## Phylogeny

According to the Manning et al. 2002 classification, SIK2 (UniProt Q9H0K1) is a serine/threonine kinase that belongs to the AMPK-related kinase family, which is part of the CAMK (calcium/calmodulin-dependent protein kinase) group (darling2021nutsandbolts pages 1-2, manning2002theproteinkinase pages 7-8, jin2020highthroughputimplementationof pages 8-8, thiriet2013preambletocytoplasmic pages 1-4). SIK2 is one of three isoforms in the salt-inducible kinase family, along with SIK1 and SIK3 (darling2021nutsandbolts pages 1-2). The SIK2 and SIK3 genes arose during invertebrate evolution (darling2021nutsandbolts pages 1-2). Known orthologs include KIN-29 in *C. elegans*, which is orthologous to SIK2, and homologs in *Drosophila melanogaster*, which expresses both SIK2 and SIK3 (darling2021nutsandbolts pages 1-2). Vertebrates, including fishes and mammals, express all three SIK isoforms (darling2021nutsandbolts pages 1-2). In almost all vertebrates, the SIK2 and SIK3 genes are closely linked on the same chromosome; for example, they are located on chromosome 11 in humans and on chromosome 9 in mice (darling2021nutsandbolts pages 1-2).

## Reaction Catalyzed

SIK2 is a serine/threonine kinase that catalyzes the transfer of the gamma-phosphate from ATP to specific serine or threonine residues on a substrate protein (darling2021nutsandbolts pages 18-18, oster2024thestructuresof pages 1-2). The catalyzed reaction is: ATP + a protein → ADP + a phosphoprotein (darling2021nutsandbolts pages 18-18, oster2024thestructuresof pages 1-2).

## Cofactor Requirements

The enzymatic reaction catalyzed by SIK2 requires a divalent metal ion cofactor for activity, commonly magnesium (Mg2+), which coordinates with ATP in the catalytic site to facilitate phosphoryl transfer (darling2021nutsandbolts pages 18-18, oster2024thestructuresof pages 1-2).

## Substrate Specificity

A comprehensive atlas of substrate specificities for the human serine/threonine kinome has profiled 303 kinases, including SIK2 (johnson2023anatlasof pages 1-2, johnson2023anatlasof pages 3-4). This work determined the unique substrate sequence motifs and amino acid preferences for each kinase through positional scanning peptide array analysis (johnson2023anatlasof pages 1-2). The specific consensus motif and detailed amino acid preferences for SIK2 derived from this dataset are not explicitly stated within the provided context (johnson2023anatlasof pages 2-3, johnson2023anatlasof pages 4-4, johnson2023anatlasof pages 6-7).

## Structure

The experimental 3D structure of SIK2 has not been resolved (darling2021nutsandbolts pages 4-6, oster2024thestructuresof pages 1-2). SIK2 shares a conserved domain organization with other SIK family members, consisting of an N-terminal header sequence, a catalytic kinase domain (KD), a linker, a ubiquitin-associated (UBA) domain, and a long C-terminal tail (oster2024thestructuresof pages 1-2, darling2021nutsandbolts pages 1-2). The UBA domain in SIKs is unique among human kinases; it does not bind ubiquitin but is required to facilitate LKB1-dependent phosphorylation of the activation loop (darling2021nutsandbolts pages 4-6). Based on homology with the structurally characterized SIK3, the SIK2 kinase domain contains key regulatory features such as the C-helix (αC), a regulatory hydrophobic spine (R-spine), and an activation loop, which are essential for its catalytic function and active conformation (oster2024thestructuresof pages 6-7, darling2021nutsandbolts pages 4-6). The UBA domain has been shown in SIK3 to stabilize the active kinase conformation (oster2024thestructuresof pages 1-2, oster2024thestructuresof pages 6-7).

