1. Phylogeny  
   Serine/threonine‐protein kinase 32C (STK32C), also known as YANK3 or PKE (“Yet another novel kinase 3”), is a member of the STK32 family of kinases, which comprises three closely related paralogues: STK32A, STK32B, and STK32C (sorrell2020stk32aisa pages 1-5). STK32C is classified within the broad AGC kinase group and, like other Hanks-type serine/threonine kinases, shares a common catalytic domain architecture characteristic of this superfamily (janczarek2018hankstypeserinethreonineprotein pages 8-10). Phylogenetic analysis indicates that among the STK32 family members, STK32C is the most recently evolved isoform and is found exclusively in bony vertebrates, whereas STK32A is conserved across opisthokonts and STK32B appears later in bilateral animals (sorrell2020stk32aisa pages 1-5). Sequence alignments reveal that STK32C shares approximately 65–67% identity in its kinase domain with its closest paralogs, while exhibiting only about 36% sequence identity when compared with other human AGC kinases outside the family (sorrell2020stk32aisa pages 1-5). This evolutionary context places STK32C within a lineage of kinases that have diverged to acquire distinct regulatory and substrate recognition features relative to the classical AGC kinases (sorrell2020stk32aisa pages 15-18).
2. Reaction Catalyzed  
   STK32C catalyzes the transfer of the γ‐phosphate from adenosine triphosphate (ATP) to the hydroxyl group of serine or threonine residues on protein substrates, resulting in the production of adenosine diphosphate (ADP) and a phosphoprotein bearing a phosphoserine or phosphothreonine residue, along with the release of a proton (han2012comprehensivephosphoproteomeanalysis pages 11-12).
3. Cofactor Requirements  
   The catalytic activity of STK32C, in common with other serine/threonine kinases, is dependent on the presence of divalent metal cations. Mg²⁺ is the primary cofactor required for efficient ATP binding and phosphoryl transfer, while experimental assays using related STK32 family members have demonstrated that Mn²⁺ can enhance phosphorylation efficiency under certain conditions (sorrell2020stk32aisa pages 7-10).
4. Substrate Specificity  
   Experimental substrate profiling of the STK32 family, particularly of the STK32A isoform, has shown a strong preference for acidic peptide substrates. The consensus substrate motifs identified for STK32A include the enrichment of aspartate (D) and glutamate (E) residues at positions P‑4, P+1, P+2, and P+3 relative to the phosphorylated serine or threonine residue (sorrell2020stk32aisa pages 7-10). Although detailed substrate specificity assays have not been directly reported for STK32C, the high degree of conservation in substrate-binding residues—such as the basic residues that line the binding groove—across STK32 family members suggests that STK32C likely exhibits a similar acidophilic substrate preference (sorrell2020stk32aisa pages 12-15). This inferred substrate motif is consistent with the dual-specificity nature observed in the family, where phosphorylation of serine/threonine residues is prominent and the presence of adjacent acidic residues facilitates substrate recognition (sorrell2020stk32aisa pages 7-10).
5. Structure  
   Although no experimentally solved three-dimensional structure exists exclusively for STK32C, the extensive structural characterization of its close family member STK32A provides a robust framework for inferring the structural features of STK32C. Like other AGC kinases, STK32C is predicted to possess a central catalytic kinase domain arranged in a two-lobed configuration. The N-terminal lobe typically comprises five β-strands and a conserved αC-helix, whereas the larger C-terminal lobe is predominantly α-helical and contains the activation loop essential for substrate binding and catalysis (sorrell2020stk32aisa pages 10-12). Key catalytic features, such as the ATP-binding site, are conserved; notably, the presence of a small valine gatekeeper residue in the ATP-pocket is shared among STK32 isoforms, forming an enlarged inhibitor-binding pocket (sorrell2020stk32aisa pages 15-18). In addition, the C-terminal hydrophobic or “HF” motif, which in canonical AGC kinases normally contains a phosphorylatable serine or threonine residue, is altered in STK32 kinases; in STK32A the motif conforms to an F–X–X–F–N–R sequence and lacks the classic activating phospho-acceptor residue, and by sequence conservation, a similar non-canonical HF motif is expected for STK32C (sorrell2020stk32aisa pages 10-12, sorrell2020stk32aisa pages 12-15). Furthermore, STK32C isoform 1 is distinguished by an extended 67-residue N-terminal region rich in proline, alanine, arginine, and serine residues, which is predicted to be intrinsically disordered and may serve regulatory functions, although its precise structural role remains to be elucidated (sorrell2020stk32aisa pages 1-5). Overall, the predicted three-dimensional organization for STK32C encompasses a well-folded kinase core with the classical AGC fold, along with unique structural adaptations in the hydrophobic motif and N-terminal extension that may underlie its specific regulatory features (sorrell2020stk32aisa pages 15-18, janczarek2018hankstypeserinethreonineprotein pages 8-10).
