1. Phylogeny  
   Serine/threonine‐protein kinase SGK1 belongs to the AGC kinase family and is one of three SGK isoforms (SGK1, SGK2, and SGK3) that are conserved across vertebrates, with orthologs present in all mammalian species. SGK1 shares evolutionary relationships with other AGC kinases such as Akt/PKB, and its catalytic domain is highly conserved relative to these kinases (jang2022serumandglucocorticoidregulated pages 1-3, maestro2020serumandglucocorticoidinduced pages 3-4). The kinase forms part of the evolutionary core of TOR pathway regulators alongside PDK1, PKB (Akt), RSK, and other AGC kinases, an ancient set traceable to the common ancestor of eukaryotes (maestro2020serumandglucocorticoidinduced pages 3-4, akhoon2019computationalinsightsinto pages 1-4).
2. Reaction Catalyzed  
   SGK1 catalyzes the phosphorylation reaction in which ATP and a protein substrate containing a serine or threonine residue are converted into ADP, the phosphorylated protein, and a proton:  
     ATP + [protein]‑(L‑serine or L‑threonine) → ADP + [protein]‑(L‑serine/threonine‑phosphate) + H⁺ (akhoon2019computationalinsightsinto pages 1-4).
3. Cofactor Requirements  
   The catalytic activity of SGK1 depends on the presence of divalent metal ions, with Mg²⁺ being required as a cofactor for proper ATP binding and phosphoryl transfer during catalysis (akhoon2019computationalinsightsinto pages 1-4).
4. Substrate Specificity  
   SGK1 primarily phosphorylates substrates on serine and threonine residues in a consensus sequence that generally features basic amino acids upstream of the phospho-acceptor site. Biochemical studies indicate that SGK1, similar to Akt, shows a substrate preference for motifs characterized by arginine residues at defined positions, with evidence supporting a consensus pattern resembling R‑X‑R‑X‑X‑[S/T] (douglass2012identifyingproteinkinase pages 12-12, maestro2020serumandglucocorticoidinduced pages 3-4).
5. Structure  
   SGK1 is organized into distinct domains that contribute to its catalytic function and regulation. The protein contains an N-terminal PX-like domain that is implicated in subcellular localization and possibly membrane association, a central kinase domain responsible for catalytic activity, and a C-terminal hydrophobic motif. The catalytic domain displays the typical bilobal architecture seen in serine/threonine kinases, with an N-terminal lobe composed primarily of β-strands and a C-terminal lobe predominantly made up of α-helices. Key conserved motifs within the kinase domain include the DFG motif in the activation loop, which is essential for coordinating ATP and the required divalent cation, as well as a regulatory αC helix that adopts distinct conformations in active versus inactive states (akhoon2019computationalinsightsinto pages 4-7, jang2022serumandglucocorticoidregulated pages 1-3). Structural studies and molecular dynamics simulations have highlighted that in the inactive conformation, SGK1 may lack a fully formed αC helix, whereas phosphorylation-dependent activation induces the inward movement of the helix and assembly of the regulatory spine (akhoon2019computationalinsightsinto pages 7-9, maestro2020serumandglucocorticoidinduced pages 4-6).
6. Regulation  
   The full activation of SGK1 is achieved through a series of phosphorylation events. Primarily, phosphorylation occurs on Thr256 within the activation loop by 3‑phosphoinositide‑dependent protein kinase 1 (PDK1) following priming by mTOR complex 2 (mTORC2), which phosphorylates the hydrophobic motif at Ser422. This two‐step phosphorylation process is crucial for stabilizing the active conformation of the kinase (jang2022serumandglucocorticoidregulated pages 1-3, maestro2020serumandglucocorticoidinduced pages 3-4). In addition to these activating events, SGK1 is transcriptionally induced by serum and glucocorticoids and is further regulated by rapid ubiquitination and proteasome-mediated degradation, resulting in a short half-life for both its mRNA and protein forms (maestro2020serumandglucocorticoidinduced pages 3-4, akhoon2019computationalinsightsinto pages 1-4). Conformational plasticity, as evidenced by molecular dynamics studies, also contributes to its regulation by facilitating transitions between inactive (DFG-out) and active (DFG-in) states (akhoon2019computationalinsightsinto pages 19-22).
7. Function  
   SGK1 plays multifaceted roles in cellular physiology and stress response by regulating a wide array of substrates. It modulates ion channel activities, including the up-regulation of epithelial Na⁺ channels (ENaC) through the phosphorylation of the NEDD4L ubiquitin E3 ligase, which prevents ENaC degradation; it also regulates various K⁺, Ca²⁺, and Cl⁻ channels. SGK1 controls membrane transporter function by affecting multiple solute carrier proteins, including glucose transporters (GLUT1 and GLUT4), amino acid transporters, and sodium-dependent nutrient cotransporters. In addition, SGK1 phosphorylates key intracellular enzymes such as glycogen synthase kinase 3 (GSK3A/B) and modulates transcription factors including FOXO1 and FOXO3, thereby influencing cell growth, survival, migration, and apoptosis (jang2022serumandglucocorticoidregulated pages 1-3, maestro2020serumandglucocorticoidinduced pages 7-8). SGK1 also impacts neuronal functions by phosphorylating proteins such as TAU, which is involved in microtubule dynamics and neurite formation, and it contributes to cardiac repolarization and memory consolidation through its effects on ion channels and transporter expression. Furthermore, SGK1 can phosphorylate MDM2, leading to enhanced ubiquitination of p53, and it modulates the activity of MAP kinases (MAPK1/ERK2) by facilitating their interaction with upstream activators (maestro2020serumandglucocorticoidinduced pages 7-8, jang2022serumandglucocorticoidregulated pages 13-14).
8. Other Comments  
   Several small-molecule inhibitors targeting SGK1 have been developed for experimental purposes. Notable inhibitors include GSK650394, EMD638683, SI113, and herbacetin, which have been evaluated in various preclinical models. These inhibitors are of interest due to SGK1’s involvement in pathophysiological conditions such as hypertension, diabetic nephropathy, cardiac hypertrophy, and various cancers. Elevated levels and sustained activity of SGK1 have been correlated with increased sodium retention, insulin-dependent salt sensitivity of blood pressure, and drug resistance mechanisms in breast cancer. Inhibitors of SGK1 may prove beneficial in modulating its activity to address these disease states (jang2022serumandglucocorticoidregulated pages 13-14, jang2022serumandglucocorticoidregulated pages 4-5, banerjee2013phosphorylationubiquitylationand pages 26-29).
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