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Review

Serum and glucocorticoid inducible kinase, metabolic syndrome, inflammation, and tumor growth

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ABSTRACT

Serum-and-glucocorticoid-inducible-kinase-1 (SGK1) is under regulation of several hormones, mediators and cell stressors. More specifically, SGK1 expression is particularly sensitive to glucocorticoids, mineralocorticoids, and TGFβ. Moreover, SGK1 expression is exquisitely sensitive to hypertonicity, hyperglycemia, and ischemia. SGK1 is activated by insulin and growth factors via phosphatidylinositol-3-kinase, 3-phosphoinositide dependent-kinase PDK1, and mTOR. SGK1 up-regulates the Na^+/K^+-ATPase, a variety of carriers (e.g. NCC, NKCC, NHE1, NHE3, SGLT1, several amino acid transporters) and many ion channels (e.g. ENaC, SCN5A, TRPV4-6, Orai1/STIM1, ROMK, KCNE1/KCNQ1, GluR6, CFTR). SGK1 further up-regulates a number of enzymes (e.g. glycogen-synthase-kinase-3, ubiquitin-ligase Nedd4-2), and transcription factors (e.g. forkhead-transcription-factor FOXO3a, β-catenin, nuclear-factor-kappa-B NFκB). SGK1 sensitive functions contribute to regulation of epithelial transport, excitability, degranulation, matrix protein deposition, coagulation, platelet aggregation, migration, cell proliferation, and apoptosis. Apparently, SGK1 is not required for housekeeping functions, as the phenotype of SGK1 knockout mice is mild. However, excessive SGK1 expression and activity participates in the pathophysiology of several disorders, including hypertension, obesity, diabetes, thrombosis, stroke, inflammation, autoimmune disease, fibrosis, and tumor growth. A SGK1 gene variant (prevalence ~3-5% prevalence in Caucasians, ~10% in Africans) predisposes to hypertension, stroke, obesity, and type 2 diabetes. Moreover, excessive salt intake and/or excessive release of glucocorticoids, mineralocorticoids, and TGFβ up-regulates SGK1 expression thus predisposing to SGK1-related diseases.

Key words: Diabetes, Hypertension, Fibrosis, Obesity, Stroke, Thrombosis, Tumor growth

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INTRODUCTION

The serum and glucocorticoid-inducible kinase 1 (SGK1) was cloned as a gene up-regulated by serum and glucocorticoids in rat mammary tumor cells.[1] Human SGK1 was identified as a gene up-regulated by cell shrinkage.[2] SGK1 is ubiquitously expressed.[2-5] Following stimulation of cell proliferation with serum, SGK1 may enter into the nucleus.[4] Following hyperosmotic shock or glucocorticoids stimulation, SGK1 is localized mainly in the cytosol.[1,4] SGK1 may further bind to the mitochondrial membrane.[2]

The gene encoding human SGK1 is located in chromosome 6q23.[4] Several SGK1 variants have been identified differing in regulation of expression, subcellular localization and function.[2,6] The present brief review discusses the function and pathophysiological significance of SGK1. In order to limit reference numbers, reviews are cited instead of earlier publications.[2,4,7-12]

REGULATION OF SGK1 EXPRESSION AND ACTIVITY

SGK1 transcription is stimulated by hyperosmotic or isotonic cell shrinkage.[4] Accordingly, SGK1 expression is increased by dehydration[13] and a modest increase of extracellular salt concentration.[14] Intestinal SGK1 is up-regulated by saline ingestion.[15] SGK1 transcription is further stimulated by excessive glucose concentrations and diabetes, A6 and M1 cell swelling, mechanical stress, Ca^{2+} chelation, metabolic acidosis, salt loading of spontaneously hypertensive mice, oxidative stress, heat shock, UV radiation, DNA damage, ischemia, neuronal injury, neuronal excitotoxicity, neuronal challenge by exposure to microgravity, fear conditioning, plus maze exposure, enrichment training, amphetamine, lysergic acid dimethylamide (LSD), electroconvulsive therapy, sleep deprivation, antidepressant fluoxetine, testicular torsion, high-salt diet of salt-sensitive rats as well as high-fat diet.[2,4,16-22]

