The Role of Serum and Glucocorticoid-Regulated Kinase-1 (SGK1) in Prognosis and Therapy of Prostate Adenocarcinoma

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ABSTRACT

Prostate adenocarcinoma is an epithelial malignant neoplasm originating from the prostate, ranking as the second most common cancer in men. In Indonesia, around 50% of prostate adenocarcinoma cases are found to be metastatic. The condition of castrate-resistant prostate cancer (CRPC) that occurs during long-term administration of androgen deprivation therapy (ADT) has a significant impact on morbidity and mortality. Serum and glucocorticoid-regulated kinase-1 (SGK1) has been identified as having characteristics of a tumor-promoting gene. SGK1 expression is increased in several tumors, including prostate adenocarcinoma. SGK1 can be activated through several signaling pathways involved in prostate adenocarcinoma, including the phosphoinositide-3 kinase (PI3K) pathway, the androgen receptor (AR) pathway, and the glucocorticoid receptor (GR) pathway. SGK1 expression was found to be positively correlated with progression and metastasis of prostate adenocarcinoma. This shows that SGK1 can be a positive predictor of prostate adenocarcinoma metastasis. The significant relationship between high SGK1 expression and the occurrence of CRPC indicates that SGK1 can act as a prognostic biomarker for prostate adenocarcinoma which can develop into CRPC. Specific inhibitors of SGK1 significantly interfere with the migration and invasion of prostate adenocarcinoma cells through silencing SGK1 which causes G2/M cycle arrest, activation of apoptosis and autophagy in prostate adenocarcinoma cells.

Keywords: SGK1; Prostate adenocarcinoma; Prognosis; Targeted therapy.

INTRODUCTION

Prostate adenocarcinoma is an epithelial malignant neoplasm originating from the prostate.[1] Based on the Global Cancer Observatory in 2022, prostate adenocarcinoma is the second most common cancer case in men in the world.[2] The incidence of local prostate adenocarcinoma in developed countries is reported to be higher than metastatic prostate adenocarcinoma, whereas in Indonesia around 50% of prostate adenocarcinoma patients are diagnosed with metastases.[3]

The majority (80-90%) of prostate adenocarcinomas are androgen-sensitive and respond well to androgen deprivation therapy (ADT) at the start of treatment.[4,5] However, after giving ADT for a long time (around 2-3 years), cancer cells can progress to androgen-independent or castrate-resistant prostate cancer (CRPC).[5,6] Almost all patients with metastatic prostate adenocarcinoma will develop CRPC and this has a significant impact on morbidity and mortality.[7]

In recent years, research on prostate adenocarcinoma aims to find new biomarkers as predictors of progression and recurrence, and also as a therapeutic strategy that can suppress cancer development, one of which is serum and glucocorticoid-regulated kinase-1 (SGK1).[8-10] The involvement of SGK1 in many processes development and growth of various tumors makes SGK1 predicted to have potential as a prognostic or predictive biomarker.[11] SGK1 has been identified as having characteristics as a tumor-promoting gene and the presence of SGK1 dysregulation is found in several types of malignancy including prostate adenocarcinoma.[12,13] This literature review aims to understand the role of SGK1 as a biomarker of prostate adenocarcinoma progression and its potential as a therapeutic target.

Structure and Function of Serum and Glucocorticoid-Regulated Kinase-1 (SGK1)

Serum and Glucocorticoid-regulated Kinase (SGK) is a serine/threonine protein kinase, a member of the A, G, and C families (AGC kinase family). It has three isoforms, namely SGK1, SGK2, and SGK3. The SGK1 gene was first identified in 1993 in mouse mammary gland tumor cells, transcription of this gene is regulated by serum and glucocorticoids. Several years later, in humans, the SGK1 gene was found to have characteristics as a serine/threonine protein kinase that increased during cell shrinkage events. The human SGK1 gene is located on chromosome 6q23.[11,12,14-16]

