## Phylogeny

SIK3 is classified within the Ca²⁺/calmodulin-dependent kinase (CAMK) group as an AMPK-related kinase alongside SIK1 and SIK2 (darling2021nutsandbolts pages 1-2).  
Large-scale kinome surveys corroborate this placement within the salt-inducible kinase clade (henriksson2012theampkrelatedkinase pages 11-11).  
Orthologs are conserved in mouse (Sik3), rat (Sik3), zebrafish (sik3), Drosophila (Sik3 and Sik2), Caenorhabditis elegans (KIN-29) and yeast AMPK-family kinases, indicating deep evolutionary conservation (sahin2020saltinduciblekinases pages 21-22).  
In vertebrates, Sik2 and Sik3 genes reside in synteny on the same chromosome, whereas Sik1 is located separately, consistent with segmental duplication events (bicanovsky2025genemodelfor pages 5-6).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr → ADP + [protein]-Ser/Thr-P (darling2021nutsandbolts pages 4-6).

## Cofactor Requirements

Catalytic activity depends on a divalent metal ion; Mg²⁺ is preferred, while Mn²⁺ can substitute in vitro, consistent with other AMPK-related kinases (darling2021nutsandbolts pages 16-18).

## Substrate Specificity

Basophilic consensus motif: LxB(S/T)xSxxxL, where B = Lys/Arg, generating 14-3-3 docking sites upon phosphorylation (darling2021nutsandbolts pages 2-4).  
Validated physiological sites include CRTC2 Ser171, CRTC3 Ser273 and HDAC4 Ser246/Ser467 (sonntag201814‐3‐3proteinsmediate pages 14-17).

## Structure

The protein comprises an N-terminal bilobed kinase domain followed by a three-helix ubiquitin-associated (UBA) domain and a long regulatory C-terminal tail (oster2024thestructuresof pages 2-3).  
Crystal structures of the M59–R385 fragment in complex with inhibitors (PDB 8R4V, 8R4O, 8R4Q, 8R4U) show an active DFG-in/αC-in conformation stabilised by phospho-Thr221 in the activation loop (oster2024thestructuresof pages 5-6).  
Key catalytic motifs VAIK, HRD, DFG and a threonine gatekeeper (Thr142) shape an enlarged back pocket exploited by selective inhibitors (oster2024thestructuresof pages 7-8).  
The UBA domain packs against the N-lobe, locking αC in place and acting as a stabilising switch analogous to MARK/MELK kinases (oster2024thestructuresof pages 12-13).  
The AlphaFold model AF-Q9Y2K2-F1 mirrors the crystal fold and predicts a largely disordered C-tail bearing multiple regulatory phosphosites (oster2024thestructuresof pages 17-18).

## Regulation

LKB1 phosphorylates Thr221 in the activation loop, enabling catalytic activity (darling2021nutsandbolts pages 1-2).  
PKA phosphorylates Thr411, Ser493, Ser551 and Ser616 in the C-tail, recruiting 14-3-3 proteins and inhibiting kinase function (darling2021nutsandbolts pages 11-12).  
PTH1R signalling suppresses SIK3 via PKA in growth-plate chondrocytes, integrating hormonal cues with kinase activity (nishimori2019saltinduciblekinasesdictate pages 1-2).  
Loss or inhibition of SIK3 leads to DEPTOR accumulation and reduced mTORC1/2 signalling (csukasi2018thepthpthrpsik3pathway pages 1-1).  
The UBA domain is required for efficient LKB1-mediated activation by stabilising the αC-in conformation (oster2024thestructuresof pages 12-13).

## Function

SIK3 mRNA is abundant in brain, liver, cartilage and immune cells, indicating broad physiological roles (unknownauthors2017saltinduciblekinasesin pages 30-33).  
In growth-plate chondrocytes, SIK3 phosphorylates DEPTOR, thereby enhancing mTORC1/2 activity to drive hypertrophic differentiation and ossification (csukasi2018thepthpthrpsik3pathway pages 6-8).  
The kinase functions downstream of PTH1R to couple hormonal signals with nutrient sensing during skeletogenesis (csukasi2018thepthpthrpsik3pathway pages 5-6).  
In metabolic tissues, active SIK3 phosphorylates CRTC2/3 and class IIa HDACs, retaining them in the cytoplasm and suppressing CREB- and MEF2-dependent transcription (sonntag201814‐3‐3proteinsmediate pages 14-17).  
Pharmacological or genetic inhibition of SIK3 in macrophages skews differentiation toward an anti-inflammatory phenotype with elevated IL-10 (darling2017inhibitionofsik2 pages 7-8).

## Inhibitors

HG-9-91-01: first-generation pan-SIK inhibitor, IC₅₀ = 430 nM for SIK3 (peixoto2024discoveryofclinical pages 3-3).  
YKL-05-099: optimized analogue, IC₅₀ = 30 nM for SIK3 and efficacious in AML models (peixoto2024discoveryofclinical pages 3-3).  
ARN-3236: dual SIK2/SIK3 inhibitor, IC₅₀ = 6.6 nM for SIK3; enhances paclitaxel response in ovarian cancer (peixoto2024discoveryofclinical pages 3-3).  
MRIA9: tool compound, IC₅₀ = 22 nM for SIK3, co-crystalised to map binding determinants (peixoto2024discoveryofclinical pages 3-3, oster2024thestructuresof pages 8-10).  
GLPG3312 and related analogues provide improved pharmacokinetics for pan-SIK inhibition (temallaib2023optimizationofselectivity pages 4-6).

## Other Comments

A homozygous catalytic-domain mutation p.R129C abolishes kinase activity, causes DEPTOR accumulation and results in recessive metaphyseal skeletal dysplasia with immune deficiency (csukasi2018thepthpthrpsik3pathway pages 3-5).  
Sik3-null mice display disorganised growth plates and delayed chondrocyte hypertrophy, recapitulating human pathology (csukasi2018thepthpthrpsik3pathway pages 6-8).

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