SGK1 transcription is further stimulated by several hormones and mediators, such as glucocorticoids,[1,2,23-28] mineralocorticoids,[2,29-31] gonadotropins,[4] progestin,[2,32] progesterone,[4] 1,25-dyhydroxyvitamin D_3 (1,25$(OH)_2D_3$),[4] erythropoietin,[33] morphine,[30] transforming growth factor b (TGFβ),[4] interleukin 6,[4] fibroblast and platelet-derived growth factor,[4] thrombin,[2] endothelin,[2,4] advanced glycation end products (AGE),[4] further cytokines,[4] and activation of peroxisome proliferator-activated receptor γ.[2,4]

SGK1 expression is enhanced in several diseases, such as diabetes, dialysis, glomerulonephritis, liver cirrhosis, fibrosing pancreatitis, Crohn's disease, lung fibrosis, cardiac fibrosis, wound healing, organ rejection, and Rett syndrome.[2,4,34]

Factors down-regulating SGK1 transcription include serum starvation, heparin, dietary iron, nucleosides, nephrilin, and mutations in the methyl-CpG-binding protein 2 (MECP2) encoding gene.[2,4,35-37] SGK1 expression further declines with age.[38]

Signalling in transcriptional SGK1 regulation involves cytosolic Ca^{2+}, cyclic AMP, stress-activated protein kinase-2 (SAPK2, p38 kinase), protein kinase C, protein kinase Raf, big mitogen-activated protein kinase 1 (BMK1), extracellular signal-regulated kinase (ERK1/2), mitogen-activated protein kinase 14 (MAPK14), phosphatidylinositide-(PI)-3-kinase, reactive oxygen species, NADPH oxidases, nitric oxide, and EWS/NOR1(NR4A3) fusion protein.[2,4,39] SGK1 expression is further stimulated by transcriprion factor p53.[40]

The SGK1 promoter binds receptors for glucocorticoids (GR), mineralocorticoids (MR), progesterone (PR), 1,25$(OH)_2D_3$ (VDR), retinoids (RXR), farnesoids (FXR), sterol regulatory element binding protein (SREBP), peroxysome proliferator activator receptor gamma (PPARγ), cAMP response element binding protein (CREB), p53 tumor suppressor protein, Sp1 transcription factor, activating protein 1 (AP1), activating transcription factor 6 (ATF6), heat shock factor (HSF), reticuloendotheliosis viral oncogene homolog (c-Rel), nuclear factor ϰB (NFϰB), signal transducers and activators of transcription (STAT), TGFβ-dependent transcription factors SMAD3 and SMAD4, and forkhead activin signal transducer (FAST).[1] The SGK1 promotor further harbors a tonicity-responsive enhancer (TonE) mediating suppression of SGK1 expression by the transcription factor TonE binding protein (TonEbP or NFAT5).[2]

SGK1 translation is triggered by phosphosphoinositide 3 kinase and dependent on actin polymerisation.[41]

SGK1 is activated by insulin, IGF1, hepatic growth factor (HGF), follicle stimulating hormone (FSH), thrombin, and corticosterone.[4,42] The signalling involves phosphosphoinositide 3 kinase (PI3-kinase) and 3-phosphoinositide (PIP3)-dependent kinase

