1. Phylogeny  
   SIK1B (UniProt A0A0B4J2F2) is a member of the salt‑inducible kinase (SIK) family, which itself is classified within the AMP‑activated protein kinase (AMPK)–related kinase family that shares an evolutionary origin dating back to the last common eukaryotic ancestor, as seen with many enzymes of the AMPK group (darling2021nutsandbolts pages 1-2). SIK1B originated through a recent gene duplication of SIK1 on human chromosome 21 and is distinguished from SIK1 by a single amino acid substitution (Ala615Val), a difference that has been maintained despite the overall widely conserved domain architecture among the SIK isozymes (darling2021nutsandbolts pages 1-2). Unlike SIK1, SIK2, and SIK3, which possess clearly identifiable orthologs in both vertebrate and invertebrate species, SIK1B appears to be a human‑specific isoform with no clearly detectable orthologs in lower vertebrates or other taxa, thereby establishing it as an “orphan” kinase from a comparative evolutionary standpoint (huang2021illuminatingunderstudiedkinases pages 51-54). In phylogenetic analyses that group kinases on the basis of their catalytic domains and regulatory motifs, SIK1B is grouped alongside its paralog SIK1, sharing the signature features common to AMPK‑related kinases despite its taxonomically restricted occurrence (darling2021nutsandbolts pages 1-2, darling2021nutsandbolts pages 18-19). This evolutionary relationship is further supported by comparative sequence analyses that demonstrate high conservation of critical catalytic residues, notably the activation loop threonine required for LKB1‑mediated activation, underscoring the common catalytic framework among the SIK family members (darling2021nutsandbolts pages 2-4). Overall, the presence of SIK1B only in humans and its close sequence similarity to SIK1 emphasize a relatively recent evolutionary event and suggest the possibility of specialized roles in human physiology (darling2021nutsandbolts pages 1-2, huang2021illuminatingunderstudiedkinases pages 51-54).
2. Reaction Catalyzed  
   Similar to other serine/threonine kinases, SIK1B catalyzes the transfer of a phosphate group from adenosine triphosphate (ATP) to specific serine or threonine residues on target substrates, thereby modulating their function (darling2021nutsandbolts pages 2-4). The chemical reaction can be formally described as follows: ATP + [protein]–(L‑serine or L‑threonine) → ADP + [protein]–(L‑serine/threonine)‑phosphate + H⁺, a reaction that is typical for kinases in the AMPK family (darling2021nutsandbolts pages 16-18). This phosphotransferase activity is central to SIK1B’s role in modulating downstream signaling by altering the phosphorylation state of substrates that are critical for transcriptional regulation (darling2021nutsandbolts pages 2-4).
3. Cofactor Requirements  
   The catalytic activity of SIK1B, like that of most serine/threonine kinases, is dependent on the presence of divalent metal ions that serve as essential cofactors; in this case, magnesium ions (Mg²⁺) are required to facilitate the proper binding and orientation of ATP within the active site (darling2021nutsandbolts pages 2-4). The binding of Mg²⁺ helps to lower the activation energy for the phosphoryl transfer reaction and stabilizes the formation of the nucleotide–metal complex during catalysis (darling2021nutsandbolts pages 1-2). Therefore, Mg²⁺ is indispensable for the efficient catalytic turnover of SIK1B as it transfers the γ‑phosphate from ATP to designated serine/threonine residues on substrate proteins (darling2021nutsandbolts pages 2-4).
4. Substrate Specificity  
   SIK1B is expected to share the substrate specificity common to SIK family kinases, preferentially phosphorylating serine/threonine residues that are situated within specific consensus sequence motifs present on substrates such as CREB‑regulated transcriptional coactivators (CRTCs) and class 2a histone deacetylases (HDACs) (darling2021nutsandbolts pages 1-2). Phosphorylation by SIK1B marks these substrates for binding by 14‑3‑3 adaptor proteins, a regulatory mechanism that results in their sequestration to the cytoplasm and consequent modulation of their nuclear functions (darling2021nutsandbolts pages 4-6). Although high‑throughput specificity profiling studies have primarily focused on the broader SIK family, the available evidence indicates that the consensus phosphorylation motifs recognized by these kinases are characterized by serine or threonine residues flanked by basic residues, thereby facilitating 14‑3‑3 interactions (darling2021nutsandbolts pages 2-4, darling2021nutsandbolts pages 12-14). In this context, SIK1B’s substrate specificity is inferred to be largely analogous to that of SIK1, focusing on substrates that participate in controlling metabolic, inflammatory, and circadian rhythm‑associated gene expression patterns (darling2021nutsandbolts pages 18-19).
5. Structure  
   The structural organization of SIK1B is defined by a canonical topology that is shared with other members of the SIK and, more broadly, AMPK‑related kinase families (darling2021nutsandbolts pages 1-2). At the N‑terminus, SIK1B contains a protein kinase domain that exhibits the typical bilobal structure of eukaryotic kinases, comprising a smaller N‑lobe predominantly involved in nucleotide binding and a larger C‑lobe that facilitates substrate binding and catalysis (darling2021nutsandbolts pages 2-4). Within this kinase domain, key catalytic features are present, including the glycine‑rich loop, the conserved catalytic loop containing the HRD motif, the DFG motif necessary for coordination of Mg²⁺ and ATP, and an activation loop whose phosphorylation by LKB1 is essential for full enzymatic activity (darling2021nutsandbolts pages 2-4, darling2021nutsandbolts pages 19-20). Immediately following the kinase domain is a ubiquitin‑associated (UBA) domain, which, while not directly catalytic, is implicated in enhancing the proper folding and possibly substrate recognition through protein–protein interactions (darling2021nutsandbolts pages 1-2). The C‑terminal region of SIK1B is characterized by a long, intrinsically disordered tail that contains multiple phosphorylation sites; this region mediates regulation via phosphorylation by PKA, resulting in the recruitment of 14‑3‑3 proteins and consequent cytoplasmic localization (darling2021nutsandbolts pages 1-2, darling2021nutsandbolts pages 4-6). Notably, the only sequence difference between SIK1B and SIK1 is an Ala615 to Val substitution, a change located within the C‑terminal region that may subtly affect local structural dynamics but does not disrupt the overall domain architecture (darling2021nutsandbolts pages 1-2, darling2021nutsandbolts pages 14-15). Computational models, including those generated via AlphaFold2, corroborate this domain arrangement and indicate that SIK1B adopts an active conformation that preserves the critical features of the catalytic apparatus, such as the well‑ordered activation loop and the C‑helix, which are necessary for its phosphoryl transfer activity (faezov2023alphafold2modelsof pages 20-23, pei2023computationalanalysisof pages 1-2).
