1. Phylogeny  
   Serine/threonine‐protein kinase Sgk2 (SGK2) is classified as a member of the serum and glucocorticoid‐regulated kinase (SGK) family, which itself is a subfamily of the larger AGC kinase group that also comprises proteins such as protein kinase A (PKA), protein kinase C (PKC), and protein kinase B (AKT) (Manning2002theproteinkinase pages 2-3, Miranda‐Saavedra2007classificationandfunctional pages 1-2). SGK2, along with its paralogs SGK1 and SGK3, shares significant sequence homology within their catalytic domains; notably, SGK1 and SGK3 exhibit approximately 80% identity in their kinase domains, and SGK2 is similarly related though it is characterized by a distinct, shortened N-terminal region (Guerriero2020serumandglucocorticoidinducible pages 3-5, Maestro2020serumandglucocorticoidinduced pages 3-4). Comparative phylogenetic analyses based on kinase domain sequences have placed SGK2 firmly within the evolutionary core of the AGC kinases—a set of signaling proteins that emerged early during eukaryotic evolution and have been conserved across multiple species (Manning2002theproteinkinase pages 2-3, Miranda‐Saavedra2007classificationandfunctional pages 1-2). In mammals, the presence of SGK2 along with other SGK isoforms has been documented in numerous tissues, with orthologs that display a high degree of conservation of the catalytic domain despite divergence in regulatory regions, suggesting that the fundamental enzymatic functions of these kinases have been maintained since the last common eukaryotic ancestor (Guerriero2020serumandglucocorticoidinducible pages 3-5, Jehle2022ahumankinase pages 12-13). Phylogenetic classification tools employing hidden Markov models have efficiently resolved the SGK family from the rest of the kinome, relying on subtle differences in the catalytic and accessory domain sequences; these analyses consistently assign SGK2 to the AGC kinase subfamily (Miranda‐Saavedra2007classificationandfunctional pages 1-2, Manning2002theproteinkinase pages 2-3). As such, SGK2 is evolutionarily related not only to its SGK counterparts but also to other key kinases involved in growth and survival pathways, affirming its place within a molecular network that includes kinases from the TOR signaling cascade and the PI3K/PDK1 axis (Guerriero2020serumandglucocorticoidinducible pages 3-5, Maestro2020serumandglucocorticoidinduced pages 3-4).
2. Reaction Catalyzed  
   SGK2 catalyzes the transfer of a phosphate group from adenosine triphosphate (ATP) to the hydroxyl group of serine or threonine residues present on substrate proteins; the chemical reaction can be formally represented as follows: ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺ (Firestone2003stimulusdependentregulationof pages 1-2). This phosphorylation reaction is characteristic of serine/threonine kinases and is fundamental to the regulation of protein function by altering their conformation, activity, and interaction with other macromolecules (Firestone2003stimulusdependentregulationof pages 1-2). The catalytic process involves precise orientation and binding of ATP in the active site, coordinated by essential catalytic residues that mediate phosphate transfer (Firestone2003stimulusdependentregulationof pages 1-2, Maestro2020serumandglucocorticoidinduced pages 3-4).
3. Cofactor Requirements  
   The enzymatic activity of SGK2 depends on the presence of divalent metal ions, with Mg²⁺ serving as the critical cofactor required for ATP coordination and catalysis (Maestro2020serumandglucocorticoidinduced pages 4-6). Mg²⁺ binds to ATP within the kinase’s active site, facilitating the proper orientation of the nucleotide’s phosphate groups for efficient transfer to substrate proteins (Firestone2003stimulusdependentregulationof pages 1-2). The requirement for Mg²⁺ is a common feature shared by kinases of the AGC family and is essential for driving the chemical reaction under physiological conditions, ensuring that SGK2 activity is tightly coupled to the intracellular levels of both ATP and Mg²⁺ (Maestro2020serumandglucocorticoidinduced pages 4-6, Firestone2003stimulusdependentregulationof pages 1-2).
4. Substrate Specificity  
   The substrate specificity of SGK2 is defined by a consensus phosphorylation motif that has been identified for the SGK family. SGK2 preferentially phosphorylates serine or threonine residues located within substrates that contain the R-X-R-X-X-(S/T) motif, where “R” stands for arginine, “X” represents any amino acid, and “S/T” is the phospho-acceptor residue (Maestro2020serumandglucocorticoidinduced pages 4-6). This recognition sequence directs SGK2 to a range of target proteins that are involved in the regulation of ion transport and membrane excitability. In particular, SGK2 has been functionally associated with the up-regulation of a diverse set of membrane channels and transporters, including the epithelial sodium channel (SCNN1A/ENAC), potassium channels such as KCNA3/Kv1.3, KCNE1, and KCNQ1, the amino acid transporter SLC6A19, glutamate transporter SLC1A6/EAAT4, glutamate receptors GRIA1/GLUR1 and GRIK2/GLUR6, as well as the Na(+)/H(+) exchanger SLC9A3/NHE3 and the Na(+)/K(+) ATPase (Guerriero2020serumandglucocorticoidinducible pages 3-5). This consensus sequence is shared among SGK isoforms and relates to the ability of these kinases to phosphorylate substrates that function in cellular processes ranging from ionic regulation to signal transduction, thereby ensuring precise modulation of numerous physiological pathways (Tessier2006serumandglucocorticoid‐regulated pages 5-7, Maestro2020serumandglucocorticoidinduced pages 4-6).
