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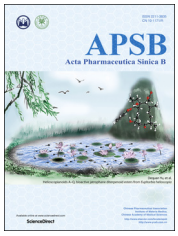

PERSPECTIVE

Serum and glucocorticoid inducible protein kinases (SGKs): a potential target for cancer intervention

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Abstract The serum and glucocorticoid inducible protein kinase (SGK) family members share similar structure, substrate specificity and function with AKT and signal downstream of the phosphatidylinositol 3-kinase (PI3K) signalling pathway. They regulate a range of fundamental cellular processes such as cell proliferation and survival, thereby playing an important role in cancer development. This perspective intends to give an overview on the involvement of SGKs (particularly SGK3) in cancer progression, and compares the actions of SGK3 and AKT in cell cycle regulation, oncogenic signalling, and the potential as a therapeutic target for cancer.

Abbreviations: ER, estrogen receptor; mTORC2, mammalian target of rapamycin complex 2; PDK1, phosphoinositide-dependent kinase-1; PH, pleckstrin homology; PI3K, phosphatidylinositol 3-kinase; PX, Phox; SGK, serum and glucocorticoid inducible protein kinase

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1. Introduction

The phosphatidylinositol 3-kinase (PI3K) signalling pathway controls a range of fundamental cellular processes. The serum and glucocorticoid inducible protein kinase (SGK) family signals downstream of the PI3K pathway, and shares similar structure, substrate specificity and function with AKT. Like AKT, SGK is involved in the regulation of cell proliferation and survival. In addition, SGK also plays an important role in cancer development *via* an AKT-independent signalling pathway. In order to identify novel compounds capable of inhibiting SGK activities, a high-throughput screening campaign against one of the three SGK isoforms, namely SGK3, was carried out and a dozen of hits with IC_{50} values in the low micromolar to sub-micromolar range were subsequently discovered and characterized[1]. Since SGK3 is less well-known among the scientific community, this perspective intends to give an overview on the role of SGK3 in cancer progression downstream of PI3K, and compares the potential roles of SGK3 and AKT in cellular regulation, oncogenic signalling, and the potential as a therapeutic target for cancer.

2. Structure and activation of SGKs

Dysregulation and hyperactivation of the phosphatidylinositol 3-kinase (PI3K) signalling pathway occurs frequently in many human cancers[2,3]. It is one of the major pathways activated following growth factor stimulation: it activates a cascade of downstream signalling proteins and responses to control cell proliferation, survival, metabolism and migration[4]. SGK is a family consisting of three isoforms: SGK1, SGK2, and SGK3 encoded by the genes *SGK1, SGK2* and *SGK3,* respectively, and they are activated downstream of the PI3K pathway[5]. The SGK isoforms are highly similar in structure, with almost 80% sequence identity within the catalytic domains and almost 50% within the C-terminus region. The major differences in structure between the isoforms are at the N-terminus. Specifically, SGK1 has four distinct variants which all differ in the N-terminal area. The presence of a six amino acid hydrophobic motif in the most abundant variant of SGK1 is responsible for its localization to the endoplasmic reticulum and degradation through the 26S proteasome[6]. Both SGK2 and SGK3 produce two types of variants; however, the functional consequence of SGK2 and SGK3 variants are not yet understood[6]. SGK1 and SGK3 isoforms are ubiquitously expressed, and SGK2 expression is restricted to the liver, kidney, pancreas, and brain[7]. SGKs have two key regulatory sites: a Thr residue in the activation loop of the catalytic domain (Thr 320 in SGK3) and a Ser residue in the C-terminal hydrophobic motif (Ser 486 in SGK3, Fig. 1), and phosphorylation of both sites are required for complete activation[5,7,8]. In addition to phosphorylation, SGK1 expression can also be transcriptionally regulated and degraded by ubiquitination. SGK3 is phosphorylated at Thr 320 by phosphoinositide-dependent kinase-1 (PDK1), and mammalian target of rapamycin complex 2 (mTORC2) is proposed to phosphorylate SGK3 at Ser 486[9]. SGK3 is distinct from the other two SGK isoforms and the AKT family: it has a Phox (PX) domain in the N-terminal region (amino acids 12–120) which is important for its protein kinase activity and responsible for targeting SGK3 to endosomal compartments and vesicle-like structures[9–11].

