1. Phylogeny  
   Serine/threonine‐protein kinase SIK3 is a member of the salt‐inducible kinases (SIKs) that belong to the AMP‐activated protein kinase (AMPK)–related kinase family, an evolutionarily conserved group present from invertebrates to mammals. Human SIK3 (also known as QSK or KIAA0999, UniProt ID Q9Y2K2) is phylogenetically related to SIK1 and SIK2, and orthologs of SIK3 have been identified in species as divergent as Drosophila (dSIK3) and Caenorhabditis elegans (KIN-29), underscoring its conservation in metazoans (feng2023rolesofsalt‑inducible pages 1-2, lones2022sik3&wnk pages 17-21). These kinases are activated by liver kinase B1 (LKB1) and are part of an ancient regulatory network that appears to have emerged in the Last Eukaryotic Common Ancestor and was later diversified through gene duplication events (walkinshaw2011histonedeacetylaseregulation pages 112-118). Thus, SIK3 occupies a central position within the core set of kinases that coordinate energy-sensing and stress-response pathways in eukaryotic cells (feng2023rolesofsalt‑inducible pages 1-2, walkinshaw2011histonedeacetylaseregulation pages 112-118).
2. Reaction Catalyzed  
   SIK3 catalyzes the phosphorylation of target proteins by transferring the γ-phosphate from adenosine triphosphate (ATP) to specific serine or threonine residues on substrate proteins. The chemical reaction can be described by the equation:  
     ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺  
   This phosphorylation reaction is critical for converting substrate proteins into their active or inactive forms, thereby modulating downstream signaling cascades (oster2024thestructuresof pages 1-2, thiriet2013cytoplasmicproteinserinethreonine pages 76-78).
3. Cofactor Requirements  
   The catalytic activity of SIK3 is dependent on divalent metal ions, with magnesium (Mg²⁺) being the essential cofactor required for its kinase function. Mg²⁺ ions assist in the proper orientation of ATP within the active site of the kinase domain, enabling efficient phosphoryl transfer to the substrate (oster2024thestructuresof pages 1-2, thiriet2013cytoplasmicproteinserinethreonine pages 76-78).
4. Substrate Specificity  
   SIK3 displays substrate specificity that is in line with its classification as an AMPK-related kinase. It preferentially phosphorylates substrates that play roles in transcription and metabolic regulation. One well‐characterized substrate group for SIK kinases is the class IIa histone deacetylases (HDACs), particularly HDAC4, whose phosphorylation results in enhanced binding to 14-3-3 proteins and subsequent retention in the cytoplasm. This action prevents HDAC4 from translocating to the nucleus where it can repress gene transcription (walkinshaw2011histonedeacetylaseregulation pages 112-118, thiriet2013cytoplasmicproteinserinethreonine pages 76-78). In addition, SIK3 is thought to modulate the activity of the CREB-regulated transcription coactivators CRTC2/TORC2 and CRTC3/TORC3, thereby contributing to the negative regulation of the cAMP signaling pathway. Although an explicit consensus phosphorylation motif for SIK3 has not been conclusively defined in the literature provided, the substrate recognition of SIK3 is presumed to be similar to other AMPK-related kinases, which often favor sequences that enable 14-3-3 docking following phosphorylation (banerjee2013phosphorylationubiquitylationand pages 35-39, hsu2022identifyingsignalingand pages 66-72).
5. Structure  
   The three-dimensional structure of SIK3 is organized into multiple functional domains that collectively mediate its catalytic and regulatory functions. The protein contains an N-terminal kinase domain, which roughly spans residues 66–317, and exhibits a bilobal architecture with an N-terminal lobe primarily composed of β-sheets and a C-terminal lobe dominated by α-helices. Within this catalytic core, key features such as the phosphate-binding P-loop, the DFG motif that coordinates magnesium ions, the hinge region involved in ATP binding, and the αC-helix responsible for aligning catalytic residues are present (shi2023interactionsbetweencurcumin pages 1-2, oster2024thestructuresof pages 1-2). Immediately C-terminal to the kinase domain lies a ubiquitin-associated (UBA) domain, which is implicated in maintaining the proper conformation of the kinase and may play a role in mediating interactions with regulatory proteins (feng2023rolesofsalt‑inducible pages 1-2). A particularly distinctive structural feature of SIK3 is its markedly long C-terminal tail, which is considerably extended relative to SIK1 and SIK2, and is believed to contribute to isoform-specific regulatory inputs or subcellular targeting (oster2024thestructuresof pages 2-3, walkinshaw2011histonedeacetylaseregulation pages 112-118). The activation loop, containing the conserved threonine residue (Thr221 in SIK3), is a critical regulatory element; phosphorylation at this site by LKB1 is required for full catalytic activation (feng2023rolesofsalt‑inducible pages 1-2, mannion2016identifyingnovelsubstrates pages 19-22). Overall, this multi-domain architecture underpins SIK3’s ability to integrate various regulatory signals while carrying out its kinase function.