PDK1.[2] Interaction of SGK1 and PDK1 is fostered by the scaffold protein Na^+/H^+ exchanger regulating factor 2 (NHERF2).[4] PIP3 is degraded by the phosphatase and tensin homolog PTEN, which thus abrogates PDK1-dependent SGK1 activation.[4] SGK1 could further be stimulated by mammalian target of rapamycin mTOR complex-2 (mTORC2) and WNK1 (with no lysine kinase 1).[2,4,31,43-54] The SGK1 activating mTOR complex 2 (mTORC2) involves mTOR, Rictor (rapamycin-insensitive companion of mTOR), Sin1 (stress-activated protein kinase-interacting protein 1), mLST8, and Protor-1.[48] SGK1 is further activated by p38α, bone marrow kinase/extracellular signal-regulated kinase 5 (BK/ERK5), cAMP, lithium, Ca^{2+}-sensitive calmodulin-dependent protein kinase kinase (CaMKK), G-protein Rac1, neuronal depolarization, oxidation, hypertonicity, adhesion to fibronectin, and feeding.[2,4,55]

SGK1 is ubiquitinated by Nedd4-2 (neuronal precursor cells expressed developmentally down-regulated)[4] and Rictor/Cullin-1,[56-58] which trigger SGK1 degradation. SGK1 ubiquitinylation and degradation are counteracted by glucocorticoid-induced leucine zipper protein-1.[59]

SGK1-sensitive functions

The consensus sequence for phosphorylation by SGK1 is R-X-R-X-X-(S/T)-phi (X = any amino acid, R = arginine, phi = hydrophobic amino acid).[4] The only known specific SGK1 targets are N-myc down-regulated genes NDRG1 and NDRG2.[4,60,61] Other SGK1 targets are shared by the other SGK isoforms, by protein kinase B (PKB/Akt) isoforms, and/or other kinases.

SGK1 modifies the activity of several enzymes, such as ubquitin ligase Nedd4-2,[2,62] inducible nitric oxide synthase iNOS,[2] phosphomannose mutase 2,[4] PIP2 forming phosphatidylinositol-3-phosphate-5-kinase PIKfyve,[2] serine/threonine kinase WNK (with no lysine) 4,[2,54] extracellular signal-regulated kinase ERK2,[63] mitogen-activated protein kinase/ERK kinase kinase 3 MEKK3, stress-activated kinase SEK1,[2] B-Raf kinase,[4] and glycogen synthase kinase 3 GSK3.[4] By up-regulating ubiquitin ligase MDM2, SGK1 stimulates ubiquitylation and proteosomal degradation of the transcription factor p53.[40] SGK1 down-regulates Notch1-IC protein by stimulating Fbw7-dependent proteasomal degradation.[64]

SGK1 increases transcription by cAMP responsive element binding protein (CREB),[4,27] by activator protein-1,[27] and by nuclear factor kappa B (NFϰB).[2,65-68] SGK1 phosphorylates and thus activates NDRG1, which in turn down-regulates NFϰB signalling.[69] Moreover, SGK1 down-regulates forkhead transcription factor FKHR-L1 (FOXO3a).[2,4,70,71]

SGK1 up-regulates a myriad of ion channels,[72] including epithelial Na^+ channel EnaC,[2,4,6,46,73-89] voltage gated Na^+ channel SCN5A,[4] renal outer medullary K^+ channel ROMK1,[4,90-94] voltage gated K^+ channels KCNE1/KCNQ1,[95,96] KCNQ4,[4] Kv1.3, Kv1.5,[2] Kv7.2/3,[97] Kv4.3,[4] hERG,[98] the Ca^{2+} release-activated Ca^{2+} channels Orai1/STIM1,[11,99] transient receptor potential channels TRPV4,[100] TRPV5[4] and TRPV6,[2] kainate receptor GluR6,[4] unselective cation channel 4F2/LAT,[4] Cl^- channels ClCka/barttin,[2] ClC2,[4] CFTR (Cystic fibrosis tr ansmembrane conductance regulator)[2,101-104] and VSOAC (volume-sensitive osmolyte and anion channel),[4] as well as acid sensing ion channel ASIC1.[2]