SGK1 is expressed in almost all tissues and its subcellular location is related to the functional condition of the cell.[12,13] The expression and function of SGK1 are triggered by many intracellular and extracellular factors including growth factors, hormones such as insulin, insulin-like growth factor 1 (IGF1), steroids such as aldosterone, glucocorticoids, peptide hormones, and cytokines such as interleukin-2 (IL-2) and transforming growth factor-β (TGF- β).[14-16] Various stimuli that can also regulate SGK1 expression include dehydration, salt consumption, heat shock, and various cellular stresses such as cell swelling, cell shrinkage, metabolic acidosis, neuronal excitotoxicity, oxidative stress, ultraviolet light, DNA damage, and ischemia.[12,13,15 -17]

As a serine/threonine kinase, SGK 1 catalyzes the phosphorylation of various target proteins, including N-Myc downstream-regulated gene 1 (NDRG1), forkhead transcriptiton factor 3a (Foxo3a), neuronal precursor cell expressed developmentally downregulated 4-2 (Nedd4-2), tuberous sclerosis complex 2 (TSC2), Unc-51 like autophagy activating kinase 1 (ULK1) and β-catenin.[14] With its broad targets, SGK1 influences various biological functions, including ion channel activity, salt balance, glucose metabolism, memory consolidation, reproductive processes, cell growth and proliferation, survival, cell migration, and apoptosis, as well as T cell development, which shows SGK1 plays an important role in various diseases including hypertension, diabetes, hypercoagulability, autoimmune diseases, and tumors.[11-14,17]

SGK1 Signaling Pathway in Prostate Adenocarcinoma

SGK1 can be activated through several signaling pathways involved in prostate adenocarcinoma including the phosphorinositide-3 kinase (PI3K) pathway, androgen receptor (AR) pathway, and glucocorticoid receptor (GR) pathway.[18-20]

1. **Phosphoinositide-3 kinase (PI3K) pathway**

   The PI3K-AKT-mTOR signaling pathway is one of the important pathways for cell survival, growth, proliferation, invasion, inhibition of apoptosis, and angiogenesis.[13] Oncogenic activation of the PI3K-AKT-mTOR pathway often occurs in prostate adenocarcinoma which facilitates tumor growth, disease progression, and therapy resistance. PI3K-AKT-mTOR signaling is increased in the majority of prostate adenocarcinoma patients. Genetic changes in the PI3K pathway occur in 42% of primary prostate adenocarcinomas and 100% of metastatic prostate adenocarcinomas. The CRPC condition is also associated with increased activation of the PI3K-AKT-mTOR pathway.[18]

   Deregulation that occurs in the PI3K pathway shows various genetic changes, especially loss of PTEN function due to homozygous deletion, mutation, heterozygous deletion, or epigenetic silencing, which reaches 60% in cases of advanced prostate adenocarcinoma or CRPC. Other genetic changes in the PI3K pathway that often occur in prostate adenocarcinoma include MTOR amplification, gain-of-function mutations or PI3K amplification, and PDK1 amplification. SGK1 mutations are rare in prostate adenocarcinoma (≤ 0.41%) while SGK1 amplification can occur in around 2.5%.[18]

   Activation of PI3K will initiate downstream signals by synthesizing PIP3 from PIP2 to mediate cell growth, proliferation, autophagy, and apoptosis.

PTEN is a tumor suppressor that negatively regulates the PI3K-AKT-mTOR pathway by converting PIP3 to PIP2 again. Increasing PIP3 levels will activate various kinases including PDK1 which will phosphorylate downstream targets such as AKT and SGK1. PI3K also activates mTORC2 which will phosphorylate various downstream targets including AKT and SGK1 that mediate cell survival, cell development, cell cycle, and actin remodeling.[18,21]

SGK1 shares 54% catalytic domain similarity with AKT and is indicated as an AKT-independent effector in the PI3K-mTOR pathway.[9,13] SGK1 and AKT have several same target genes which synergize each other to provide effects downstream PI3K signaling or other kinase inhibition.[13,14] AKT and SGK1 mediate cyclin-dependent kinase inhibitor 1B (CDKN1B) phosphorylation which will inhibit G1 arrest p27-mediated thus increasing proliferation, survival, and tumor growth.[11]

