1. Phylogeny  
   Ribosomal protein S6 kinase alpha-1 (RPS6KA1, commonly known as RSK1) belongs to the MAPK‐activated protein kinase (MAPKAPK) family, which is a subfamily of serine/threonine kinases evolutionarily conserved across eukaryotes (cargnello2011activationandfunction pages 1-2). RSK1 is present in a wide array of species including mammals and amphibians, with orthologs identified in species such as Xenopus laevis; this conservation underscores its critical role in mitogenic and stress-induced signaling cascades (roux2004erkandp38 pages 8-9). Within the human kinome, RSK1 is grouped together with three other kinases (RSK2, RSK3, and RSK4) that have arisen from gene duplication events early in animal evolution, an event that contributed to diversification of substrate selectivity and regulatory modes (cargnello2011activationandfunction pages 1-2, roux2004erkandp38 pages 9-11). Phylogenetic analyses indicate that although RSK1 shares several common features with its paralogs, its evolutionary trajectory has rendered it somewhat distinct in its regulatory features and tissue distribution, with RSK1 being widely expressed but showing higher abundance in tissues such as kidney, lung, and pancreas (cargnello2011activationandfunction pages 1-2, thiriet2013cytoplasmicproteinserinethreonine pages 60-63). Moreover, RSK1 is part of an evolutionarily conserved core set of signaling proteins that also includes other AGC kinases such as PDK1 and AKT, all of which are integral to signal transduction pathways that originated early in eukaryotic evolution (roux2004erkandp38 pages 8-9). This core group of kinases ensures integration of mitogenic signals with cellular growth and survival responses and can be traced back to the Last Eukaryotic Common Ancestor (cargnello2011activationandfunction pages 1-2).
2. Reaction Catalyzed  
   RSK1 catalyzes a phosphorylation reaction in which a phosphate group is transferred from ATP to a serine or threonine residue on substrate proteins, thereby converting ATP into ADP and yielding a phosphorylated protein (roux2004erkandp38 pages 11-12). The canonical chemical reaction is represented as: ATP + [protein]–(L‐serine/threonine) → ADP + [protein]–(L‐serine/threonine)‐phosphate + H⁺, a reaction consistent with that catalyzed by most protein kinases (thiriet2013cytoplasmicproteinserinethreonine pages 60-63). This catalytic activity is critical for propagating signals initiated by extracellular ligands such as growth factors and stress signals that ultimately converge on transcription factors and components of the protein synthesis machinery (cargnello2011activationandfunction pages 17-18).
3. Cofactor Requirements  
   The enzymatic activity of RSK1 is ATP-dependent and requires magnesium ions (Mg²⁺) as essential cofactors, which facilitate the correct positioning of the ATP molecule in the active site and stabilize the transition state during phosphate transfer (thiriet2013cytoplasmicproteinserinethreonine pages 60-63, roux2004erkandp38 pages 11-12). The dependence on Mg²⁺ is a common feature of serine/threonine kinases, ensuring that the phosphorylation reaction proceeds with high catalytic efficiency (thiriet2013cytoplasmicproteinserinethreonine pages 60-63).
4. Substrate Specificity  
   RSK1 phosphorylates serine/threonine residues within specific consensus motifs that are often enriched in basic amino acids such as arginine or lysine near the phospho-acceptor residue. Its substrate specificity is defined by a motif that can be represented as Arg/Lys–X–Arg–X–X–p[Ser/Thr], where the presence of basic residues at positions –3 and –2 relative to the phosphorylated serine or threonine is critical for efficient substrate recognition (cargnello2011activationandfunction pages 12-13, wajrt2023therapeutictargetingof pages 15-15). RSK1 exhibits a marked preference for phosphorylating serine over threonine, with quantitative analyses indicating a roughly fivefold higher catalytic preference for serine phosphorylation (cargnello2011activationandfunction pages 13-15). In cellular contexts, RSK1 phosphorylates numerous substrates including transcription factors such as CREB1, ETS family proteins such as ETV1/ER81, the orphan nuclear receptor NR4A1/NUR77, as well as components of the translational machinery like ribosomal protein S6 (RPS6) and eukaryotic initiation factor 4B (EIF4B) (arul2013arisingcancer pages 9-10, wright2023therapeutictargetingof pages 15-15). The specificity conferred by these motifs ensures that the phosphorylation events directly modulate processes such as immediate-early gene expression, translation initiation, and cell cycle progression (cargnello2011activationandfunction pages 12-13).
5. Structure  
   RSK1 possesses a unique bipartite architecture that consists of two distinct kinase domains within a single polypeptide chain. The structure is organized with an N-terminal kinase domain (NTKD), which belongs to the AGC kinase family and is primarily responsible for the phosphorylation of downstream substrates, and a C-terminal kinase domain (CTKD) that is structurally related to calcium/calmodulin-dependent kinases (CAMK) and plays a critical role in the autophosphorylation events required for full activation (cargnello2011activationandfunction pages 13-15, thiriet2013cytoplasmicproteinserinethreonine pages 63-66). These two domains are connected by a flexible linker region that contains several regulatory phosphorylation sites; phosphorylation within this linker not only contributes to the activation of the NTKD by facilitating the recruitment of phosphoinositide-dependent kinase-1 (PDK1) but also serves as a docking platform for upstream kinases such as ERK1/2 (roux2004erkandp38 pages 8-9, cargnello2011activationandfunction pages 27-27). In addition to the catalytic kinase domains, RSK1 contains motifs that mediate interactions with regulatory proteins. For instance, it possesses an ERK docking (D) domain that is essential for its phosphorylation by ERK1/2, and its regulatory regions include nuclear localization signals (NLS) that contribute to its dynamic subcellular localization in response to mitogenic stimuli (roux2004erkandp38 pages 8-9, cargnello2011activationandfunction pages 27-28). Although high-resolution crystal structures have been reported for closely related isoforms such as RSK2, homology modeling and experimental evidence indicate that RSK1 exhibits similar overall domain organization with conserved activation loops, a hydrophobic spine, and a regulatory C-helix that are critical for its activity (wright2023therapeutictargetingof pages 11-12, cargnello2011activationandfunction pages 13-15).