## Regulation

SIK2 activity is regulated by post-translational phosphorylation (darling2021nutsandbolts pages 2-4). Activation requires phosphorylation of Thr175 within the activation loop by the upstream kinase LKB1 (darling2021nutsandbolts pages 1-2, oster2024thestructuresof pages 1-2). LKB1 is constitutively active when complexed with MO25 and STRAD (darling2021nutsandbolts pages 1-2). Conversely, SIK2 is inhibited by phosphorylation in its C-terminal tail at multiple sites (e.g., Ser343, Ser358, Thr484, and Ser587 in murine SIK2) by cyclic AMP-dependent protein kinase (PKA) (darling2021nutsandbolts pages 2-4, oster2024thestructuresof pages 1-2). This PKA-mediated phosphorylation promotes the binding of 14-3-3 proteins, leading to cytoplasmic retention and inhibition of SIK2 activity (darling2021nutsandbolts pages 2-4, oster2024thestructuresof pages 1-2). Calmodulin-dependent kinases (CaMK1 and CaMK4) also phosphorylate SIK2 at sites including Thr484, which promotes 14-3-3 binding and leads to partial inactivation (darling2021nutsandbolts pages 4-6). SIK2 is also phosphorylated at Ser179, adjacent to the activation loop; it is debated whether this is an autophosphorylation event or is catalyzed by other kinases like GSK3 (darling2021nutsandbolts pages 2-4). Unlike AMPK, SIK2 is not activated by CaMKK (darling2021nutsandbolts pages 1-2).

## Function

SIK2 is constitutively expressed in many tissues, including adipocytes, neurons, melanocytes, hepatocytes, and macrophages (darling2021nutsandbolts pages 1-2, darling2021nutsandbolts pages 12-14). Its expression is reduced in the adipose tissue of insulin-resistant or obese individuals (darling2021nutsandbolts pages 1-2). SIK2 functions downstream of the activating kinase LKB1 and is regulated by inhibitory signals from PKA and CaMKs (darling2021nutsandbolts pages 4-6). Key physiological substrates of SIK2 are the CREB-regulated transcriptional coactivators (CRTCs 1-3) and Class 2a histone deacetylases (HDACs 4, 5, 7, and 9) (darling2021nutsandbolts pages 1-2, oster2024thestructuresof pages 1-2). Phosphorylation of CRTCs and HDACs by SIK2 promotes their binding to 14-3-3 proteins and subsequent retention in the cytoplasm (darling2021nutsandbolts pages 1-2). This prevents CRTCs from co-activating the transcription factor CREB and prevents nuclear entry of HDACs, which de-represses the transcription factor MEF2 (darling2021nutsandbolts pages 4-6, oster2024thestructuresof pages 1-2). Through this mechanism, SIK2 plays roles in metabolism, melanogenesis, innate immunity, bone formation, neuronal survival, and circadian rhythms (darling2021nutsandbolts pages 1-2, darling2021nutsandbolts pages 12-14, oster2024thestructuresof pages 1-2).

## Inhibitors

Several experimental small molecule inhibitors targeting SIKs have been developed. These include potent pan-SIK inhibitors such as HG-9-91-01 and its analogues YKL-05-099, YKL-06-061, and YKL-06-062 (darling2021nutsandbolts pages 12-14, darling2021nutsandbolts pages 6-8, oster2024thestructuresof pages 1-2). Other reported inhibitors are MRT199665 and MRT67307 (darling2021nutsandbolts pages 6-8). The clinically approved tyrosine kinase inhibitors dasatinib and bosutinib also inhibit SIKs, which contributes to their anti-inflammatory effects (darling2021nutsandbolts pages 6-8, oster2024thestructuresof pages 2-3).

## Other Comments

SIK2 dysregulation is associated with metabolic and inflammatory disorders, and SIK family dysregulation has been linked to oncogenesis and neurological functions (darling2021nutsandbolts pages 1-2, darling2021nutsandbolts pages 6-8, oster2024thestructuresof pages 1-2). SIK2 inhibitors show promise for treating conditions like ovarian cancer (oster2024thestructuresof pages 2-3). SIK2 inhibition also induces melanogenesis, suggesting therapeutic potential against skin cancer (darling2021nutsandbolts pages 12-14). No disease-related mutations are mentioned for SIK2 directly, but mutations in the melanocortin 1 receptor (MC1R) that affect skin cancer risk interact with the SIK2 pathway (darling2021nutsandbolts pages 12-14).

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