SGK3 endosomal membrane localization is required for complete kinase activity[9]. Mutation of the PX domain prevents phospholipid binding and endosomal localization, and subsequently results in decreased SGK3 activity[11]. Binding of PI(3)P to the PX domain promotes phosphorylation and activation of SGK3 by PDK1,

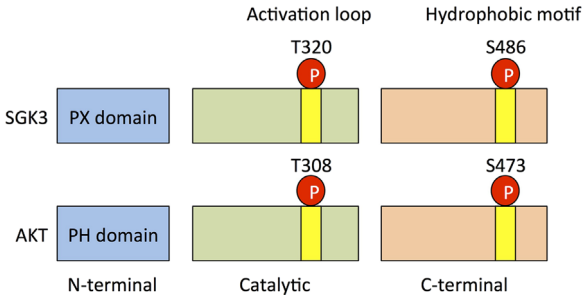

Figure 1 Domain organization of SGK3 and AKT. SGK3 and AKT share a common domain organization consisting of an N-terminal domain, a catalytic domain and a C-terminal domain. They also share similar phosphorylation sites: a Thr residue in the activation loop of the catalytic domain and a Ser residue in the hydrophobic motif of the C-terminal domain.

however this dependence is lost after phosphorylation of the hydrophobic motif at the C-terminal region[6], suggesting that membrane binding *via* the PX domain is important to co-localize SGK3 and mTORC2, the kinase proposed to phosphorylate SGK3 at the hydrophobic motif. Activation of SGK3 is slower than AKT, implying that the endosomal location of SGK3 causes a delay in the activation process compared with activation of AKT at the plasma membrane[7]. In addition, unlike AKT, association of SGK with the cell membrane is not essential for activation[9].

3. Structure and activation of AKT

The AKT family also has three isoforms: AKT1, AKT2, and AKT3[12,13]. All three isoforms share a conserved structure that includes three functional domains: an N-terminal pleckstrin homology (PH) domain, a central catalytic domain, and a C-terminal regulatory domain containing the hydrophobic motif (Fig. 1)[13,14]. SGK isoforms share the same substrate consensus phosphorylation motif and have similar structural and biological functions to that of the AKT family[6]. AKT and SGK3 substrates control a range of cellular responses to growth factors and other extracellular stimuli including cell proliferation, survival, migration, metabolism, and angiogenesis[6,7,13,15]. Given the similarity in structure and substrate specificity, the SGK family is also considered as a second AKT family in cancer signalling[6]. AKT has two key regulatory sites, Thr 308 in the activation loop of the catalytic domain and Ser 473 in the C-terminal hydrophobic motif, and similar to SGK, both sites require phosphorylation for complete activation[16,17]. AKT is phosphorylated at Thr 308 by PDK1 and at Ser 473 by mTORC2[16]. AKT signals downstream of class 1A and 1B PI3K, which are activated by tyrosine kinase and G-protein-coupled receptors, respectively[18]. Once activated, PI3K phosphorylates the 3 hydroxyl group of the inositol ring of $PI(4,5)P_2$ to generate $PI(3,4,5)P_3$ at the lipid membrane[19,20]. AKT is then recruited to the plasma membrane when its PH domain binds to PIP_3, allowing phosphorylation at Thr 308 and partial activation of AKT by PDK1. AKT is fully activated when it is also phosphorylated by mTORC2 at Ser 473[15].

4. SGK and AKT in cancer

Despite the critical role of AKT in tumor development, the function of downstream effectors that signal independently