SGK3 (CISK) may induce tumor angiogenesis (Hypothesis)

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Abstract. Serum- and glucocorticoid-inducible protein kinase 3 (SGK3), also known as cytokine-independent survival kinase (CISK), encoded by chromosome 8q12.2, is a downstream mediator of phosphatidylinositol 3-kinase (PI3K) oncogenic signaling. As a downstream target of PI3K, SGK3 has been reported to mediate pivotal roles in oncogenic progress in various cancers, including breast cancer, ovarian cancer and hepatocellular carcinoma. Functionally parallel to v-akt murine thymoma viral oncogene homolog (AKT)/protein kinase B, SGK3 serves as a hallmark mediating glycogen synthase kinase-β (GSK3-β), B-cell lymphoma (Bcl)-2-associated death promoter, forhead family of transcription factors, Bcl-extra large, Bcl-2, mammalian target of rapamycin, C-X-C chemokine receptor type 4 (CXCR4) and numerous other molecules in cell proliferation, growth, survival, migration and even tumor angiogenesis. Tumor angiogenesis is recognized as an essential step for tumor growth, invasion and metastasis, and it has become an intriguing target for anticancer drug development for tumor investigators worldwide. An abundance of experiments have been performed to investigate the role of the phosphoinositide 3-kinase (PI3K)/AKT pathway in regulating tumor angiogenesis. The mechanism of angiogenesis regulated by the PI3K/AKT pathway is, to a certain extent, clear. Although a number of SGK3 target molecules, including CXCR4 and GSK3β, have demonstrated potential roles in promoting angiogenesis, the exact association between angiogenesis and SGK3 remains unclear. Thus, we hypothesize that SGK3, parallel to AKT, may also be important in mediating angiogenesis. Identifying the role of SGK3 in tumor angiogenesis will certainly present a novel perspective on the malignant transformation of tumors, as well as a target for tumor therapy.

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1. Introduction

V-akt murine thymoma viral oncogene homolog [SGK3; also known as cytokine-independent survival kinase (CISK)], as a downstream target of the phosphoinositide 3-kinase (PI3K) cascade and a member of the AGC family of kinases, has certain similar substrates and shares certain target-signaling molecules with v-akt murine thymoma viral oncogene homolog (AKT) in cell proliferation, growth and survival (1-4). SGK3 is a serine/threonine protein kinase, and its key phosphorylation sites are Thr308 and Ser123/124 (5). The residues of SGK3 (also known as CISK) equivalent to those of AKT are targeted by 3-phosphoinositide-dependent kinase 1 (PDK1) and PDK2 respectively (5). Functionally parallel to AKT, SGK3 is involved in the malignant transformation of tumors by regulating cell proliferation, cell growth, cell survival and cell migration (4,6). The oncogenic effect of SGK3 in tumors has been demonstrated by in vitro and in vivo functional assays (2,3). Xu et al (2) reported that the positive correlation between SGK3 expression and tumor prognosis varies with tumor grade and lymph node status. Angiogenesis is a key process in tumor malignant transformation, which involves blood vessel endothelial cell proliferation and migration. The signaling pathways of the cellular processes that SGK3 mediates, particularly in cell survival, have been well studied. However, angiogenesis, another tumor malignant transformation process, is seldom reported in comparison to AKT. Therefore, the present study aims to find evidence that SGK3 may be involved in angiogenesis.
2. Hypothesis

An abundance of experiments have been performed to investigate the function of the PI3K/AKT pathway in regulating tumor angiogenesis, and so the mechanism of angiogenesis regulated by the PI3K/AKT pathway is, to a certain extent, clear. However, the association between angiogenesis and SGK3 remains unclear. As they are downstream mediators of the PI3K/PDK1 signaling pathway, AKT and SGK3 have certain similar substrates and share certain targeting molecules. Thus, we hypothesize that a strong signaling connection may exist between angiogenesis and SGK3, contributing to tumor malignant transformation.

