1. Phylogeny  
   Serine/threonine‐protein kinase SGK3 (also known as cytokine-independent survival kinase, CISK, or SGKL) is a member of the serum/glucocorticoid‐regulated kinase family that belongs to the AGC kinase superfamily. SGK3 shares evolutionary conservation with other SGK family members (SGK1 and SGK2) as well as with related kinases such as protein kinase B (Akt) and protein kinase A (PKA); its catalytic core and regulatory domains are preserved across vertebrates, indicating that its functions have been maintained since the early divergence of eukaryotes (endicott2012thestructuralbasis pages 12-13). The kinase is classified within the AGC group, a set of protein kinases defined by conserved domains and regulatory motifs that include a characteristic activation loop and hydrophobic motif, with orthologous sequences found in most mammals and other eukaryotic organisms (pei2023computationalanalysisof pages 15-16). In addition, SGK3 is distinguished by a unique N-terminal phosphoinositide-binding (PX) domain that underlies its specialized subcellular localization compared to its paralogs; this domain is critical for binding phosphatidylinositol 3-phosphate and directs the kinase to endosomal membranes, further supporting its assignment within the evolutionarily conserved AGC kinase core (jang2022serumandglucocorticoidregulated pages 3-4).
2. Reaction Catalyzed  
   SGK3 catalyzes the transfer of a phosphate group from ATP to serine or threonine residues on substrate proteins. The chemical reaction can be represented as follows:  
     ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺.  
   This phosphorylation event modulates the function of its substrates and is fundamental to the regulation of various cellular processes (endicott2012thestructuralbasis pages 4-6).
3. Cofactor Requirements  
   The catalytic activity of SGK3 is dependent on the presence of Mg²⁺ ions, which serve to stabilize the binding of ATP in the active site and facilitate the phosphoryl transfer reaction. Mg²⁺ is essential for aligning the ATP molecule properly, thus ensuring efficient catalysis by the kinase (endicott2012thestructuralbasis pages 4-6, blazquez2020potentialforprotein pages 1-2).
4. Substrate Specificity  
   As a serine/threonine kinase within the AGC family, SGK3 exhibits substrate specificity that often involves the recognition of basic amino acid residues proximal to the phosphorylation site. Its substrates typically display a consensus motif resembling Arg-X-Arg-X-X-[Ser/Thr], a motif that is common among AGC kinases such as Akt and SGK1. This preference for positively charged residues at defined positions helps position the substrate for efficient catalysis by aligning the target hydroxyl group with the γ-phosphate of ATP (endicott2012thestructuralbasis pages 4-6, jang2022serumandglucocorticoidregulated pages 3-4).
5. Structure  
   SGK3 is organized into several distinct domains that are critical for its function. At the N-terminus, SGK3 contains a phosphoinositide-binding PX domain that mediates the localization of the kinase to phosphatidylinositol 3-phosphate–rich endosomal membranes; this domain is unique to SGK3 among the SGK family and underpins its specialized regulatory roles in membrane trafficking and spatial signaling. Following this, the conserved catalytic kinase domain is present, which adopts the canonical bilobal structure seen in eukaryotic protein kinases. The N-terminal lobe primarily binds ATP via a glycine-rich loop (P-loop) and contains a conserved catalytic lysine in the VAIK motif, while the C-terminal lobe is responsible for substrate recognition and catalysis and includes conserved motifs such as the HRD sequence in the catalytic loop and the DFG motif at the start of the activation segment. A hydrophobic motif located toward the C-terminus further participates in stabilizing the active conformation of the enzyme through intramolecular interactions with a hydrophobic pocket typically found in the N-lobe; such features are common to AGC kinases and are critical for full catalytic activity (maestro2020serumandglucocorticoidinduced pages 4-6, endicott2012thestructuralbasis pages 12-13). Structural studies, including crystallographic analyses and advanced prediction methods like AlphaFold, have revealed that phosphorylation-induced conformational rearrangements—particularly within the activation loop as well as an accompanying reorientation of the C-helix—are key determinants in converting SGK3 from its inactive to its active state (blazquez2020potentialforprotein pages 1-2, jang2022serumandglucocorticoidregulated pages 3-4).
