## Phylogeny

• Human SIK1B emerged from a recent duplication of SIK1 on chromosome 21 and differs by a single amino-acid substitution, placing it within the salt-inducible kinase (SIK) subfamily of the AMP-activated protein kinase–related (ARK) branch of the SNF1/AMPK kinome (darling2021nutsandbolts pages 1-2).  
• Conserved orthologs: mouse Sik1, zebrafish sik1, Caenorhabditis elegans KIN-29, and Drosophila melanogaster SIK2/SIK3, underscoring deep metazoan conservation (darling2021nutsandbolts pages 1-2).  
• The SIK subfamily shares evolutionary relationships and domain architecture with other ARKs such as MARK and MELK (oster2024thestructuresof pages 16-17).

## Reaction Catalyzed

• ATP + [protein]-Ser/Thr → ADP + [protein]-O-phospho-Ser/Thr (darling2021nutsandbolts pages 18-18).

## Cofactor Requirements

• Catalytic turnover requires divalent metal ions, typically Mg²⁺ or Mn²⁺, to coordinate ATP (sun2020thepotentroles pages 2-3).

## Substrate Specificity

• Preferred consensus motif: LX(R/K/H)(S/T)XSXXXL, characteristic of SIK substrates (sun2020thepotentroles pages 1-2).  
• Phosphoproteomic motif LxB(S/T)xS*xxxL captures many in-cellulo SIK phosphorylation sites (wein2018saltinduciblekinasesphysiology pages 1-2).*  
*• Numerous sites contain an S*-x-P arrangement that recruits 14-3-3 adapters after phosphorylation (darling2021nutsandbolts pages 4-6).  
• Validated substrates include CRTC1-3 (e.g., CRTC2 Ser171), class IIa HDACs 4/5/7/9, and PDE4D (unknownauthors2017insightsintothe pages 20-24, oster2024thestructuresof pages 1-2).

## Structure

• Domain organisation: N-terminal kinase domain (KD) → ubiquitin-associated (UBA) module → proline-rich C-terminal tail (oster2024thestructuresof pages 1-2, shi2024understandingtheroles pages 1-2).  
• Catalytic hallmarks within the KD: activation-loop Thr182, ordered C-helix, and an intact hydrophobic spine consistent with an active ARK conformation (darling2021nutsandbolts pages 1-2, oster2024thestructuresof pages 16-17).  
• Autophosphorylation hotspot Ser186 lies adjacent to the activation loop (darling2021nutsandbolts pages 2-4).  
• The distal C-terminus harbours an autoinhibitory/nuclear-localisation segment (shi2024understandingtheroles pages 1-2).  
• High-confidence AlphaFold models exist for SIK1B, while crystal structures of the paralogous SIK3 (PDB 8R4Q/8R4O/8R4U) reveal a UBA-stabilised active state that is conserved across SIK isoforms (oster2024thestructuresof pages 15-16).

## Regulation

• Activation: LKB1 phosphorylates Thr182, generating the active enzyme (darling2021nutsandbolts pages 1-2).  
• Positive modulation: autophosphorylation at Ser186 (darling2021nutsandbolts pages 2-4).  
• Inhibition: PKA phosphorylates C-terminal residues such as Thr473 and Ser575, promoting 14-3-3 binding and cytoplasmic sequestration (darling2021nutsandbolts pages 2-4, wein2018saltinduciblekinasesphysiology pages 1-2).  
• Calcium-responsive modulation: CaMK1/4 add further inhibitory phosphorylations under Ca²⁺ influx (darling2021nutsandbolts pages 4-6).  
• Transcriptional control: cAMP signalling acutely induces SIK1B mRNA expression (darling2021nutsandbolts pages 1-2).

## Function

• Expression: inducible by high dietary salt, ACTH, glucagon, neuronal depolarisation, and circadian cues; basal transcripts detected in adrenal cortex, adipose tissue, brain, and developing myocardium (darling2021nutsandbolts pages 1-2, sun2020thepotentroles pages 1-2, shi2024understandingtheroles pages 15-15).  
• Metabolic regulation: phosphorylation of CRTC2 suppresses CREB-driven gluconeogenic gene expression in liver (unknownauthors2017insightsintothe pages 20-24).  
• Transcriptional repression: phosphorylation of class IIa HDACs retains them in the cytoplasm, limiting MEF2 programmes (wein2018saltinduciblekinasesphysiology pages 1-2).  
• Ion transport: phosphorylation of PME-1 regulates Na⁺/K⁺-ATPase activity in renal proximal tubules (sun2020thepotentroles pages 2-3).  
• Cardiac development: modulates cell-cycle inhibitors during cardiomyogenesis (shi2024understandingtheroles pages 15-15).  
• Additional roles: adipocyte glucose uptake, neuronal survival, macrophage polarisation, and sleep-need signalling, mediated through interactions with CRTCs, HDACs, CREB, MEF2 and 14-3-3 proteins (darling2021nutsandbolts pages 18-18, oster2024thestructuresof pages 1-2).

## Inhibitors

• Pan-SIK inhibitors HG-9-91-01 and YKL-05-099 serve as chemical probes (oster2024thestructuresof pages 1-2).  
• Pyrido[2,3-d]pyrimidin-7(8H)-one derivatives (e.g., compound 219) show emerging isoform selectivity (oster2024thestructuresof pages 16-17).  
• Broad-spectrum tyrosine kinase inhibitors dasatinib and bosutinib inhibit SIKs off-target and have co-crystal structures with SIK3 (oster2024thestructuresof pages 16-17, oster2024thestructuresof pages 15-16).  
• Orally active bone-anabolic inhibitors with measured SIK1 potency have been reported (sato2022structurebaseddesignof pages 8-9).

## Other Comments

• Pathogenic missense and truncation variants in SIK1 cause “SIK1 syndrome” with developmental epilepsy; high SIK1B sequence identity suggests potential relevance for similar phenotypes (darling2021nutsandbolts pages 11-12).  
• Dysregulated SIK signalling contributes to pulmonary arterial hypertension, inflammatory disorders, and broader cardiometabolic disease (oster2024thestructuresof pages 16-17, shi2024understandingtheroles pages 15-15).

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