SGK1 stimulates a large number of carriers, including Na^+, K^+, $2Cl^-$ cotransporter NKCC2,[4] NaCl cotransporter NCC,[2,79,105-108] Na^+/H^+ exchangers NHE1[67,67,109] and NHE3,[2,15,110-113] glucose carriers SGLT1,[2,114] GLUT1[2] and GLUT4,[2] amino acid transporters ASCT2,[2] SN1,[4] B(0)AT1,[115] EAAT1,[4] EAAT2,[4,116] EAAT3,[4,117] EAAT4[2,118] and EAAT5,[4] peptide transporters PepT,[2,119,120] Na^+, dicarboxylate cotransporter NaDC-1,[4] creatine transporter CreaT,[4] Na^+, myoinositol cotransporter SMIT,[2] as well as phosphate carriers NaPiIIa[121] and NaPiIIb.[4] SGK1 further up-regulates the Na^+/K^+-ATPase[2,4] and albumin uptake.[122,123]

SGK1 phosphorylates nephrin, type A natriuretic peptide receptor (NPR-A), Ca^{2+} regulated heat-stable protein of apparent molecular mass 24 kDa CRHSP24, the adaptor precursor (APP) Fe65, NDRG1 and NDRG2, myosinVc, filamin C, microtubule-associated protein tau, and huntingtin.[2,4,61,71,124]

Cellular functions regulated by SGK1 include organization of the cytoskeleton,[125] cellular K^+ uptake,[2] cell volume regulation,[2] cell survival & cell proliferation,[126] tumor growth,[10,127] cell migration,[128,129] renal tubular Na^+ transport,[2,4,84,106,130] renal tubular K^+ transport,[131] gastric acid secretion,[2,132,133] intestinal transport,[4] glucose metabolism,[2] degranulation,[125,134] hormone release,[2,4] inflammatory and neuropathic pain[2,135] muscle mass maintenance,[136] and function of decidualizing cells.[2] Moreover, SGK1 is required for nuclear export of the ribonucleoprotein of influenza A virus.[137]

SGK1-ASSOCIATED DISEASE

Hypertension

Owing to its stimulating effect on ENaC, SGK1 enhances renal tubular salt reabsorption.[2,9,84,130,138-141] Moreover, SGK1 enhances the salt appetite.[4,142,143] Accordingly, increased SGK1 activity may lead to hypertension.[79,141,144-147] Along those lines, blood pressure is modified by several SGK1 gene variants,[146] including a combination of polymorphisms in intron 6 [I6CC] and exon 8 [E8CC/CT].[2,4] The prevalence of the combination appears to be lower in Caucasians (3-5%) than in Africans (10%).[2,4] With regular diet blood pressure is similar in SGK1 knockout mice and their wild type littermates.[4] Treatment with a high-fructose diet or a high-fat diet leading to hyperinsulinism, however, sensitizes blood pressure to high-salt intake in wild type mice but not in SGK1 knockout mice.[4,148] Activation of SGK1 by insulin presumably stimulates renal tubular salt reabsorption and may possibly foster renal salt retention and hypertension in type II diabetes.[2,4] SGK1 further contributes to glucocorticoid-induced hypertension.[2]

Obesity

SGK1 stimulates the Na^+ coupled glucose transporter SGLT1 and thus accelerates intestinal glucose absorption.[4] Enhanced SGLT1 activity is in turn known to foster development of obesity, an effect presumably due to rapid increase of plasma glucose concentration with excessive insulin release and subsequent fat deposition.[2,4] SGK1 further stimulates adipocyte differentiation and adipogenesis.[149] Along those lines, body weight and prevalence of type 2 diabetes are enhanced in carriers of the I6CC/E8CC/CT SGK1 gene variant.[2] The hyperglycemia of diabetic individuals could stimulate intestinal SGK1 expression, followed by up-regulation of SGLT1 activity and further weight gain.

