## Phylogeny

Serine/threonine-protein kinase Sgk1 (SGK1) is a member of the AGC kinase group, which comprises 63 human kinases and is conserved across species including yeast, worm, and fly (manning2002theproteinkinase pages 1-2). Phylogenetic analysis classifies SGK1 within the AGC family, which also includes protein kinase A (PKA), protein kinase G (PKG), and protein kinase C (PKC) families (johnson2023anatlasof pages 4-5). SGK1 is evolutionarily related to the AKT/PKB kinase family, sharing conserved kinase domains and functional similarities (johnson2023anatlasof pages 4-5, johnson2023anatlasof pages 7-7). Kinome mapping places SGK1 alongside the related kinases AKT1, AKT2, and AKT3, which underscores their close evolutionary relationship within the AGC group (johnson2023anatlasof pages 4-4).

## Reaction Catalyzed

As a serine/threonine kinase, SGK1 catalyzes the transfer of the γ-phosphate group from an ATP molecule to the hydroxyl group of serine or threonine residues on a protein substrate (johnson2023anatlasof pages 1-2, johnson2023anatlasof pages 6-7, johnson2023anatlasof pages 12-18). This phosphorylation reaction is a post-translational modification that modulates the activity, localization, or interactions of the target protein (johnson2023anatlasof pages 3-4, johnson2023anatlasof pages 5-6).

## Cofactor Requirements

The catalytic activity of SGK1 is dependent on ATP as the phosphate donor cofactor (johnson2023anatlasof pages 9-10, johnson2023anatlasof pages 4-4). The phosphoryl transfer reaction also requires divalent metal ion cofactors, typically Mg²⁺ or Mn²⁺, to stabilize the ATP molecule and facilitate catalysis (johnson2023anatlasof pages 2-3, johnson2023anatlasof pages 7-7, johnson2023anatlasof pages 12-18).

## Substrate Specificity

SGK1 is classified as a basophilic kinase that belongs to Cluster 1 based on substrate motif preferences, indicating a preference for basic residues like arginine (R) near the phosphorylation site (johnson2023anatlasof pages 12-18, johnson2023anatlasof pages 2-3). The specific consensus substrate motif for SGK1 is RxRxxS/T, which denotes a requirement for an arginine residue at the -5 and -3 positions relative to the phospho-acceptor serine (S) or threonine (T) (johnson2023anatlasof pages 18-20, johnson2023anatlasof pages 12-18). Substrate recognition is determined by both positive selection for specific residues within the motif and negative selection against non-cognate amino acids to ensure fidelity (johnson2023anatlasof pages 1-2).

## Structure

SGK1 is structurally typical of AGC family kinases, comprising three primary domains: an N-terminal region, a central catalytic kinase domain responsible for phosphorylation, and a C-terminal hydrophobic motif that is critical for regulation (johnson2023anatlasof pages 12-18, johnson2023anatlasof pages 18-20). Key structural features within the catalytic domain include the activation loop, which must be phosphorylated for kinase activation, and the C-helix, which is essential for positioning the ATP binding site to facilitate catalysis (johnson2023anatlasof pages 12-18, johnson2023anatlasof pages 18-20). While no specific PDB ID for SGK1 is provided in the context, structural models are based on homologous kinase-substrate complexes, such as AKT1 bound to a GSK3β substrate peptide (PDB: 1O6K) (johnson2023anatlasof pages 18-20, johnson2023anatlasof pages 12-18).

## Regulation

SGK1 activity is regulated by post-translational modifications, primarily activating phosphorylations (johnson2023anatlasof pages 6-6, johnson2023anatlasof pages 5-6). Full activation of SGK1 requires dual phosphorylation: PDK1 phosphorylates the activation loop at residue Thr256, and mTORC2 phosphorylates the hydrophobic motif at Ser422 (johnson2023anatlasof pages 12-18, johnson2023anatlasof pages 5-5). In addition to activation, SGK1 is subject to inhibitory regulation via ubiquitination mediated by the E3 ubiquitin ligase NEDD4L, which can target the kinase for proteasomal degradation (johnson2023anatlasof pages 12-18, johnson2023anatlasof pages 5-5).

## Function

SGK1 functions as a key downstream effector in the PI3K (phosphoinositide 3-kinase) signaling pathway, where it is activated following PDK1-mediated phosphorylation (johnson2023anatlasof pages 6-6). It regulates numerous cellular processes, including ion transport, cell survival, proliferation, and metabolism, by phosphorylating downstream substrates (johnson2023anatlasof pages 6-6). Notable substrates of SGK1 include the E3 ubiquitin ligase NEDD4L, which regulates the epithelial sodium channel (ENaC), and glycogen synthase kinase 3 beta (GSK3B), which modulates glycogen metabolism and cell survival pathways (johnson2023anatlasof pages 6-6, johnson2023anatlasof pages 3-4, johnson2023anatlasof pages 4-5).

## Inhibitors

The activity of SGK1 can be experimentally inhibited by small molecule compounds. Validated inhibitors used to study SGK1-specific functions in cellular and biochemical assays include GSK650394 and EMD638683 (johnson2023anatlasof pages 6-6, johnson2023anatlasof pages 4-5).

## Other Comments

Dysregulation of SGK1 is implicated in several human diseases. It is linked to hypertension through its effects on renal sodium handling and blood pressure control (johnson2023anatlasof pages 6-6). It is also associated with cancer due to its roles in promoting cell proliferation and survival, and with metabolic syndrome via its influence on glucose metabolism and cell growth pathways (johnson2023anatlasof pages 6-6, johnson2023anatlasof pages 4-5).

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