6. Regulation  
   The regulation of SIK1B is achieved through phosphorylation‐dependent mechanisms that are characteristic of the SIK family (darling2021nutsandbolts pages 1-2). Activation of SIK1B requires phosphorylation of a conserved threonine residue located in the activation loop by the upstream kinase LKB1; this phosphorylation event is indispensable for establishing the proper conformation of the kinase domain and for catalytic activity (darling2021nutsandbolts pages 2-4). Conversely, phosphorylation by cyclic AMP‑dependent protein kinase A (PKA) on multiple serine/threonine residues within the flexible C‑terminal tail generates binding sites for 14‑3‑3 proteins. The recruitment of these adaptor molecules leads to a conformational shift in SIK1B, resulting in its translocation from the nucleus to the cytoplasm and consequent inhibition of kinase activity (darling2021nutsandbolts pages 2-4, darling2021nutsandbolts pages 16-18). This dual layer of regulation, in which LKB1 activates the kinase while PKA‐mediated phosphorylation imposes negative regulation through sequestration, enables SIK1B to function as a molecular switch that integrates cellular energy signals and cAMP levels to modulate downstream signaling pathways (darling2021nutsandbolts pages 1-2, darling2021nutsandbolts pages 19-20).
7. Function  
   SIK1B is implicated in the control of several essential cellular processes through its ability to modulate the phosphorylation status of key regulatory proteins (darling2021nutsandbolts pages 18-19). By phosphorylating substrates such as CREB‑regulated transcriptional coactivators (CRTCs) and class 2a histone deacetylases (HDACs), SIK1B influences gene expression patterns that are vital for metabolic homeostasis, immune response modulation, circadian rhythm regulation, and potentially bone remodeling (darling2021nutsandbolts pages 1-2, darling2021nutsandbolts pages 4-6). The phosphorylation of these substrates generally results in their binding to 14‑3‑3 proteins and subsequent cytoplasmic retention, thereby preventing them from coactivating nuclear transcription factors such as CREB and MEF2; this process serves as a brake on transcriptional programs that would otherwise promote excessive gluconeogenesis, inflammatory cytokine production, or dysregulated circadian gene expression (darling2021nutsandbolts pages 2-4, darling2021nutsandbolts pages 18-19). In addition, network‐based regulatory studies have integrated SIK1B into broader signaling cascades that relate to the pathogenesis of metabolic disorders and certain cancers, such as type 2 diabetes mellitus and breast cancer, where SIK regulatory dynamics appear to influence disease progression (durrani2025networkingsaltinducible pages 6-9, darling2021nutsandbolts pages 16-18). Although direct experimental characterization of SIK1B’s tissue‑specific expression remains limited, its inclusion in analyses of the kinome suggests that it is expressed at levels sufficient to contribute to the fine‑tuning of cellular responses under conditions of metabolic and environmental stress (darling2021nutsandbolts pages 8-10).
8. Other Comments  
   SIK1B is considered an understudied or “orphan” kinase because, despite its close homology to SIK1, it is unique in that it appears to be human‑specific with no clear orthologs in other species, as determined by stringent orthology inference methods (huang2021illuminatingunderstudiedkinases pages 51-54). There are currently no well‑documented disease‑associated mutations that are specific to SIK1B; however, its integration into regulatory networks that impact metabolic signaling and inflammatory responses has prompted interest in its potential involvement in diseases such as type 2 diabetes and cancer (durrani2025networkingsaltinducible pages 6-9). While several pan‑SIK inhibitors (for example, HG‑9‑91‑01, YKL‑05‑099, dasatinib, and bosutinib) have been employed experimentally to inhibit SIK family activity, there is a paucity of data regarding compounds that selectively target SIK1B specifically, and further studies are needed to establish its precise inhibitor profile (darling2021nutsandbolts pages 12-14, darling2021nutsandbolts pages 15-16). In the absence of an experimentally determined three‑dimensional structure for SIK1B, computational approaches such as AlphaFold2 modeling have been used to predict its active conformation, providing insights into its catalytic domain features—including the activation loop, C‑helix, DFG motif, and regulatory regions—that are consistent with those observed in other active forms of protein kinases (faezov2023alphafold2modelsof pages 20-23, pei2023computationalanalysisof pages 1-2). These computational predictions reinforce the concept that SIK1B, despite its minimal sequence divergence from SIK1, retains the essential catalytic and regulatory elements that define the functional capabilities of the SIK family. Its status as an understudied kinase underscores the need for further biochemical characterization and functional validation, which may ultimately reveal novel aspects of SIK‑mediated regulation in human physiology (darling2021nutsandbolts pages 1-2, huang2021illuminatingunderstudiedkinases pages 51-54).

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