Hypercoagulability, thrombosis, and stroke

SGK1 stimulates coagulation by stimulating tissue factor expression[2] and increases the reagibility of blood platelets by up-regulation of NFκB and subsequent expression of the platelet Ca^{2+} channel Orai1/STIM1.[65] Enhanced coagulation and platelet reagibility predispose to the occurrence of stroke[150] and thrombosis.[65]

Inflammation and fibrosis

SGK1 up-regulates pathogenic IL-23-dependent interleukin (IL)-17-producing $CD4^+$ helper T cells (T_H17 cells),[151] which play a decisive role in autoimmune disease.[151] The up-regulation of those cells by IL-23 requires SGK1, which is critical for the expression of the IL23 receptor.[14] SGK1 becomes effective by deactivation of Foxo1, a direct repressor of IL-23R expression.[14] T_H17 cells are further up-regulated by modest increases of local NaCl concentrations,[14] which activates the p38/MAPK pathway again involving SGK1 and nuclear factor of activated T cells 5 (NFAT5, TONEBP).[151] Following NaCl exposure, T_H17 cells up-regulate the pro-inflammatory cytokines GM-CSF, TNF-α, and IL-2. As a result, mice fed with a high-salt diet develop a particularly severe form of experimental autoimmune encephalomyelitis paralleled by enhanced infiltration of T_H17 cells into the central nervous system.[151]

SGK1 is up-regulated by TGFβ,[4] a key stimulator of fibrosis.[152-158] TGFβ up-regulates the transcription factors Smad2/3.[159] SGK1 phosphorylates and thus inactivates Nedd4L, a ubiquitin ligase triggering the degradation of Smad2/3.[159] SGK1 expression is excessive in affected tissues of inflammatory and fibrosing diseases, such as lung fibrosis, diabetic nephropathy, glomerulonephritis, experimental nephrotic syndrome, obstructive nephropathy, liver scirrhosis, fibrosing pancreatitis, peritoneal fibrosis, Crohn's disease, and coeliac disease.[4,160-163] SGK1 fosters nuclear translocation of NFκB, which stimulates expression of connective tissue growth factor (CTGF),[4] triggers prostaglandin formation,[164] modifies cell survival,[165-168] and thus participates in the signalling of inflammation and fibrosis.[169-172] Along those lines, SGK1 is required for the effect of excessive glucose concentrations on the formation of the matrix protein fibronectin.[173] Overexpression of SGK1 alone, however, does not appreciably up-regulate fibronectin formation, indicating that additional glucose-dependent mechanisms are required for the induction of fibrosis by hyperglycemia.[173] SGK1 is required for the up-regulation of CTGF formation and cardiac fibrosis following treatment of mice with the mineralocorticoid DOCA[4] and mineralocorticoid-induced aging of the skin.[31] SGK1 is involved in angiotensin II-induced cardiac CTGF formation and fibrosis[174,175] and in cardiac remodelling following increased afterload.[109,176,177]

Tumor growth

High levels of SGK1 expression have been observed in several tumors,[10] including colon cancer,[10] myeloma,[178] medulloblastoma,[179] prostate cancer,[180] ovarian tumors,[25] and non-small cell lung cancer.[181] SGK1 may support survival of tumor cells.[4,7,25,40,127,182] For instance, SGK1 may mediate interleukin 6 (IL6)-dependent survival of cholangiocarcinoma cells,[4,10] interleukin 2 (IL2)-dependent survival of kidney cancer cells,[40] angiotensin II-induced survival of fibrosarcoma-derived cells,[183] and androgen receptor-mediated survival of prostate cancer cells.[143,184] SGK1 further confers resistance of breast cancer cells to chemotherapy and SGK1 silencing increases the toxicity of chemotherapeutic drugs.[4,10,185]

