## Phylogeny

Serine/threonine-protein kinase SGK2 is a member of the AGC kinase group, SGK subfamily, and is paralogous to the AKT/PKB, PKA/PKG/PKC and S6K/RSK branches of the human kinome (Tessier & Woodgett, 2006; Lang et al., 2006). Orthologues are present in mouse (Sgk2α/β), rat, zebrafish and Xenopus; a single homologue (sgk-1) exists in Caenorhabditis elegans, but none is detected in Drosophila melanogaster (Unknown Authors, 2010; Firestone et al., 2003). Mammalian SGKs can rescue the essential Ypk1/Ypk2 function in budding yeast, indicating deep evolutionary conservation (Firestone et al., 2003).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr ⇌ ADP + protein-L-Ser/Thr-phosphate (Kobayashi et al., 1999).

## Cofactor Requirements

Catalytic activity requires Mg²⁺; kinase assays were performed with MgATP, and no Mn²⁺ substitution has been reported (Kobayashi et al., 1999).

## Substrate Specificity

SGK2 prefers the consensus sequence R-X-R-X-X-S/T, with an obligatory Arg at –3 and a second basic residue at –5. Threonine is marginally favoured over serine (Kobayashi et al., 1999; Firestone et al., 2003; Tessier & Woodgett, 2006).

## Structure

• N-terminal variable segment (~1–80) contains a nuclear-localisation signal (NLS 131–141) but no PH/PX domains (Firestone et al., 2003).  
• Bilobal catalytic core (83–355) harbours Lys127 (β3), the HRD Asp, the DFG Phe and the activation-loop Thr278 (Firestone et al., 2003; Kobayashi et al., 1999).  
• C-terminal hydrophobic motif includes Ser356 and a PY motif (295–298) for Nedd4-2 docking (Kobayashi et al., 1999; Firestone et al., 2003).  
Homology models show the canonical AGC fold; the phosphorylated hydrophobic motif binds a conserved basic pocket that stabilises the C-helix (Firestone et al., 2003; Frödin et al., 2002). SGK2 lacks the classical αC helix and instead contains a short antiparallel β-sheet influencing ATP binding (Maestro et al., 2020).

## Regulation

Post-translational control  
• Ser356 is phosphorylated by mTORC2, priming the kinase for PDK1 binding (Frödin et al., 2002; Di Cristofano, 2017).  
• PDK1 then phosphorylates Thr278 in the activation loop, completing activation (Kobayashi et al., 1999).  
• Oxidative stress (H₂O₂) and IGF-1 stimulate phosphorylation through the PI3K pathway (Maestro et al., 2020).  
• The C-terminal PY motif recruits Nedd4-2, facilitating ubiquitin-dependent regulation (Firestone et al., 2003).

Conformational/localisation control  
The NLS mediates nuclear-cytoplasmic shuttling; phosphorylation shifts the equilibrium towards the cytoplasm (Firestone et al., 2003). SGK2 transcription is largely constitutive and not serum-inducible, unlike SGK1 (Di Cristofano, 2017).

## Function

Expression pattern  
Highest expression in liver, kidney proximal tubule and pancreas; lower in brain; minimal induction by glucocorticoids or serum (Tessier & Woodgett, 2006; Di Cristofano, 2017).

Signalling context  
Acts downstream of PI3K–mTORC2–PDK1 signalling in parallel with AKT (Firestone et al., 2003).

Documented substrates/targets  
Phosphorylates NDRG1 in cells (Najafov et al., 2011). Regulates multiple transporters and ion channels, including ENaC, Kv1.3, KCNE1/KCNQ1, SLC6A19, EAAT4, AMPA/KA receptors, NHE3 and Na⁺/K⁺-ATPase (Lang et al., 2006; Basnet et al., 2018). Catalyses PTOV1 Ser36/Ser53 phosphorylation, promoting 14-3-3 binding (Unknown Authors, 2021).

## Inhibitors

• GSK650394: 7-azaindole ATP-competitive inhibitor, IC₅₀ ≈ 103 nM for SGK2, ~30-fold selectivity over most off-targets (Jang et al., 2022).  
• EMD638683: benzohydrazide scaffold with cross-isoform activity; precise SGK2 potency not reported (Basnet et al., 2018).  
• Limited isoform selectivity across current chemotypes (Unknown Authors, 2020).  
• Indirect inhibition: the PDK1 inhibitor GSK2334470 blocks SGK2 Thr278 phosphorylation at ~30 nM (Najafov et al., 2011).

## Other Comments

SGK2 participates in PI3K-driven oncogenic programmes, but isoform-specific disease mutations or pathologies remain less documented than for SGK1/3 (Basnet et al., 2018).

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