1. Phylogeny  
   Serine/threonine‐protein kinase H1 (PSKH1; UniProt P11801) is a member of the eukaryotic protein kinase (ePK) superfamily and is categorically placed within the serine/threonine kinases. Several studies have placed PSKH1 in the Ca²⁺/calmodulin–dependent kinase (CAMK) branch based on its sequence characteristics. Notably, Brede et al. demonstrated considerable sequence similarity between PSKH1 and members of the CaMK family – with approximately 50% identity in the catalytic domain relative to rat CaMKI – and assigned it to a unique subfamily within the serine/threonine kinases (brede2000characterizationofpskh1 pages 3-6). In addition, phylogenetic analyses have revealed that although PSKH1 is conserved across certain vertebrate lineages, it is absent from the mouse kinome, suggesting a lineage-specific gene loss in the rodent branch (caenepeel2004themousekinome pages 2-3). Cataloguing efforts by Shrestha et al. further corroborate that PSKH1 represents a canonical active kinase in vertebrates while being distinct from its close paralog, the pseudokinase PSKH2 (shrestha2020cataloguingthedead pages 12-14). Collectively, this pattern of conservation and selective loss places PSKH1 in an evolutionary context as part of an ancient CAMK-related module within the human kinome (manning2010eukaryotickinomesgenomics pages 1-2).
2. Reaction Catalyzed  
   PSKH1 catalyzes the transfer of a phosphate group from ATP to target proteins on serine or threonine residues. The reaction can be summarized as:  
   ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺ (anti2009nonspecificserinethreonineprotein pages 1-7).
3. Cofactor Requirements  
   The catalytic activity of PSKH1, like that of many serine/threonine kinases, requires the presence of divalent metal ion cofactors. In particular, the enzyme’s activity is dependent on Mg²⁺, which coordinates with the phosphate groups of ATP to facilitate phosphoryl transfer (anti2009nonspecificserinethreonineprotein pages 1-7).
4. Substrate Specificity  
   The substrate specificity of PSKH1 is functionally linked to its role in regulating pre-mRNA processing. PSKH1 is implicated in phosphorylating components of nuclear splice factor compartments, notably non-snRNP splicing factors that contain serine/arginine-rich (SR) domains. The reversible phosphorylation of these SR proteins modulates their intranuclear distribution, thereby influencing alternative splicing decisions. Although a precise consensus substrate motif has not been defined for PSKH1, the evidence points toward its preferential activity on substrates enriched for serine/arginine repeats (berson1999identificationandcharacterization pages 4-5, shrestha2020cataloguingthedead pages 12-14).
5. Structure  
   PSKH1 is a relatively small kinase, comprising approximately 305 amino acids. Its domain organization features an amino-terminal segment of 19 residues that includes multiple potential fatty acylation sites—a myristoylation site at glycine 2 and palmitoylation sites at cysteines 6 and 8—which are flanked by basic residues that resemble membrane-targeting SH4 domains (berson1999identificationandcharacterization pages 4-5). The catalytic domain of PSKH1 spans roughly residues ~20 to 294 and exhibits the 12 conserved kinase subdomains typical of active serine/threonine kinases. Key catalytic residues within this domain include lysine at position 49, which is essential for ATP binding, and histidine at position 146, with the conserved APE motif commencing at alanine 200. Such features support a canonical active fold with an N-terminal β-sheet rich lobe and a C-terminal α-helical lobe, forming a catalytic cleft. The overall structural organization, largely derived from experimental studies and bioinformatics predictions, indicates that the intrinsically disordered regions are minimal, with the majority of the protein comprising the conserved catalytic machinery necessary for phosphotransfer (berson1999identificationandcharacterization pages 4-5).
6. Regulation  
   The regulatory mechanisms of PSKH1 are multi-faceted. A unique characteristic of PSKH1 is its post-translational modification via dual fatty acylation. The myristoylation at glycine 2 is obligatory for subsequent palmitoylation at cysteines 6 and 8; these lipid modifications are critical for targeting PSKH1 to membrane compartments (berson1999identificationandcharacterization pages 4-5). In cellular expression systems, kinase assays have demonstrated that PSKH1 is capable of autophosphorylation primarily on threonine residues, and it also phosphorylates exogenous substrates such as PHAS-I. Furthermore, PSKH1’s regulation does not appear to involve a classical calmodulin-binding domain, although a stretch resembling a CaMKI calmodulin-binding motif is present in the N-terminal region, as noted in the detailed characterization reports (brede2000characterizationofpskh1 pages 3-6, shrestha2020cataloguingthedead pages 12-14). Taken together, these findings indicate that the regulatory state of PSKH1 is controlled by a combination of lipid-mediated membrane association and phosphorylation-dependent modulation of its catalytic activity.
7. Function  
   PSKH1 functions as a serine/threonine protein kinase involved in the regulation of pre-mRNA processing. Specifically, it is proposed to phosphorylate components of nuclear splice factor compartments, notably SR proteins that possess serine/arginine-rich domains. The reversible phosphorylation of these splicing factors is thought to modulate their release into the nucleoplasm, thereby altering their local concentration and influencing alternative splicing decisions. This role places PSKH1 at a crucial nodal point linking post-transcriptional regulation to broader gene expression programs. In addition, PSKH1 has been reported to exhibit a distinct subcellular distribution; several studies associate it with membrane structures such as the Golgi apparatus owing to its validated membrane-targeting motif generated by its acyl modifications (shrestha2020cataloguingthedead pages 12-14). Although the precise substrates of PSKH1 in vivo and its integration into signaling cascades are still being elucidated, the available data underscore its involvement in nuclear RNA processing and potentially in the regulation of alternative splicing events (berson1999identificationandcharacterization pages 4-5).
8. Other Comments  
   PSKH1 is catalogued under the Enzyme Commission number EC 2.7.11.1, which includes non-specific serine/threonine protein kinases. It has been referred to as Protein serine kinase H1 in alternative nomenclature systems. The absence of PSKH1 from the mouse kinome—as shown in comprehensive kinome comparisons—further highlights an interesting case of lineage-specific gene loss in rodents (caenepeel2004themousekinome pages 2-3). Moreover, while PSKH1 has not been extensively linked to specific disease states in the available literature, its role in the regulation of alternative splicing posits a potential involvement in conditions where splicing misregulation is a hallmark. No well-characterized inhibitors have been reported exclusively targeting PSKH1 at this time; however, its classification within the serine/threonine kinase family suggests that inhibitors developed against similar kinases may provide a starting point for probing its function. The convergence of post-translational acylation events and phosphorylation-based regulation in PSKH1 underscores its potential as a modulator of pre-mRNA processing and cellular localization dynamics (berson1999identificationandcharacterization pages 4-5, shrestha2020cataloguingthedead pages 12-14).
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