3. Evidence and discussion

The deteriorative progress of tumor growth includes several alterations that collectively dictate malignant transformation, including insensitivity to growth-inhibitory signals, evasion of cell apoptosis, limitless cell proliferation, sustained angiogenesis, and tissue invasion and metastasis (8). SGK3, a downstream effector of PI3K, induces several pro-malignant pathways through the PI3K/PDK1/SGK3 route. Functionally parallel with AKT (Fig. 1) (3,4), SGK3 participates in cell growth, cell survival and cell migration (1,2,9,10). In contrast to the AKT pleckstrin homology domain, SGK3 contains a phox homology domain, through which SGK3 binds to phosphatidylinositol 3-phosphate-rich endosomal and vesicular compartments to remain active. Overexpression of SGK3 increases cell cycle progression through G1 by inactivating glycogen synthase kinase-β (GSK3-β) and stabilizing CCND1, as previously observed in hepatocellular carcinoma (3,7,9). Similar to AKT, SGK3 is involved in cell growth signaling by the increase of phosphorylated tuberous sclerosis factor 2, ribosomal protein S6, proline-rich AKT substrate of 40 kDa and eIF4E-binding protein 1 in normal
cell physiology and malignant transformation (9,11). Induced by interleukin (IL)-3 (4), SGK3 increases the level of B-cell lymphoma-extra large (Bcl-xL), and inhibits the pro-apoptotic proteins Bcl-2-associated death promoter (BAD) and forkhead family of transcription factors (FKHRs) (3,4,9,10), thus promoting cell survival. Consistent with the fact that SGK3 and AKT are functionally parallel, SGK3 and AKT have synergetic responses to the cell survival pathways through Bcl-xL, BAD and FKHRs. SGK3 mediates estrogen receptor-positive cancer cell survival by phosphorylating its co-activator, flightless-I (2,6). Observations by Slagsvold et al (12) support the potential role of SGK3 as a cell survival effector by the downregulation of C-X-C chemokine receptor type 4 (CXCR4) through the interaction with ubiquitin ligase atrophin-1-interacting protein 4. CXCR4 is strongly associated with promoting cell invasion, migration and adhesion during the process of metastasis in breast cancer and liver tumor cells (13,14), showing the potentially significant role of SGK3 in cell migration. Thereby, further studies are required to more specifically characterize the role of SGK3 in these processes.

Tumor angiogenesis is recognized as an essential step for tumor growth, invasion and metastasis, and has become an intriguing target of tumor investigators worldwide for the development of anticancer drugs. A number of studies have shown that vascular endothelial growth factor (VEGF)/VEGF receptor are essential in the tumor angiogenesis process (15,16).

Study has also been focused on the role of the PI3K/AKT pathway in angiogenesis (Fig. 1) (17). Inhibition of GSK3-β by PI3K/AKT upregulates the expression of hypoxia-inducible factor-1α, inducing VEGF transcriptional activation to promote angiogenesis (17). In early 2013, Su et al (18) reported that PI3K/AKT is mediated by inhibitor of DNA binding/differentiation 1 to enhance endothelial progenitor cell angiogenesis in ovarian cancer. In a study by You et al (19), extracellular signal-regulated kinases and PI3K signaling pathways showed strong involvement in the forkhead box protein C2-mediated angiogenesis process. Zhou et al (20) showed the promotion of human immunodeficiency virus type 1 transactivator of transcription in Kaposi's sarcoma-associated herpesvirus viral IL-6-induced angiogenesis by regulating the PI3K/phosphatase and tensin homolog/AKT/GSK-3-β pathway in vivo. A recent study revealed that PI3K/AKT is activated by resistin and increases the interaction with specificity protein 1, resulting in the upregulation of VEGF expression to promote angiogenesis (21).

The stromal cell-derived factor 1/CXCR4 receptor ligand system has also been reported to play a potential role in cancer metastases via the upregulation of VEGF expression to promote angiogenesis (22-24).

Bevacizumab, a monoclonal antibody targeted against VEGF, and a number of other anti-angiogenesis molecules have been used in numerous anti-angiogenesis strategies (25). The use of anti-angiogenesis strategies may present a new epoch in tumor research, however, the exact pathway of the angiogenesis mechanism remains unknown.

Since PI3K/AKT plays an important role in tumor angiogenesis, we hypothesize that SGK3, as a downstream target of PI3K and functionally parallel to AKT, may also be involved in the malignant transformation of tumors by promoting angiogenesis. It has also been reported that CXCR4 and GSK3-β, both downstream of SGK3, may also have potential capacity in angiogenesis (3,17). These facts demonstrated the potential role of SGK3 in promoting angiogenesis and is evidence that confirms our hypothesis (Fig. 1).

SGK3 has been studied in depth with regard to tumor malignant transformation, but the exact association between angiogenesis and SGK3 is rarely reported. Possible reasons for this include the fact that SGK3 does not significantly correlate with angiogenesis, or that the amplification and overexpression of SGK3 may be an early stage event in tumor growth (3).

In conclusion, the mechanism of SGK3 in oncogenesis is, to a certain extent, clear. However, its role in malignant transformation, particularly in angiogenesis, remains to be elucidated. Based on the present datum, detailed characterization of any role of SGK3 in the promotion of angiogenesis via CXCR4 and GSK3-β, the association between SGK3 and VEGF, and the exact mechanisms behind this are required.

4. Clinical implications

These data generate an overall impression of SGK3 as an important oncogenic signaling mediator, and stresses the vital nature of further research on the elucidation of the signaling mechanisms associated with SGK3 in tumor angiogenesis. Determining the role of SGK3 in tumor angiogenesis will surely present a novel perspective on tumor malignant transformation, as well as a target for tumor therapy.

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