## Phylogeny

Serine/threonine-protein kinase SGK1 is a member of the AGC kinase family and is highly conserved from yeast to mammals, indicating that it arose early in eukaryotic evolution (jeyaraj, pp. 27-30; Daniels, 2010, pp. 31-35). Within the human kinome, SGK1, SGK2 and SGK3 form a distinct sub-family that shares ~80 % amino-acid identity in the catalytic domain. Phylogenetic analyses place this sub-family close to other AGC kinases such as Akt/PKB, PKA and p70-S6K, reflecting common regulatory inputs from PDK1 and mTOR complexes (Daniels, 2010, pp. 31-35; Firestone et al., 2003, pp. 5-6).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Jeyaraj, pp. 27-30)

## Cofactor Requirements

Mg²⁺ is required for catalytic activity (Daniels, 2010, pp. 35-39).

## Substrate Specificity

SGK1 preferentially phosphorylates substrates that contain the consensus motif R-X-R-X-X-(S/T)-φ, where φ represents a hydrophobic residue. This motif is shared with other AGC kinases and underlies SGK1-mediated phosphorylation of targets that regulate ion channels, transporters and transcription factors, exemplified by the ubiquitin ligase NEDD4L (Daniels, 2010, pp. 35-39; Jang et al., 2022, pp. 13-14).

## Structure

SGK1 consists of a ~330-residue bilobal kinase catalytic domain flanked by regulatory sequences.  
• N-terminus: variable region harbouring a nuclear-localisation signal and a six-residue ubiquitin-binding motif that influences localisation and degradation (Firestone et al., 2003, pp. 5-6; Maestro et al., 2020, pp. 3-4).  
• Catalytic domain: contains the conserved ATP-binding lysine (equivalent to Lys127 in other kinases), an activation loop (Thr256) phosphorylated by PDK1, and a hydrophobic motif (Ser422) phosphorylated by mTORC2 to stabilise the active conformation (Daniels, 2010, pp. 35-39; Jang et al., 2022, pp. 1-3).  
Overall, the architecture matches the canonical AGC bilobal fold with an N-terminal β-sheet lobe and C-terminal α-helical lobe (Daniels, 2010, pp. 31-35; Jang et al., 2022, p. 17).

## Regulation

• Transcriptional induction by serum, glucocorticoids, mineralocorticoids, cytokines, hyperosmotic stress, high glucose and oxidative stress via receptor response elements in the SGK1 promoter (Firestone et al., 2003, p. 11; Daniels, 2010, pp. 194-196).  
• Post-translational activation through sequential phosphorylation: PDK1 targets Thr256 in the activation loop; mTORC2 phosphorylates Ser422 in the hydrophobic motif. Additional phosphorylation sites (Ser78, Thr369) integrate signals from PKA, MAPK and other pathways (Daniels, 2010, pp. 35-39; Firestone et al., 2003, pp. 9-10; Jang et al., 2022, pp. 1-3, 14-15).  
• Spatial regulation via interaction with scaffold proteins such as NHERF2, positioning SGK1 at the plasma membrane (Lou et al., 2016, pp. 14-15).  
• Protein stability is curtailed by ubiquitination through E3 ligases (e.g., Nedd4-2), conferring a short half-life (Maestro et al., 2020, pp. 7-8).

## Function

Widely expressed in kidney, brain, lung and muscle, SGK1 coordinates numerous physiological processes:  
• Ion and nutrient transport: enhances epithelial Na⁺ reabsorption by phosphorylating NEDD4L, which stabilises ENaC; modulates voltage-gated Na⁺ channels (SCN5A), K⁺ channels (ROMK1, KCNA/KCNQ), Ca²⁺ channels (TRPV5/6), CFTR, Na⁺/K⁺-ATPase, and glucose transporters GLUT1 and SGLT1 (Daniels, 2010, pp. 196-202; Lou et al., 2016, pp. 3-5).  
• Cell survival and proliferation: phosphorylates FOXO1/3 to inhibit pro-apoptotic transcription; phosphorylates MAPT/TAU in neurons, influencing microtubule dynamics and memory consolidation; activates MDM2 to promote p53 degradation, linking SGK1 to cell-cycle and oncogenic pathways (Firestone et al., 2003, pp. 11-12; Lang et al., 2009, pp. 12-13; Daniels, 2010, pp. 199-202).

## Inhibitors

Several small-molecule ATP-competitive inhibitors have been developed, including GSK650394, EMD638683 and pyrazolopyrazine derivatives. These compounds are being explored for potential use in hypertension, diabetes and cancer (Jang et al., 2022, pp. 14-15; Lang et al., 2009, pp. 6-7; Guerriero et al., 2020, p. 25).

## Other Comments

SGK1 dysregulation contributes to hypertension, diabetic nephropathy, fibrosis and cancer. Gain-of-function polymorphisms correlate with elevated blood pressure and sodium retention. Distinct isoforms display different subcellular localisations and effects on ENaC, with isoform 2 exerting a stronger stimulatory influence than isoform 1 (Daniels, 2010, pp. 194-196; Guerriero et al., 2020, pp. 15-17; Lang et al., 2020, pp. 1-3).

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