## Phylogeny

Serine/threonine-protein kinase SGK2 belongs to the AGC kinase group, SGK subfamily, and is paralogous to AKT/PKB, PKA/PKG/PKC and S6K/RSK branches within the human kinome (tessier2006serumandglucocorticoid‐regulated pages 1-2, lang2006(patho)physiologicalsignificanceof pages 28-29).  
Orthologs are documented in mouse (Sgk2α/β), rat, zebrafish and Xenopus; a single homolog (sgk-1) exists in Caenorhabditis elegans, whereas no ortholog is detected in Drosophila melanogaster (unknownauthors2010functionalcharacterizationof pages 10-13, firestone2003stimulusdependentregulationof pages 2-3).  
Mammalian SGK isoforms can rescue yeast Ypk1/Ypk2 deficiency, highlighting deep functional conservation from Saccharomyces cerevisiae to vertebrates (firestone2003stimulusdependentregulationof pages 2-3).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr ⇌ ADP + protein-L-Ser/Thr-phosphate (kobayashi1999characterizationofthe pages 5-7).

## Cofactor Requirements

Catalytic turnover requires Mg²⁺ as the divalent cofactor; kinase assays were performed with MgATP, and no manganese substitution has been reported (kobayashi1999characterizationofthe pages 7-8).

## Substrate Specificity

Preferred consensus: R-X-R-X-X-S/T with an essential Arg at –3 and a second basic residue at –5; threonine is marginally favored over serine (kobayashi1999characterizationofthe pages 5-7, firestone2003stimulusdependentregulationof pages 6-8, tessier2006serumandglucocorticoid‐regulated pages 5-7).

## Structure

Domain organisation  
• N-terminal variable region (1-~80) lacking PH/PX domains; contains a nuclear-localisation signal (NLS 131-141) (firestone2003stimulusdependentregulationof pages 6-8).  
• Bilobal catalytic domain (83-355) with Lys127 in the glycine-rich/β3 region, HRD-motif Asp, DFG-motif Phe and activation-loop Thr278 (firestone2003stimulusdependentregulationof pages 5-6, kobayashi1999characterizationofthe pages 5-7).  
• C-terminal hydrophobic motif harbouring Ser356 and a PY-motif (295-298) for Nedd4-2 docking (kobayashi1999characterizationofthe pages 3-5, firestone2003stimulusdependentregulationof pages 6-8).

3-D information  
Homology modelling of residues 83-355 shows the canonical AGC fold; the phosphorylated hydrophobic motif docks into a conserved phosphate-binding pocket formed by two basic residues that stabilise the C-helix (firestone2003stimulusdependentregulationof pages 6-8, frodin2002aphosphoserinethreoninebindingpocket pages 9-10).  
SGK2, like SGK1, lacks the classical αC helix and instead contains a short antiparallel β-sheet that modulates ATP binding (maestro2020serumandglucocorticoidinduced pages 3-4).

## Regulation

Post-translational modifications  
• Ser356 phosphorylation by mTORC2 primes the kinase for PDK1 binding (frodin2002aphosphoserinethreoninebindingpocket pages 9-10, cristofano2017sgk1thedark pages 1-4).  
• PDK1 subsequently phosphorylates Thr278 in the activation loop, completing activation (kobayashi1999characterizationofthe pages 5-7).  
• Oxidative stress (H₂O₂) and IGF-1 trigger phosphorylation via the PI3K pathway (maestro2020serumandglucocorticoidinduced pages 4-6).  
• The PY motif recruits Nedd4-2, enabling ubiquitin-dependent control (firestone2003stimulusdependentregulationof pages 6-8).

Conformational / localisation control  
The NLS mediates stimulus-dependent nuclear-cytoplasmic shuttling; phosphorylation shifts the equilibrium toward the cytoplasm (firestone2003stimulusdependentregulationof pages 1-2).  
SGK2 expression is largely constitutive and not serum-inducible, contrasting with the transcriptionally regulated SGK1 (cristofano2017sgk1thedark pages 1-4).

## Function

Expression profile  
Highest in liver, kidney proximal tubule and pancreas; lower in brain; negligible induction by glucocorticoids or serum (tessier2006serumandglucocorticoid‐regulated pages 2-5, cristofano2017sgk1thedark pages 1-4).

Signalling context  
Acts downstream of PI3K-mTORC2-PDK1 signalling, operating in parallel to AKT (firestone2003stimulusdependentregulationof pages 5-6).

Documented substrates / targets  
Phosphorylates NDRG1 in cells (najafov2011characterizationofgsk2334470 pages 4-5).  
Up-regulates multiple transport proteins and ion channels, including ENaC, Kv1.3, KCNE1/KCNQ1, SLC6A19, EAAT4, AMPA/KA receptors, NHE3 and Na⁺/K⁺-ATPase (lang2006(patho)physiologicalsignificanceof pages 1-2, basnet2018serumandglucocorticoid pages 2-4).  
Catalyses PTOV1 Ser36/Ser53 phosphorylation, promoting 14-3-3 binding (unknownauthors2021themechanismof pages 26-32).

## Inhibitors

• GSK650394: 7-azaindole ATP-competitive inhibitor; IC₅₀ 103 nM for SGK2, ~30-fold selectivity versus most off-targets (jang2022serumandglucocorticoidregulated pages 9-11).  
• EMD638683: benzohydrazide scaffold with cross-isoform activity; detailed SGK2 potency not reported (basnet2018serumandglucocorticoid pages 4-5).  
• Current chemotypes show limited isoform selectivity; optimisation is required (unknownauthors2020synthesisandbiological pages 43-47).  
• Indirect inhibition via the PDK1 inhibitor GSK2334470 abrogates SGK2 Thr278 phosphorylation at ~30 nM (najafov2011characterizationofgsk2334470 pages 4-5).

## Other Comments

SGK2 participates in PI3K-driven oncogenic programmes; however, isoform-specific disease mutations or pathologies remain sparsely documented relative to SGK1/3 (basnet2018serumandglucocorticoid pages 4-5).

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