6. Regulation  
   Regulatory mechanisms for STK32C have not been extensively characterized; however, several lines of experimental evidence provide insight into its post-translational modification profile. In phosphoproteomic analyses performed on INS-1 pancreatic beta-cells, STK32C was identified with a phosphorylation event at serine 18 (S18), which has been experimentally verified by mass spectrometry (han2012comprehensivephosphoproteomeanalysis pages 11-12). Information derived from studies on the closely related STK32A suggests that autophosphorylation events are a common regulatory mechanism within the STK32 family, with multiple serine, threonine, and tyrosine residues undergoing modification in vitro (sorrell2020stk32aisa pages 7-10). Although detailed mapping of other post-translational modifications such as ubiquitination has not been reported for STK32C, the conservation of key kinase regulatory domains implies that its activity may be modulated by phosphorylation-dependent conformational changes and potential interactions with upstream kinases or phosphatases (sorrell2020stk32aisa pages 1-5). Thus, the available data indicate that phosphorylation is the primary post-translational regulator observed for STK32C, with the S18 site representing one of the few experimentally verified modifications at this time (han2012comprehensivephosphoproteomeanalysis pages 11-12).
7. Function  
   STK32C is expressed ubiquitously in human tissues, and its pattern of expression within the STK32 kinase family appears to be less tissue-restricted than that of STK32A or STK32B (sorrell2020stk32aisa pages 1-5). Functional studies, primarily utilizing genetic and phosphoproteomic approaches, have implicated STK32 family members in a range of cellular processes. In pancreatic beta-cells, STK32C was identified as being phosphorylated at S18, providing biochemical evidence of its kinase activity in an endocrine context (han2012comprehensivephosphoproteomeanalysis pages 11-12). In addition, knockout mouse models for STK32C have demonstrated abnormal locomotor behavior, and genetic association studies have linked polymorphisms and epigenetic modifications in STK32C with neuropsychiatric conditions, including adolescent depression and psychiatric risk in Down Syndrome patients (sorrell2020stk32aisa pages 1-5). These findings suggest that STK32C may play a role in signaling pathways that affect neural function and behavior, although precise downstream substrates and interacting partners have not been fully delineated. The kinase’s inclusion in inhibitor screening panels, in which STK32 family members have shown binding to several clinically used kinase inhibitors, further supports a functional role in modulating cellular signaling networks in diverse tissue types (sorrell2020stk32aisa pages 15-18).
8. Other Comments  
   In biochemical inhibitor screening studies, members of the STK32 family have demonstrated binding affinity for a range of clinically relevant kinase inhibitors, including compounds developed for analogue-sensitive kinases such as 1NM-PP1 and PP-121; this binding is attributed to the conserved small valine gatekeeper residue that creates an enlarged ATP-binding pocket (sorrell2020stk32aisa pages 15-18). STK32C is also annotated in phosphoproteomic studies, ensuring its status as an active serine/threonine kinase, although specific inhibitors or detailed medicinal chemistry studies focused on STK32C have not been reported in the available literature. In addition, data from functional genetic screens, including those available on the Open Targets platform, indicate associations between STK32C and neurodegenerative as well as neuropsychiatric conditions, with evidence derived from genome-wide association studies and CRISPR interference screens performed in neuronal and microglial cell lines (OpenTargets Search: -STK32C). No disease-relevant mutations or reports of ubiquitination have been experimentally established for STK32C in the current corpus of peer-reviewed literature. STK32C displays alternative nomenclature, being referred to as YANK3, further emphasizing its placement within the STK32 kinase family (sorrell2020stk32aisa pages 1-5).
9. References
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