## Phylogeny

Salt-inducible kinase 2 (SIK2; UniProt Q9H0K1) is one of three vertebrate SIK isoforms and belongs to the AMPK-related kinase family within the CAMK group of the eukaryotic protein kinase superfamily (Manning et al., 2002; Darling & Cohen, 2021). The SIK2 and SIK3 genes emerged in invertebrates; most vertebrates possess tightly linked SIK2 and SIK3 loci (e.g., chromosome 11 in humans, chromosome 9 in mice) (Darling & Cohen, 2021). Orthologues include KIN-29 in Caenorhabditis elegans and both SIK2 and SIK3 in Drosophila melanogaster (Darling & Cohen, 2021).

## Reaction Catalyzed

ATP + protein ⇌ ADP + phospho-protein (Darling & Cohen, 2021; Öster et al., 2024).

## Cofactor Requirements

Mg²⁺ is required to coordinate ATP and support catalysis (Darling & Cohen, 2021; Öster et al., 2024).

## Substrate Specificity

High-throughput peptide arrays profiling 303 human Ser/Thr kinases defined a unique sequence preference for SIK2, although the exact consensus motif was not detailed in the provided text (Johnson et al., 2023). The study confirms that SIK2 phosphorylates Ser/Thr residues within context-specific motifs (Johnson et al., 2023).

## Structure

No experimental structure is available for SIK2 (Darling & Cohen, 2021; Öster et al., 2024). Predicted domain organisation comprises an N-terminal segment, a catalytic kinase domain, a linker, a ubiquitin-associated (UBA) domain, and an extended C-terminal tail. The UBA domain—unique to SIK family kinases—does not bind ubiquitin but promotes LKB1-mediated activation-loop phosphorylation and stabilises the active conformation, as shown for SIK3 (Darling & Cohen, 2021; Öster et al., 2024). Key catalytic features inferred from SIK3 structures include the αC helix, regulatory hydrophobic spine and activation loop (Öster et al., 2024).

## Regulation

• Activation: Phosphorylation of Thr175 in the activation loop by the constitutively active LKB1–STRAD–MO25 complex (Darling & Cohen, 2021; Öster et al., 2024).  
• Inhibition: PKA phosphorylates multiple C-terminal sites (Ser343, Ser358, Thr484, Ser587 in mouse SIK2), promoting 14-3-3 binding, cytoplasmic retention and reduced activity (Darling & Cohen, 2021; Öster et al., 2024). CaMK1/4 also target Thr484, yielding partial inactivation via 14-3-3 binding (Darling & Cohen, 2021).  
• Additional sites: Ser179 near the activation loop is phosphorylated; whether by autophosphorylation or another kinase (e.g., GSK3) remains uncertain (Darling & Cohen, 2021).  
• Unlike AMPK, SIK2 is not activated by CaMKK (Darling & Cohen, 2021).

## Function

SIK2 is constitutively expressed in adipocytes, neurons, melanocytes, hepatocytes and macrophages, with reduced levels in insulin-resistant or obese adipose tissue (Darling & Cohen, 2021). Downstream substrates include:  
• CREB-regulated transcriptional coactivators CRTC1-3 – phosphorylation promotes 14-3-3 binding and blocks CREB activation.  
• Class IIa histone deacetylases (HDAC4/5/7/9) – phosphorylation prevents nuclear entry, relieving repression of MEF2 (Darling & Cohen, 2021; Öster et al., 2024).  
Through these targets, SIK2 influences metabolism, melanogenesis, innate immunity, bone formation, neuronal survival and circadian rhythms (Darling & Cohen, 2021). Upstream: LKB1 (activating). Downstream: 14-3-3 proteins (binding partners upon substrate phosphorylation).

## Inhibitors

Pan-SIK small-molecule inhibitors include HG-9-91-01 and analogues YKL-05-099, YKL-06-061 and YKL-06-062, as well as MRT199665 and MRT67307 (Darling & Cohen, 2021; Öster et al., 2024). The tyrosine kinase inhibitors dasatinib and bosutinib also inhibit SIKs, contributing to anti-inflammatory actions (Darling & Cohen, 2021; Öster et al., 2024).

## Other Comments

SIK2 dysregulation is implicated in metabolic and inflammatory disorders; broader SIK family alterations relate to cancer and neurological functions (Darling & Cohen, 2021; Öster et al., 2024). Pharmacological SIK2 inhibition shows promise in ovarian cancer and enhances melanogenesis, potentially benefiting skin-cancer prevention strategies. No disease-linked SIK2 mutations are reported, though MC1R variants modulate the same pathway (Darling & Cohen, 2021).

## References

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