6. Regulation  
   RSK1 is tightly regulated by a cascade of phosphorylation events that are initiated by extracellular signals leading to activation of the ERK1/2 MAPK pathway. Upon growth factor stimulation, ERK1/2 docks to RSK1 via the ERK docking domain and phosphorylates residues located primarily in the CTKD activation loop. This phosphorylation event triggers autophosphorylation within the linker region of RSK1 and generates a binding site for PDK1, which in turn phosphorylates the activation loop of the NTKD, culminating in full kinase activation (cargnello2011activationandfunction pages 12-13, roux2004erkandp38 pages 11-12). In addition to phosphorylation by ERK1/2 and PDK1, RSK1 is subject to further regulation through association with regulatory proteins such as 14-3-3, which bind to phosphorylated sites and modulate both its catalytic activity and subcellular localization (roux2004erkandp38 pages 21-21, thiriet2013cytoplasmicproteinserinethreonine pages 63-66). These phosphorylation events occur sequentially and are highly coordinated; key phospho-acceptor sites within the CTKD and the linker region are requisite for subsequent NTKD activation and substrate phosphorylation (cargnello2011activationandfunction pages 17-18, wright2023therapeutictargetingof pages 11-12). The dynamic regulation of RSK1 by phosphorylation provides multiple nodes for modulation, ensuring that its activity is coupled precisely to the intensity and duration of upstream ERK signaling (roux2004erkandp38 pages 9-11).
7. Function  
   RSK1 functions as a critical mediator of the ERK/MAPK signaling cascade, translating extracellular mitogenic and stress signals into diverse cellular responses. It phosphorylates an array of substrates that include transcription factors, translation regulators, and proteins involved in cell cycle control. Specifically, RSK1 activates transcription factors such as CREB1, ETV1/ER81, and NR4A1/NUR77, thereby promoting the transcription of immediate-early genes that are essential for cell proliferation and differentiation (arul2013arisingcancer pages 9-10, cargnello2011activationandfunction pages 17-18). In fibroblasts, RSK1 is indispensable for EGF-stimulated phosphorylation of CREB1, leading to the expression of genes required for mitogenic responses (arul2013arisingcancer pages 2-3). Beyond transcriptional regulation, RSK1 phosphorylates components of the translational machinery such as ribosomal protein S6 (RPS6) and eukaryotic initiation factor 4B (EIF4B), thereby modulating protein synthesis and contributing to cell growth and survival (wright2023therapeutictargetingof pages 15-15, cargnello2011activationandfunction pages 27-28). Moreover, RSK1 influences signaling pathways that control cellular survival and apoptosis; it exerts anti-apoptotic effects by phosphorylating and inhibiting pro-apoptotic proteins such as BAD and DAPK1, and it interfaces with mTOR signaling pathways to regulate differentiation and metabolic responses (arul2013arisingcancer pages 9-10, wright2023therapeutictargetingof pages 14-14). Thus, RSK1 operates at the nexus of transcriptional and translational control mechanisms and is pivotal in the regulation of cell proliferation, survival, and differentiation, making it a key effector in both normal physiology and pathological conditions such as cancer (cargnello2011activationandfunction pages 16-17, wright2023therapeutictargetingof pages 3-4).
8. Other Comments  
   Several small molecule inhibitors targeting RSK kinases have been identified in the context of cancer therapeutics. Inhibitors such as SL0101 and BI-D1870 have been used experimentally to block RSK activity, although their isoform selectivity is limited due to the high structural homology among RSK isoforms (wright2023therapeutictargetingof pages 11-12, wright2023therapeutictargetingof pages 14-14). Moreover, covalent inhibitors targeting the C-terminal kinase domain, such as fluoromethylketone (FMK), have been described, offering irreversible inhibition of RSK activity (wright2023therapeutictargetingof pages 9-11). Preclinical studies of inhibitors like PMD-026, which is currently being evaluated in clinical trials for metastatic breast cancer, underscore the therapeutic potential of RSK inhibition in oncogenic settings (wright2023therapeutictargetingof pages 14-15, d’incal2022towardskinaseinhibitor pages 28-29). RSK1 dysregulation has been observed in a number of cancers, including breast, lung, and skin cancers, where aberrant ERK/RSK signaling contributes to enhanced cellular proliferation, survival, and resistance to apoptosis (arul2013arisingcancer pages 10-10, wright2023therapeutictargetingof pages 15-15). Given this clinical relevance, RSK1 is a promising target for the development of novel anticancer strategies, and ongoing efforts are focused on improving inhibitor specificity and potency to mitigate off-target effects (d’incal2022towardskinaseinhibitor pages 29-31).
9. References  
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