinase 2. Worldwide Protein Data Bank, Feb 2009. URL: https://doi.org/10.2210/pdb3g51/pdb, doi:10.2210/pdb3g51/pdb. This article has 39 citations.
7. (pearce2010thenutsand pages 1-2): Laura R. Pearce, David Komander, and Dario R. Alessi. The nuts and bolts of agc protein kinases. Nature Reviews Molecular Cell Biology, 11:9-22, Jan 2010. URL: https://doi.org/10.1038/nrm2822, doi:10.1038/nrm2822. This article has 1655 citations and is from a domain leading peer-reviewed journal.
8. (yi2021ribosomalproteins6 pages 43-44): Yong Weon Yi, Kyu Sic You, Jeong-Soo Park, Seok-Geun Lee, and Yeon-Sun Seong. Ribosomal protein s6: a potential therapeutic target against cancer? International Journal of Molecular Sciences, 23:48, Dec 2021. URL: https://doi.org/10.3390/ijms23010048, doi:10.3390/ijms23010048. This article has 96 citations and is from a peer-reviewed journal.
9. (zhao2015drosophilas6kinase pages 2-4): Guoli Zhao, Yingga Wu, Li Du, Wenhua Li, Ying Xiong, A. Yao, Qifu Wang, and Yong Q. Zhang. Drosophila s6 kinase like inhibits neuromuscular junction growth by downregulating the bmp receptor thickveins. PLoS Genetics, Mar 2015. URL: https://doi.org/10.1371/journal.pgen.1004984, doi:10.1371/journal.pgen.1004984. This article has 31 citations and is from a domain leading peer-reviewed journal.
10. (hanks1995theeukaryoticprotein pages 1-1): Steven K. Hanks and Tony Hunter. The eukaryotic protein kinase superfamily: kinase (catalytic) domain structure and classification 1. The FASEB Journal, 9:576-596, May 1995. URL: https://doi.org/10.1096/fasebj.9.8.7768349, doi:10.1096/fasebj.9.8.7768349. This article has 3994 citations.
11. (hanks1995theeukaryoticprotein pages 3-4): Steven K. Hanks and Tony Hunter. The eukaryotic protein kinase superfamily: kinase (catalytic) domain structure and classification 1. The FASEB Journal, 9:576-596, May 1995. URL: https://doi.org/10.1096/fasebj.9.8.7768349, doi:10.1096/fasebj.9.8.7768349. This article has 3994 citations.
12. (hanks1995theeukaryoticprotein pages 7-8): Steven K. Hanks and Tony Hunter. The eukaryotic protein kinase superfamily: kinase (catalytic) domain structure and classification 1. The FASEB Journal, 9:576-596, May 1995. URL: https://doi.org/10.1096/fasebj.9.8.7768349, doi:10.1096/fasebj.9.8.7768349. This article has 3994 citations.
13. (kurinov2009structuraldiversityof pages 1-2): I. Kurinov. Structural diversity of the active conformation of the n-terminal kinase domain of p90 ribosomal s6 kinase 2. Worldwide Protein Data Bank, Feb 2009. URL: https://doi.org/10.2210/pdb3g51/pdb, doi:10.2210/pdb3g51/pdb. This article has 39 citations.
14. (yi2021ribosomalproteins6 pages 19-21): Yong Weon Yi, Kyu Sic You, Jeong-Soo Park, Seok-Geun Lee, and Yeon-Sun Seong. Ribosomal protein s6: a potential therapeutic target against cancer? International Journal of Molecular Sciences, 23:48, Dec 2021. URL: https://doi.org/10.3390/ijms23010048, doi:10.3390/ijms23010048. This article has 96 citations and is from a peer-reviewed journal.
15. (yi2021ribosomalproteins6 pages 41-43): Yong Weon Yi, Kyu Sic You, Jeong-Soo Park, Seok-Geun Lee, and Yeon-Sun Seong. Ribosomal protein s6: a potential therapeutic target against cancer? International Journal of Molecular Sciences, 23:48, Dec 2021. URL: https://doi.org/10.3390/ijms23010048, doi:10.3390/ijms23010048. This article has 96 citations and is from a peer-reviewed journal.
16. (yi2021ribosomalproteins6 pages 53-54): Yong Weon Yi, Kyu Sic You, Jeong-Soo Park, Seok-Geun Lee, and Yeon-Sun Seong. Ribosomal protein s6: a potential therapeutic target against cancer? International Journal of Molecular Sciences, 23:48, Dec 2021. URL: https://doi.org/10.3390/ijms23010048, doi:10.3390/ijms23010048. This article has 96 citations and is from a peer-reviewed journal.