2. Androgen Receptor (AR) Pathway

AR signals regulate growth, differentiation, migration, and cell survival and play an important role as transcriptional regulators in prostate development, normal prostate tissue homeostasis, and prostate adenocarcinoma.[18] Prostate adenocarcinoma growth can be AR-dependent or AR-independent. The majority of prostate adenocarcinomas are AR-positive or AR-dependent, androgen activity is the central axis in the pathogenesis of prostate adenocarcinoma.[22,23] AR plays a role in activating specific target genes that cause the initiation and progression of prostate adenocarcinoma.[24] Aberrant AR signals often occur in prostate adenocarcinoma, reaching 56% in primary cases and 100% in metastatic cases.[18] AR expression is found in almost all primary and metastatic prostate adenocarcinomas, regardless of grade or stage of prostate adenocarcinoma.[4]

Increased activity of the AR signaling pathway in prostate adenocarcinoma not only occurs due to mutations or amplification in AR which causes an increase in the AR gene, reaching 50-80% in metastatic prostate adenocarcinoma, but also due to mutations in the AR cofactor, namely speckle-type POZ protein (SPOP) or forkhead box A1 (FOXA1), reaching 15% in primary prostate adenocarcinoma and 10% in metastatic prostate adenocarcinoma, as well as genetic rearrangement which causes the fusion of regulated genes androgen, namely TMPRSS2-ERG, which reaches 70% in prostate adenocarcinoma.[23-25] AR also plays an important role in CRPC condition.[24] CRPC is associated with genetic changes in AR (activation due to mutation, gene amplification, presence of androgen-independent AR splice variants, loss of AR), addition of androgen biosynthesis, adrenal androgens, bypass of AR signaling by GR that share the same AR target gene, trans-differentiation into neuroendocrine prostate cancer and activation through other cascade pathways for example in the PI3K-AKT-mTOR pathway.[18]

SGK1 is a direct transcriptional target of AR which can stimulate prostate adenocarcinoma development.[26] Shanmugam et al[19] found that SGK1 is a gene that plays an important role in the expression and survival of AR-dependent prostate adenocarcinoma cells. SGK1 mRNA levels significantly increased after androgen stimulation. Analysis of the SGK1 promoter shows that AR interacts with the proximal and distal parts of the SGK1 promoter which will activate the SGK1 promoter after androgen stimulation. Overexpression of SGK1 blocks apoptosis by AR small-interfering RNA (siRNA) and increases AR trans-activation even in the absence of androgens. This suggests a positive feedback effect of androgen-induced SGK1 expression on survival and AR-dependent SGK1 gene expression.[19]

3. Glucocorticoid Receptor (GR) Pathway

GR is expressed in almost all tissues and is associated with metabolic functions, growth, stress response, and inflammation.[22] GR is another steroid receptor that has structural and functional properties similar to AR.[27] GR is present in high levels in normal prostate tissue but decreases in the development of AR-dependent prostate adenocarcinoma.[22] GR expression decreases in primary prostate adenocarcinoma tissue but increases in metastatic lesions.[28] The AR-dependent mechanism is the main pathway in the development of CRPC. AR bypass signaling is another mechanism that may be involved in resistance to AR-targeted therapy. GR contributes to resistance to AR-targeted therapy by bypassing AR blockade in CRPC.[27] GR expression is significantly increased upon long-term anti-androgen therapy (abiraterone or enzalutamide) indicating upregulation of GR as a cellular mechanism for bypassing AR blockade.[8,28] GR stimulation accelerates disease progression by increasing the survival of

androgen-insensitive prostate adenocarcinoma cells.[28]

AR and GR have several target genes in common including SGK1. SGK1 is also a direct target of GR activation in epithelial cells.[8] Inhibition of the AR pathway by blocking androgens causes an increase in GR expression. GR activation then induces SGK1 gene expression through activating glucocorticoid response element (GRE) in the promoter region (5'-flanking) which will increase prostate adenocarcinoma cell survival.[20,29]

