## Phylogeny

SIK1 belongs to the salt-inducible kinases (SIKs), a family of serine/threonine kinases which are a subfamily of the AMP-activated protein kinase-related kinases (AMPK-RKs) (berdeaux2011metabolicregulationby pages 1-3, unknownauthors2017saltinduciblekinasesin pages 33-37). The SIK family is composed of three isoforms: SIK1, SIK2, and SIK3 (chen2019saltinduciblekinase2 pages 1-2). Based on the kinome classification by Manning et al. 2002, SIKs are assigned to the calcium/calmodulin-dependent protein kinase (CAMK) group (darling2021nutsandbolts pages 2-4, darling2021nutsandbolts pages 6-8, sonntag201814‐3‐3proteinsmediate pages 14-17). One source places SIK1 within the SNF1/AMPK kinome group (du2016thediverseoncogenic pages 3-3). The human gene encoding SIK1 is located on chromosome 21 (du2016thediverseoncogenic pages 3-3, darling2021nutsandbolts pages 1-2).

## Reaction Catalyzed

SIK1 is a serine/threonine kinase that catalyzes the transfer of the terminal phosphate group from ATP to the hydroxyl group of serine or threonine residues on protein substrates (berdeaux2011metabolicregulationby pages 1-3, darling2021nutsandbolts pages 18-18, darling2021nutsandbolts pages 16-18).

Protein-L-serine/threonine + ATP → Protein-L-phosphoserine/phosphothreonine + ADP

## Cofactor Requirements

The catalytic activity of SIK1 is dependent on the presence of divalent cations, which are required to coordinate ATP binding and catalysis (berdeaux2011metabolicregulationby pages 1-3, darling2021nutsandbolts pages 18-18). These cofactors are typically Mg2+ or Mn2+ (darling2021nutsandbolts pages 16-18, du2016thediverseoncogenic pages 3-3).

## Substrate Specificity

SIK1 phosphorylates serine/threonine residues within specific consensus motifs. One reported motif is L-x-[HKR]-[ST]-x-S-X(3)-L, which is similar to that of other AMPK-related kinases (unknownauthors2017saltinduciblekinasesin pages 40-43, chen2019saltinduciblekinase2 pages 1-2). Another described pattern is LxB(S/T)xS*xxxL, where B is a basic amino acid and S* is the site of phosphorylation (darling2021nutsandbolts pages 2-4). Substrate recognition shows a preference for an arginine residue at the -3 or -4 position relative to the phospho-acceptor site (unknownauthors2017saltinduciblekinasesin pages 40-43). The sources note that consensus motifs have been described in Johnson et al. 2023, but the specific motifs are not detailed within the provided context (berdeaux2011metabolicregulationby pages 1-3, sato2022structurebaseddesignof pages 9-9). SIK1 can also phosphorylate variant motifs lacking N-terminal basic residues, such as SLPDL (unknownauthors2017saltinduciblekinasesin pages 40-43).

## Structure

SIK1 is a 776-amino acid protein with three main domains: an N-terminal kinase domain (KD; residues 27–278), a central ubiquitin-associated (UBA) domain, and a long C-terminal domain (CTD) (du2016thediverseoncogenic pages 3-3, shi2024understandingtheroles pages 1-2). AlphaFold models and partial PDB structures for SIK1 are available (sato2022structurebaseddesignof pages 9-9, darling2021nutsandbolts pages 16-18).

The kinase domain contains key catalytic and regulatory features, including an αC-helix with a conserved glutamate (E74), a catalytic spine involving the catalytic lysine (K56), and an activation loop that contains the DFG motif (D167) and the critical phosphorylation site at Thr182 (T182) (du2016thediverseoncogenic pages 3-3, valdesalbuernes2025advancedmodelingof pages 12-14). Other structurally important residues include the gatekeeper residue (T103) and residues in the hinge region (E104, F105, A106) that influence inhibitor binding (valdesalbuernes2025advancedmodelingof pages 12-14). The UBA domain does not bind ubiquitin but facilitates LKB1-mediated phosphorylation (darling2021nutsandbolts pages 4-6). The CTD contains multiple regulatory phosphorylation sites and features unique to SIK1, including nuclear localization sequences (NLS) and an arginine/lysine (RK)-rich region that serves as a nuclear import signal (shi2024understandingtheroles pages 1-2, unknownauthors2017saltinduciblekinasesin pages 33-37, sonntag201814‐3‐3proteinsmediate pages 5-7).

## Regulation

SIK1 activity is primarily regulated through phosphorylation. The upstream kinase LKB1 activates SIK1 by phosphorylating Thr182 (T182) in the activation loop, a modification essential for catalytic function (darling2021nutsandbolts pages 2-4, du2016thediverseoncogenic pages 3-3). Autophosphorylation at Ser186 in the T-loop is also reported to be important for sustaining kinase activity (darling2021nutsandbolts pages 16-18, unknownauthors2017saltinduciblekinasesin pages 86-89).