5. Structure  
   SGK2 is organized into distinct domains that reflect its function as an enzyme within the AGC kinase family. The protein comprises an N-terminal variable region, a centrally located catalytic kinase domain, and a C-terminal regulatory region; the N-terminal segment in SGK2 is notably shorter relative to its paralogs SGK1 and SGK3 (Guerriero2020serumandglucocorticoidinducible pages 3-5, Maestro2020serumandglucocorticoidinduced pages 3-4). The central kinase domain adopts the characteristic bilobal structure observed in serine/threonine kinases, with the N-terminal lobe primarily constituted by β-sheets and an α-helix (often the C-helix) that contributes to ATP binding, and a larger C-terminal lobe that is rich in α-helices and is responsible for substrate recognition and catalytic efficacy (Miranda‐Saavedra2007classificationandfunctional pages 11-12, Maestro2020serumandglucocorticoidinduced pages 3-4). Key structural elements within this domain include the ATP-binding pocket, the activation loop, and the catalytic loop; the conserved lysine residue found in the ATP-binding pocket plays a pivotal role in aligning ATP for phosphate transfer, while a threonine residue within the activation loop, once phosphorylated by upstream kinases, is crucial for full enzymatic activation (Maestro2020serumandglucocorticoidinduced pages 4-6, Zhao2007crystalstructureof pages 1-2). Although a high-resolution crystal structure for SGK2 has not been reported, homology models based on the well-defined structure of SGK1 indicate that SGK2 most likely exhibits a similar overall fold, encompassing a hydrophobic spine, a well-conserved C-helix, and other regulatory motifs typical of AGC kinases (Jehle2022ahumankinase pages 12-13, Maestro2020serumandglucocorticoidinduced pages 4-6). The presence of an abbreviated N-terminal region compared to SGK1 further distinguishes SGK2 within the SGK family, and this structural variation may underlie its differential regulation and tissue-specific functions (Guerriero2020serumandglucocorticoidinducible pages 3-5, Maestro2020serumandglucocorticoidinduced pages 4-6).
6. Regulation  
   Regulation of SGK2 occurs primarily through post-translational modifications rather than robust transcriptional induction, which is in contrast to the regulation observed for SGK1 under glucocorticoid stimulation (Maestro2020serumandglucocorticoidinduced pages 4-6, Guerriero2020serumandglucocorticoidinducible pages 3-5). Activation of SGK2 is mediated via the phosphoinositide 3-kinase (PI3K) pathway; specifically, the kinase is phosphorylated by phosphoinositide-dependent kinase 1 (PDK1) at residues located within its activation loop, a modification that is essential for achieving full catalytic activity (Maestro2020serumandglucocorticoidinduced pages 4-6, Tessier2006serumandglucocorticoid‐regulated pages 5-7). Although higher concentrations of PDK1 are needed for SGK2 activation in comparison with its SGK counterparts, the overall mechanism of activation through PI3K-PDK1 signaling is conserved across the SGK family (Maestro2020serumandglucocorticoidinduced pages 4-6, Tessier2006serumandglucocorticoid‐regulated pages 5-7). In addition to phosphorylation, SGK2 regulation is influenced by its subcellular localization; the enzyme contains nuclear localization signals (NLS) that facilitate dynamic shuttling between the nucleus and the cytoplasm, thereby modulating its access to substrates that reside in distinct cellular compartments (Firestone2003stimulusdependentregulationof pages 8-9). These spatial dynamics are critical for the selective regulation of target proteins, particularly those involved in ion transport and cellular volume control. Other regulatory layers may include ubiquitination and controlled proteasomal degradation, which contribute to the transient nature of SGK2 activation; such mechanisms ensure that kinase activity is rapidly attenuated when cellular conditions change (Firestone2003stimulusdependentregulationof pages 5-6, Maestro2020serumandglucocorticoidinduced pages 4-6). Collectively, the post-translational modifications and regulated subcellular localization events serve to finely tune SGK2 activity in response to environmental and hormonal stimuli.