6. Regulation  
   The regulation of SGK3 is orchestrated via a combination of phosphorylation events and subcellular targeting that modulate its activity and access to substrates. Upstream kinases, notably phosphoinositide-dependent protein kinase 1 (PDK1) and components of the mammalian target of rapamycin complex 2 (mTORC2), phosphorylate SGK3 on key residues within the activation loop and hydrophobic motif; these modifications are essential for achieving full catalytic activity. The phosphorylation of the activation loop likely facilitates the correct positioning of essential catalytic residues within the kinase domain, while hydrophobic motif phosphorylation promotes intramolecular interactions that stabilize the active conformation. In addition, the unique PX domain of SGK3 targets the kinase to endosomes by binding phosphatidylinositol 3-phosphate, thereby confining its activity to specific membrane compartments and contributing to spatial regulation within the cell. Although detailed mapping of all regulatory phosphorylation sites on SGK3 is still emerging, the mechanisms observed for related AGC kinases suggest that SGK3 is subject to precise post-translational control, which may also include ubiquitination events leading to proteasomal degradation under certain conditions (jang2022serumandglucocorticoidregulated pages 3-4, maestro2020serumandglucocorticoidinduced pages 11-12, endicott2012thestructuralbasis pages 10-12).
7. Function  
   SGK3 plays a pivotal role in the regulation of a wide variety of ion channels and membrane transporters, thereby influencing processes such as cell growth, proliferation, survival, and migration. Functionally, SGK3 upregulates the activity of several ion channels: it enhances the function of sodium channels including SCNN1A (ENaC) and SCN5A, modulates multiple potassium channels (e.g., KCNA3/KV1.3, KCNE1, KCNQ1, KCNH2/HERG), and regulates epithelial calcium channels such as TRPV5 and TRPV6. In addition, SGK3 influences other membrane transporters such as the chloride channel BSND, the creatine transporter SLC6A8, the Na⁺/dicarboxylate cotransporter SLC13A2, the Na⁺-dependent phosphate cotransporter SLC34A2, and various amino acid and glutamate transporters including SLC1A5, SLC6A19, SLC1A3, SLC1A6, and SLC1A7, as well as glutamate receptors GRIA1 and GRIK2. Beyond its effects on ion transport, SGK3 phosphorylates key intracellular substrates such as NEDD4L and GSK3B, thereby modulating processes that regulate cellular proliferation and survival. Furthermore, SGK3 has been implicated in the regulation of renal tubular phosphate transport and bone density, and it has a role in the modulation of estrogen receptor transcription activity through phosphorylation of FLII, while it negatively regulates the function of the ITCH/AIP4 E3 ubiquitin ligase via phosphorylation. These diverse functions underscore the importance of SGK3 in maintaining cellular homeostasis and signal transduction, making it a crucial node in pathways that govern ion transport, metabolism, and cell viability (jang2022serumandglucocorticoidregulated pages 13-14, maestro2020serumandglucocorticoidinduced pages 7-8, blazquez2020potentialforprotein pages 1-2).
8. Other Comments  
   Experimental efforts to target SGK family kinases have led to the exploration of ATP-competitive inhibitors that may modulate kinase activity in disease contexts. Although specific small-molecule inhibitors tailored for SGK3 have been less extensively characterized compared with those for SGK1, the shared structural features within the AGC kinase superfamily indicate that strategies developed for other members may be adaptable for SGK3. Dysregulation of SGK3 activity has been associated with pathological processes including altered renal function, imbalances in electrolyte transport, and potential contributions to oncogenic signaling pathways. The integration of SGK3 within key signaling cascades—particularly those mediated by PI3K and mTOR—further emphasizes its relevance as a therapeutic target, with inhibitors potentially beneficial in conditions such as metabolic disorders and cancers. Ongoing biochemical and pharmacological studies are expected to further elucidate selective inhibition strategies for SGK3, with a focus on refining inhibitor specificity and assessing clinical efficacy (jang2022serumandglucocorticoidregulated pages 13-14, maestro2020serumandglucocorticoidinduced pages 13-14, blazquez2020potentialforprotein pages 1-2).
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