Conversely, SIK1 is negatively regulated by cAMP-dependent Protein Kinase A (PKA) (berdeaux2011metabolicregulationby pages 1-3, sun2020thepotentroles pages 2-3). PKA phosphorylates SIK1 at multiple sites in its C-terminal tail, including Ser575 and Thr473 (darling2021nutsandbolts pages 2-4, unknownauthors2017saltinduciblekinasesin pages 37-40). These phosphorylation events create binding sites for 14-3-3 proteins, which inhibit SIK1 activity and promote its cytoplasmic retention, thereby preventing access to nuclear substrates (darling2021nutsandbolts pages 4-6, sonntag201814‐3‐3proteinsmediate pages 5-7, sonntag201814‐3‐3proteinsmediate pages 7-8). SIK1 can also be phosphorylated by other kinases, including CaMK1 (at Thr322), PKC, and tyrosine kinases, which affects its stability and activity (du2016thediverseoncogenic pages 3-3, unknownauthors2017saltinduciblekinasesin pages 37-40).

## Function

SIK1 is widely expressed, with high levels observed in the adrenal gland, liver, skin, adipose tissue, and muscle (berdeaux2011metabolicregulationby pages 1-3, sun2020thepotentroles pages 1-2, unknownauthors2017saltinduciblekinasesin pages 33-37). Its expression is induced by stimuli including high salt diet, ACTH, and cAMP (darling2021nutsandbolts pages 1-2, hu2015anovelrole pages 1-2).

The primary function of SIK1 is to regulate gene expression by phosphorylating and inhibiting transcriptional co-regulators (berdeaux2011metabolicregulationby pages 1-3). Key downstream substrates include CREB-regulated transcriptional co-activators (CRTCs, such as CRTC2) and Class IIa histone deacetylases (HDACs, such as HDAC4 and HDAC5) (darling2021nutsandbolts pages 18-18, berdeaux2011metabolicregulationby pages 1-3). Phosphorylation of these substrates by SIK1 causes their sequestration in the cytoplasm via binding to 14-3-3 proteins, which in turn represses gene transcription controlled by the transcription factors CREB and MEF2 (darling2021nutsandbolts pages 4-6).

Through this mechanism, SIK1 participates in various signaling pathways. It acts to constrain gluconeogenic gene expression in the liver during fasting and also regulates lipogenesis (berdeaux2011metabolicregulationby pages 1-3, unknownauthors2017saltinduciblekinasesin pages 40-43). In oncology, SIK1 functions as a tumor suppressor, mediating p53-dependent anoikis (apoptosis upon loss of cell adhesion) and suppressing metastasis in breast cancer and non-small cell lung cancer (NSCLC) as part of the LKB1-SIK1 signaling axis (du2016thediverseoncogenic pages 3-3, hollstein2019theampkrelatedkinases pages 1-3). SIK1 also plays roles in promoting skeletal myocyte survival and regulating adrenal steroidogenesis and sodium transport (darling2021nutsandbolts pages 18-18, hu2015anovelrole pages 1-2).

## Inhibitors

Several experimental small-molecule inhibitors have been developed that target the SIK family. These include the pan-SIK inhibitors HG-9-91-01, YKL-05-099, MRT67307, MRT199665, and ARN-3236 (darling2021nutsandbolts pages 6-8, oster2024thestructuresof pages 1-2, tesch2021structurebaseddesignof pages 1-4). For enhanced specificity, a combination of MRT199665 and HG-9-91-01 is recommended for functional studies (darling2021nutsandbolts pages 6-8). The tyrosine kinase inhibitors dasatinib and bosutinib also demonstrate off-target SIK activity (tesch2021structurebaseddesignof pages 1-4). The development of isoform-selective inhibitors remains a challenge (oster2024thestructuresof pages 1-2).

## Other Comments

SIK1 dysregulation is implicated in various diseases. Its role in regulating gluconeogenesis and lipogenesis makes it a therapeutic target for metabolic diseases, including diabetes (berdeaux2011metabolicregulationby pages 1-3, unknownauthors2017saltinduciblekinasesin pages 40-43). SIK1 acts as a tumor suppressor in several cancers; its loss is associated with tumor growth in non-small cell lung cancer (NSCLC), while its downregulation in breast cancer correlates with increased metastasis and poor prognosis (hollstein2019theampkrelatedkinases pages 1-3, sun2020thepotentroles pages 7-8). SIK1 is also involved in cardiovascular system regulation, with associations to vascular calcification and pathological cardiac remodeling (darling2021nutsandbolts pages 18-18, shi2024understandingtheroles pages 1-2). The provided literature does not describe any specific disease-causing mutations in SIK1 (berdeaux2011metabolicregulationby pages 1-3).

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