The Potential of SGK1 as a Prognostic Biomarker

Abnormal expression of SGK1 has been found in tissues and is expected to be an indicator of cancer progression. In addition, SGK1 may be a prognostic factor in the survival of cancer patients. SGK1 is considered to have a role as a prognostic biomarker in various cancers.[12] Increased expression of SGK1 is found in several malignancies including prostate adenocarcinoma.[9, 12]

Rauhala et al[30] first studied SGK1 expression in prostate tissue using immunehistochemistry. SGK1 is strongly expressed in all normal prostate cells, benign prostate hyperplasia (BPH), and high-grade PIN. SGK1 in prostate adenocarcinoma shows varying results (not expressed to strong expression). All BPH samples were positive for SGK1 (moderate-strong expression) while approximately 48% of prostate adenocarcinomas showed weak or no expression and 52% had moderate-strong expression. SGK1 expression was not associated with clinical stage, Gleason score, or PSA level in untreated prostate adenocarcinoma. The mechanism of SGK1 downregulation that causes variable SGK1 expression in prostate adenocarcinoma is still unclear and requires further research.[30]

Szmulewitz et al[8] found that SGK1 expression was high in the majority of prostate adenocarcinomas that had not received therapy and decreased with androgen deprivation.[8,12] SGK1 is consistently highly expressed in prostate adenocarcinomas. SGK1 expression appeared stronger in the nucleus than in the cytoplasm. The strongly positive expression of SGK1 in 79% of prostate adenocarcinoma cases was a significant difference compared to 44% of prostate adenocarcinoma cases who had received androgen deprivation therapy. However, this study found no relationship between SGK1 expression and cancer stage. SGK1 expression is inversely related to cancer grade and recurrence. Low SGK1 expression is associated with higher cancer grade and increased cancer recurrence. This study has limitations in that the percentage of tumors with low SGK1 expression is only around 25% of the total sample size so the analysis is limited. Many patients also experience loss to follow-up and the follow-up interval is too wide, 6 weeks to 15 years, which can affect the progression-free survival analysis.[8]

Liu et al[9] found that SGK1 expression was significantly lower in normal prostate tissue adjacent to cancer than in non-metastatic prostate adenocarcinoma tissue, and SGK1 expression was highest in metastatic prostate adenocarcinoma tissue. This shows that SGK1 expression is positively correlated with the progression and metastasis of prostate adenocarcinoma. SGK1 is expressed in normal prostate tissue but increases in prostate adenocarcinoma tissue and increases even higher in metastatic prostate adenocarcinoma so SGK1 can be a positive predictor biomarker in metastatic prostate adenocarcinoma.[9] Liu et al[9] also showed that over-expression of SGK1 weakens autophagy (decreased LC3II levels) which will encourage invasion and migration of prostate adenocarcinoma cells through increasing protein levels of matrix metalloproteinase-3 (MMP-3) and matrix metalloproteinase-9 (MMP-9) in vitro.[9]

Isikbay et al[20] found that SGK1 plays an important role in GR-mediated CRPC progression through resistance to AR therapy. CRPC growth in the group with SGK1 over-expression grew faster than the group without SGK1 over-expression. Over-expression of SGK1 promotes CRPC progression in vivo, demonstrated by a significant association between increased CRPC initiation and over-expression of SGK1. Increased GR activation and expression under AR inhibition conditions induce SGK1 expression, which can increase cell survival and be pro-tumorigenic in prostate adenocarcinoma cells.[20]

Billianti[31] also found a significant relationship between high SGK1 expression and the occurrence of CRPC with a sensitivity of 60% and a specificity of 70,37%. SGK1 expression was higher in the CRPC group compared to non-CRPC. Patients with lower SGK1 expression immunohistochemically were less likely to develop CRPC within 2 years. This study shows that SGK1 can act as a prognostic biomarker for prostate adenocarcinoma that can progress to CRPC within 2 years. However, in determining the prognosis for prostate adenocarcinoma, the existing prognostic factors for prostate adenocarcinoma are still considered, namely stage, Gleason grading, lymphovascular invasion, and perineural invasion.[31]