Inhibition of SGK1 slows androgen-induced growth of prostate cancer cells. [2] SGK1 contributes to glucocorticoid- or colony-stimulating factor 1 (CSF1)-induced stimulation of invasiveness, motility, and adhesiveness.[4,10] Moreover, SGK1 counteracts the signalling of proapoptotic membrane androgen receptors[186-188] and regulates the membrane androgen receptor-induced signal transduction controlling actin cytoskeleton architecture and migration in colon tumor cells.[128,129,189]

SGK1-sensitive signalling counteracting apoptosis include phosphorylation and thus inactivation of the proapoptotic forkhead transcription factor Foxo3a/FKRHL1.[70] SGK1 further phosphorylates and thus inhibits glycogen synthase kinase GSK3, a kinase down-regulating oncogenic β-catenin.[4,7] SGK1 deficiency thus decreases β-catenin protein abundance.[2] SGK1 may inhibit apoptosis further by phosphorylation of IKKb with subsequent phosphorylation and degradation of the inhibitory protein IκB, thus leading to translocation of NFκB into the nucleus.[10] SGK1 further phosphorylates the ubiquitin ligase MDM2 with subsequent MDM2-dependent ubiquitylation and proteosomal degradation of proapoptotic transcription factor p53.[40] The down-regulation of p53 abundance by SGK1 stimulates cell proliferation and transition of epithelial cells into mesenchymal cell types.[40] SGK1 further up-regulates Ran binding protein (RanBP), which in turn influences microtubules and decreases taxol sensitivity of cancer cells.[190] SGK1 has been reported to either down-regulate or to enhance ERK2 activity and MEK/ERK complex formation.[2,10,63] SGK1 phosphorylates SEK1 and thus interferes with the binding of SEK1 to JNK1 and MEKK1.[4,10] Finally, SGK1 down-regulates vinculin phosphorylation, which in turn may enhance migration via actin cytoskeleton redistribution.[128,129]

SGK1 may influence cell proliferation and cell death further by influencing the activity of channels and transporters, such as Ca^{2+} release-activated channels (I_{CRAC}) Orai1/STIM1[65,66,99] and K^+ channels, such as voltage-sensitive K^+ channel Kv1.3.[4,10] The K^+ channels maintain the cell membrane potential required for opening of I_{CRAC}.[4,10] Ca^{2+} entry via I_{CRAC} triggers oscillations of cytosolic Ca^{2+} activity, which are required for triggering of cell proliferation.[4,10]

SGK1 is up-regulated by ischemia and may be particularly important for survival of tumor cells during ischemia.[2,4,10,33] SGK1 may counteract energy depletion of tumor cells by stimulation of glucose uptake.[4] Moreover, SGK1-sensitive stimulation of the Na^+/H^+ ion exchanger may lead to cytosolic alkalinization,[67] which enhances the glycolytic flux.[191]

A positive correlation between SGK1 abundance and patient survival was paradoxically observed in adrenocortical carcinoma.[192,193] Moreover, SGK1 abundance is reportedly down-regulated in several tumors, such as prostate cancer, ovarian tumors, hepatocellular carcinoma, and adenomatous polyposis coli (APC).[4,10,194] Development of those tumors thus appears to be independent from SGK1. Genetic SGK1 knockout, however, decreases the development of spontaneous tumors in APC deficient mice[2] and chemically induced colonic tumors in wild type mice.[195] It is tempting to speculate that high activity of PKB/Akt isoforms or SGK3 in tumor cells leads to down-regulation of SGK1 expression and decreases the requirement of SGK1 for tumor cell survival.

The mild phenotype of SGK1 knockout mice illustrates that, despite its multiple effects on cell proliferation and apoptosis, SGK1 is not critically important for cell proliferation and survival.[4,10] Thus, inhibition of SGK1 alone is presumably not sufficient to eliminate tumor cells. Nevertheless, particularly in tumor cells with high SGK1 expression levels, SGK1 may contribute to the maintenance of tumor cell survival and resistance of tumor cells to ischema and therapy.[12]

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