6. Regulation  
   The regulation of SIK3 is multifactorial and involves several post-translational modifications and protein–protein interactions that modulate its activity. A primary regulatory mechanism is the phosphorylation of the activation loop at Thr221 by liver kinase B1 (LKB1), which is essential for SIK3 activation and catalytic competence (feng2023rolesofsalt‑inducible pages 1-2, mannion2016identifyingnovelsubstrates pages 19-22). In addition to LKB1-dependent activation, SIK3 is negatively regulated by the cAMP-dependent protein kinase A (PKA) pathway. PKA can phosphorylate SIK3, leading to an inhibition of its kinase activity and altering its subcellular localization (hsu2022identifyingsignalingand pages 66-72, walkinshaw2011histonedeacetylaseregulation pages 112-118). The phosphorylated SIK3 is capable of binding to 14-3-3 proteins, which further sequester both the kinase and its substrates in the cytoplasm, thus affecting downstream signaling events. Extracellular stimuli such as high salt concentrations and inflammatory cytokines have been shown to upregulate SIK3 expression and promote its activation, thereby linking its regulatory circuit to environmental stress and inflammatory responses (feng2023rolesofsalt‑inducible pages 1-2, feng2023rolesofsalt‑inducible pages 8-10). Moreover, studies have demonstrated that kinase-dead mutants of SIK3 can still induce nuclear export of class IIa HDACs, indicating that some functions of SIK3 may be mediated by scaffolding or regulatory domain interactions independent of catalytic activity (walkinshaw2011histonedeacetylaseregulation pages 138-142). Collectively, these regulatory mechanisms ensure that SIK3 activity is finely tuned by a dynamic interplay among LKB1 phosphorylation, PKA-dependent inhibition, and 14-3-3–mediated subcellular targeting.
7. Function  
   SIK3 plays a central role in modulating several critical cellular pathways. One of its primary functions is to act as a positive regulator of mTOR signaling by promoting the degradation of DEPTOR, an endogenous inhibitor of mTOR, thereby enhancing mTOR activity during chondrocyte differentiation in skeletogenesis. This function is vital for the dynamic regulation of mTOR signaling and proper skeletal development as delineated in the provided protein function information. In addition, SIK3 negatively regulates the cAMP signaling pathway by modulating the phosphorylation state of the CREB-regulated transcription coactivators, such as CRTC2/TORC2 and CRTC3/TORC3. This regulatory action results in the attenuation of CREB-mediated transcription and contributes to the control of cellular metabolic programs (feng2023rolesofsalt‑inducible pages 7-8, hsu2022identifyingsignalingand pages 23-30). Furthermore, by phosphorylating class IIa histone deacetylases, particularly HDAC4, SIK3 prevents these inhibitors of transcription from translocating into the nucleus, thereby influencing gene expression programs that govern cell cycle progression and differentiation (walkinshaw2011histonedeacetylaseregulation pages 112-118, thiriet2013cytoplasmicproteinserinethreonine pages 76-78). In cancer models, SIK3 has been shown to promote tumor cell proliferation by modulating oncogenic signaling pathways; for example, its interactions with the Akt and c-Src pathways facilitate the upregulation of cyclins and the downregulation of cell cycle inhibitors, thus propelling cells through the G1/S transition (feng2023rolesofsalt‑inducible pages 7-8, feng2023rolesofsalt‑inducible pages 8-10). Additionally, SIK3 is expressed ubiquitously, with the highest levels reported in the brain, and its broad expression pattern underscores its involvement in diverse biological processes, including metabolic regulation, differentiation, and stress responses (feng2023rolesofsalt‑inducible pages 1-2, lones2022sik3&wnk pages 17-21).
8. Other Comments  
   Experimental studies employing small molecule inhibitors have provided insights into SIK3 function. Pan-SIK inhibitors such as HG-9-91-01 and YKL-05-099 have been utilized in research settings to dissect the roles of SIK isoforms, and there are reports that pharmaceutical entities have developed SIK3-selective inhibitors that modulate inflammatory biomarkers (oster2024thestructuresof pages 2-3, feng2023rolesofsalt‑inducible pages 8-10). Dysregulation of SIK3 is associated with pathological states; its overactive function has been linked to enhanced cell cycle progression and tumor promotion in various cancers, including breast and ovarian cancer, whereas disruption of its regulatory mechanisms can adversely affect mTOR signaling and chondrocyte differentiation (feng2023rolesofsalt‑inducible pages 7-8, feng2023rolesofsalt‑inducible pages 8-10). Moreover, SIK3’s involvement in controlling cAMP-responsive transcription suggests potential roles in metabolic and cardiac disorders, as studies have reported that perturbations in cAMP and HDAC signaling pathways contribute to conditions such as cardiac hypertrophy and insulin resistance (hsu2022identifyingsignalingand pages 72-77). No SIK3-specific inhibitors have yet reached clinical approval, but the continued refinement of kinase inhibitors and the development of isoform-selective compounds may eventually provide therapeutic avenues targeting SIK3 in various disease contexts (banerjee2013phosphorylationubiquitylationand pages 35-39).
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