7. Function  
   SGK2 plays a central role in the regulation of diverse cellular processes, chiefly through the modulation of ion channels and membrane transporters, and by influencing cell growth, survival, and proliferation. The kinase exerts its effects on ion transport by up-regulating channels and transporters that are essential for maintaining cellular and systemic ionic homeostasis. Among its reported targets, SGK2 enhances the activity and plasma membrane abundance of the epithelial sodium channel (SCNN1A/ENAC), which is a critical mediator of sodium uptake in epithelial tissues (Information, Guerriero2020serumandglucocorticoidinducible pages 3-5). In addition, SGK2 has been linked to the regulation of several potassium channels, including KCNA3 (also known as Kv1.3), as well as auxiliary subunits such as KCNE1 and KCNQ1, all of which contribute to the proper maintenance of the membrane potential and cellular excitability (Information, Guerriero2020serumandglucocorticoidinducible pages 3-5). The kinase also modulates the function of the amino acid transporter SLC6A19, the glutamate transporter SLC1A6/EAAT4, and glutamate receptors GRIA1/GLUR1 and GRIK2/GLUR6, thereby linking SGK2 to the regulation of neurotransmission and cellular metabolism (Information, Maestro2020serumandglucocorticoidinduced pages 4-6). Furthermore, SGK2 stimulates the Na(+)/H(+) exchanger SLC9A3 (NHE3) and the Na(+)/K(+) ATPase, which are pivotal for osmoregulation, pH balance, and overall ion homeostasis (Information, Firestone2003stimulusdependentregulationof pages 1-2). Tissue expression studies have demonstrated that SGK2 exhibits a relatively restricted pattern compared to the ubiquitously expressed SGK1; it is predominantly expressed in tissues such as the liver, kidney, and pancreas, with lower levels detected in the brain (Guerriero2020serumandglucocorticoidinducible pages 3-5). Functionally, SGK2 acts as an effector of the PI3K-PDK1 signaling cascade and is involved in transducing extracellular signals that regulate cellular responses to osmotic stress, energy metabolism, and growth factor stimulation (Firestone2003stimulusdependentregulationof pages 1-2, Maestro2020serumandglucocorticoidinduced pages 3-4). The coordinated phosphorylation of ion channels and transport proteins by SGK2 translates into modulated transport activities that are fundamental for maintaining electrolyte balance and cell volume under varying physiological conditions (Tessier2006serumandglucocorticoid‐regulated pages 5-7, Maestro2020serumandglucocorticoidinduced pages 4-6). Collectively, the multitude of substrates targeted by SGK2 underscores its integral role in orchestrating signaling pathways that govern both immediate ionic fluxes and longer-term cellular adaptations related to growth and survival.
8. Other Comments  
   Recent pharmacological studies have identified small-molecule inhibitors that target SGK family members and demonstrate selective inhibition of SGK2 in addition to SGK1. For instance, herbacetin, a naturally occurring flavonoid derived from Rhodiola species, has been reported to inhibit SGK activity, with data indicating that compounds developed for SGK1 also exhibit inhibitory activity against SGK2 due to the high degree of structural conservation within the ATP-binding pocket (Jang2022serumandglucocorticoidregulated pages 13-14). Although the detailed inhibitor profile specific to SGK2 remains less comprehensively characterized compared to SGK1, the conserved catalytic features suggest that ATP-competitive inhibitors designed to block SGK1 activity are likely to inhibit SGK2 as well. In the context of disease, dysregulation of SGK family kinases has been associated with various physiological and pathological conditions, including disturbances in ion homeostasis, aberrant cell proliferation, and altered stress responses; while many studies have predominantly focused on SGK1, emerging evidence indicates that SGK2 may also contribute to the regulation of electrolyte balance and cellular metabolic processes, particularly in tissues where its expression is enriched such as the kidney, liver, and pancreas (Guerriero2020serumandglucocorticoidinducible pages 15-17, Jang2022serumandglucocorticoidregulated pages 13-14). Additionally, genetic studies in animal models have revealed that SGK2 can function in a compensatory manner when SGK1 activity is diminished, suggesting a role for SGK2 in maintaining ionic equilibrium during conditions of salt deprivation (Guerriero2020serumandglucocorticoidinducible pages 15-17). The potential therapeutic targeting of SGK2 is thus an area of continued investigation, with the development of more selective inhibitors offering promise for conditions such as hypertension, certain cancers, and metabolic disorders in which aberrant kinase activity contributes to disease pathology (Jang2022serumandglucocorticoidregulated pages 13-14, Guerriero2020serumandglucocorticoidinducible pages 15-17). Further structural and biochemical studies are anticipated to refine our understanding of SGK2’s unique regulatory mechanisms and to facilitate the design of next-generation inhibitors with improved selectivity and efficacy.
9. References
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