## Phylogeny

Human SIK1B is a recent duplicate of SIK1 on chromosome 21 and differs by only one amino-acid residue, placing it in the salt-inducible kinase (SIK) subfamily of the AMP-activated protein kinase–related (ARK) branch of the SNF1/AMPK kinome (Darling & Cohen, 2021). Orthologues are present in mouse (Sik1), zebrafish (sik1), Caenorhabditis elegans (KIN-29) and Drosophila melanogaster (SIK2/SIK3), indicating deep metazoan conservation (Darling & Cohen, 2021). Within the ARKs, SIKs share evolutionary relationships and a common domain layout with MARK and MELK kinases (Öster et al., 2024).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr → ADP + [protein]-O-phospho-Ser/Thr (Darling & Cohen, 2021).

## Cofactor Requirements

Catalytic turnover requires divalent metal ions, typically Mg²⁺ or Mn²⁺, to coordinate ATP (Sun et al., 2020).

## Substrate Specificity

SIK1B preferentially phosphorylates substrates bearing the consensus motif LX(R/K/H)(S/T)XSXXXL or the phosphoproteomic variant LxB(S/T)xS*xxxL (Sun et al., 2020; Wein et al., 2018). Many target sites contain an S*-x-P sequence that recruits 14-3-3 adaptors once phosphorylated (Darling & Cohen, 2021). Validated cellular substrates include CRTC1-3 (e.g., CRTC2 Ser171), class IIa HDACs 4/5/7/9, and PDE4D (Unknown Authors, 2017; Öster et al., 2024).

## Structure

The protein comprises an N-terminal kinase domain (KD), a ubiquitin-associated (UBA) module and a proline-rich C-terminal tail (Öster et al., 2024; Shi, 2024). Catalytic hallmarks include activation-loop Thr182, an ordered C-helix and an intact hydrophobic spine consistent with an active ARK fold (Darling & Cohen, 2021; Öster et al., 2024). An autophosphorylation hotspot at Ser186 lies adjacent to the activation loop (Darling & Cohen, 2021). The distal C-terminus contains an autoinhibitory/nuclear-localisation segment (Shi, 2024). AlphaFold provides high-confidence models for SIK1B, while crystal structures of the paralogue SIK3 (PDB 8R4Q/8R4O/8R4U) demonstrate a UBA-stabilised active state that is conserved across SIK isoforms (Öster et al., 2024).

## Regulation

• Activation: LKB1 phosphorylates Thr182 (Darling & Cohen, 2021).  
• Positive modulation: autophosphorylation at Ser186 (Darling & Cohen, 2021).  
• Inhibition: PKA phosphorylates C-terminal sites such as Thr473 and Ser575, promoting 14-3-3-mediated cytoplasmic sequestration (Darling & Cohen, 2021; Wein et al., 2018).  
• Ca²⁺-responsive inhibition: CaMK1/4 add additional inhibitory phosphorylations during Ca²⁺ influx (Darling & Cohen, 2021).  
• Transcriptional control: cAMP signalling acutely induces SIK1B mRNA expression (Darling & Cohen, 2021).

## Function

Expression is inducible by high dietary salt, ACTH, glucagon, neuronal depolarisation and circadian cues; basal transcripts are detected in adrenal cortex, adipose tissue, brain and developing myocardium (Darling & Cohen, 2021; Sun et al., 2020; Shi, 2024).  
Key roles include:  
• Metabolic regulation – phosphorylation of CRTC2 represses CREB-driven gluconeogenic genes in liver (Unknown Authors, 2017).  
• Transcriptional repression – phosphorylation-dependent cytoplasmic retention of class IIa HDACs limits MEF2 programmes (Wein et al., 2018).  
• Ion transport – regulation of Na⁺/K⁺-ATPase via PME-1 phosphorylation in renal proximal tubules (Sun et al., 2020).  
• Cardiac development – modulation of cell-cycle inhibitors during cardiomyogenesis (Shi, 2024).  
• Additional reported functions include adipocyte glucose uptake, neuronal survival, macrophage polarisation and sleep-need signalling, mediated through interactions with CRTCs, HDACs, CREB, MEF2 and 14-3-3 proteins (Darling & Cohen, 2021; Öster et al., 2024).

## Inhibitors

Pan-SIK chemical probes HG-9-91-01 and YKL-05-099 are widely used (Öster et al., 2024). Pyrido[2,3-d]pyrimidin-7(8H)-one derivatives (e.g., compound 219) exhibit emerging isoform selectivity (Öster et al., 2024). Broad-spectrum tyrosine kinase inhibitors dasatinib and bosutinib inhibit SIKs off-target and have co-crystal structures with SIK3 (Öster et al., 2024). Orally active bone-anabolic inhibitors with measurable SIK1 potency have also been reported (Sato et al., 2022).

## Other Comments

Pathogenic missense and truncation variants in SIK1 cause “SIK1 syndrome” with developmental epilepsy; the high sequence identity of SIK1B suggests potential relevance to similar phenotypes (Darling & Cohen, 2021). Aberrant SIK signalling has been implicated in pulmonary arterial hypertension, inflammatory disorders and broader cardiometabolic disease (Öster et al., 2024; Shi, 2024).

## 9. References

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