The Potential of SGK1 as a Therapeutic Target

The various roles of SGK1 in tumorigenesis and tumor progression causing abnormal regulation, activity, and expression in cancer have made small molecule selective inhibitors of SGK1 for therapeutic purposes starting to be developed. The first SGK1 inhibitor developed for prostate adenocarcinoma was GSK650394.[10-12,32]

In recent years, SGK1 was identified as an important molecule in prostate adenocarcinoma development through apoptosis, cell cycle, invasion or migration, and cell autophagy.[12,13] Liu et al[10] found that the specific SGK1 inhibitor GSK650394 showed significant anti-tumor effects in prostate adenocarcinoma in vitro and in vivo. GSK650394 inhibits prostate adenocarcinoma cell viability by suppressing cell proliferation in vitro. SGK1 inhibition causes G2/M cycle arrest, activation of apoptosis and autophagy in prostate adenocarcinoma cells by suppressing the mTOR-Foxo3a pathway.[10,12,17] Foxo3a is an important downstream target of SGK1 and a potential tumor suppressor.[10] SGK1-induced Foxo3a phosphorylation becomes one of the mechanisms for reducing abnormal apoptosis in prostate adenocarcinoma cells. This may develop into a specific target in prostate adenocarcinoma therapy.[33]

Inhibition of SGK1 can suppress prostate adenocarcinoma growth in vivo through activation of autophagy and apoptosis with increased LC3II levels and increased p21, p27, and cleaved caspase-3.[10] The combination of suppression of SGK1 and mTOR significantly increases autophagy and has a synergistic anti-metastatic effect on prostate adenocarcinoma cells.[9,10]

Liu et al[9] found that the SGK1 inhibitor administration, GSK650394, significantly interfered with migration and invasion of prostate adenocarcinoma cells. Downregulation of SGK1 with SGK1 inhibitors induces autophagy which will attenuate epithelial-mesenchymal transition (EMT) and suppress metastasis in vitro and in vivo. SGK1 plays an important role in the EMT process of prostate adenocarcinoma. Silencing SGK1 will increase LC3II protein levels and induce characteristic changes in mesenchymal-epithelial transition (MET) both biochemically (increased E-cadherin and decreased Snail, N-cadherin, Vimentin, and Fibronectin) and functionally (decreased MMP3 and MMP9 production) thereby reducing invasion and migration capacity of prostate adenocarcinoma cells. Downregulation of SGK1 also significantly inhibits lung metastasis of prostate adenocarcinoma cells in vivo.[9]

Downregulation of SGK1 can inhibit the growth of prostate adenocarcinoma cells with or without AR so SGK1 inhibition can be a promising therapeutic strategy for androgen-resistant aggressive prostate adenocarcinoma.[10,28] Isikbay et al[20] found small molecule SGK1 inhibitors can overcome the activation of AR and GR to inhibit the growth of prostate adenocarcinoma in vitro. Administration of the SGK1 inhibitor GSK650394 decreased GR-mediated survival of prostate adenocarcinoma cells. Inhibition of SGK1 may be a treatment strategy along with therapies that inhibit AR activity (abiraterone or enzalutamide) in CRPC treatment.[20]

CONCLUSION

Prostate adenocarcinoma is the second most common cancer in men in the world. In Indonesia, there are still many cases of prostate adenocarcinoma found in metastatic conditions and can develop into CRPC. SGK1 is a tumor-promoting gene whose expression is increased in prostate adenocarcinoma. SGK1 is involved in prostate adenocarcinoma development through PI3K, AR, and GR signaling pathways that regulate apoptosis, cell cycle, invasion or migration, and cell autophagy. Increased SGK1 expression can be a predictive biomarker for prostate adenocarcinoma that will progress to CRPC and metastasis. SGK1 also has the potential to be developed as a therapeutic target for prostate adenocarcinoma, both metastatic and CRPC.

DISCLOSURE

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