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Minireview

Serum Glucocorticoid-Regulated Kinase-1 in Ischemia-Reperfusion Injury: Blessing or Curse

Mahmood S. Mozaffari

Department of Oral Biology and Diagnostic Sciences, The Dental College of Georgia, Augusta University, Augusta, Georgia

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ABSTRACT

The family of serum-glucocorticoid-regulated kinase (SGK) consists of three paralogs, SGK-1, SGK-2, and SGK-3, with SGK-1 being the better studied. Indeed, recognition of the role of SGK-1 in regulation of cell survival and proliferation has led to introduction of a number of small-molecule inhibitors for some types of cancer. In addition, SGK-1 regulates major physiologic effects, such as renal solute transport, and contributes to the pathogenesis of non-neoplastic conditions involving major organs including the heart and the kidney. These observations raise the prospect for therapeutic modulation of SGK-1 to reduce the burden of such diseases as myocardial infarction and acute kidney injury. Following a brief description of the structure and function of SGK family of proteins, the present review is primarily focused on our current understanding of the role of SGK-1 in pathologies related to ischemia-reperfusion injury involving several organs (e.g., heart, kidney). The essential role of the mitochondrial permeability transition pore in cell death coupled with the pro-survival function of SGK-1 raise the prospect that its therapeutic modulation could beneficially impact conditions associated with ischemia-reperfusion injury.

SIGNIFICANCE STATEMENT

Since the discovery of serum glucocorticoid-regulated kinase (SGK)-1, extensive research has unraveled its role in cancer biology and, thus, its therapeutic targeting. Increasingly, it is also becoming clear that SGK-1 is a major determinant of the outcome of ischemia-reperfusion injury to various organs. Thus, evaluation of existing information should help identify gaps in our current knowledge and also determine whether and how its therapeutic modulation could impact the outcome of ischemia-reperfusion injury.

Introduction

The serum glucocorticoid-regulated kinase (SGK) family, a member of the larger AGC family of serine-threonine protein kinases, consists of three different paralogs, namely SGK-1, SGK-2, and SGK-3, each encoded by a distinct gene on a different chromosome—chromosomes 6, 20 and 8, respectively, in humans (Waldegger et al., 1998; Firestone et al., 2003; Deelen et al., 2013; Hou et al., 2015; Guerriero et al., 2020). The SGK proteins share a highly homologous structural organization with the following sequence identity: C-terminal domain: 40–68%; catalytic domain: 80%; N-terminal domain: 20%; each paralog of SGK has more than one splicing isoform (i.e., SGK-1: 4; SGK-2: 2; SGK-3: 2) but distinct functional attributes of each variant remain to be better established (Guerriero et al., 2020).

SGK-1 and SGK-3 are ubiquitously expressed but SGK-2 is expressed in the kidney, liver, pancreas and brain (albeit at lower level) (Guerriero et al., 2020). The cellular localization of SGK is context- and condition-specific. For example, following serum stimulation, SGK-1 enters the nucleus while it is found in the cytosol in response to glucocorticoids or hypertonic shock. It is also found in mitochondria, likely regulating cellular energy metabolism and autophagy, and is associated with plasma membrane in both non-malignant and malignant oral lesions (Cordas et al., 2007; O'Keeffe et al., 2013; Zhou et al., 2019; Zhu et al., 2020; Mozaffari and Abdelsayed, 2021). Collectively, these observations indicate the complex and multifaceted role of SGK-1 in physiologic processes and pathologic conditions. SGK expression is regulated by diverse stimuli, which include glucocorticoids, saline ingestion, dehydration, insulin, growth factors, as well as cellular stresses, such as

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ABBREVIATIONS: AKI, ccute kidney injury; ALI, acute lung injury; ANT, adenine nucleotide transporter; CRLM, colorectal liver metastasis; ENaC, epithelial sodium channel; GSK-3β, glycogen synthase kinase-3β; HF, heart failure; HR, hypoxia reoxygenation; IGF insulin-like growth factor; IL, interleukin; IPC, ischemic preconditioning; IRI, ischemia-reperfusion injury; MI, myocardial infarction; PDK1, 3-phosphoinositide-dependent kinase-1; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species; SGK, serum glucocorticoid-regulated kinase; TILLIR, tourniquet-induced lower limb ischemia-reperfusion; TNF-α, tumor necrosis factor-α; VDAC, voltage-dependent anion carrier.

ultraviolet irradiation, DNA damage, cell swelling, and metabolic acidosis, among others (Zhu et al., 2020).

SGK-1 is the better studied member of the SGK family. *SGK-1* was discovered as an immediate early gene, encoding for a 50 kDa protein that was transcriptionally-induced in mammary cancer cells by (10% calf) serum and (1 μM) dexamethasone (Webster et al., 1993). However, it is now known that SGK-1 is also post-transcriptionally-regulated (Guerriero et al., 2020). As a member of the AGC family of proteins, SGK-1 shares about 50% homology with another member, namely Akt (protein kinase B). While Akt is the better known downstream effector of phosphoinositide 3-kinase (PI3K) signaling, increasing evidence indicates that other proteins, including SGK-1, are also regulated by PI3K-dependent signaling. Indeed, SGK-1 is activated by a two-step process involving: a) phosphorylation on Ser422 (on C-terminal domain) by the mammalian target of rapamycin complex 2, which causes the kinase to assume an open configuration and b) its subsequent full activation via phosphorylation of Thr256 (on catalytic domain) by 3-phosphoinositide-dependent kinase-1 (PDK1) (Guerriero et al., 2020) (Fig. 1). Thus, the mammalian target of rapamycin complex 2/PDK1/SGK-1 axis is an example of PI3K-dependent, but Akt-independent, signaling pathways, which can substitute for Akt in survival, migration, and growth signaling, thereby serving as a mechanism of resistance to small molecule inhibitors of Akt (Lien et al., 2017).

Aside from regulation of cell survival and proliferation, SGK-1 regulates a myriad of other processes, including ion transport, cellular enzymes, transcription factors, T cell activation, macrophage motility/function, and insulin sensitivity (Guerriero et al., 2020); such diverse effects of SGK-1 underlie its role in various conditions and pathologies. The role of SGK-1 in other fields, including regulation of ion transport and cancer biology, has been the focus of a number of reviews (Valinsky et al., 2018; Guerriero et al., 2020; Rotin and Staub 2021; Sang et al., 2021; Cicenas et al., 2022). Thus, the present review describes the role of SGK-1 primarily in ischemia reperfusion-induced pathologies of several organs. Prior to that, however, brief comments regarding the role of other SGK paralogs in such conditions are warranted. To the knowledge of this author, the role of SGK-2 with respect to ischemia-reperfusion injury (IRI) remains to be established. However, a recent study reported that overexpression of SGK-3 promoted cardiac repair and functional recovery following IRI in adult mice, an effect attributed to inhibition of glycogen synthase kinase-3β (GSK-3β) activity and upregulation of β-catenin expression (Li et al., 2021). Further, overexpression of an upstream regulator of SGK-3, i.e., cyclin-dependent kinase 9, promoted cell cycle entry of mature cardiomyocytes and cardiac repair following myocardial infarction (MI) in mice (Sun et al., 2022). With respect to the kidney, the role SGK-3 in transition from acute kidney injury (AKI) to

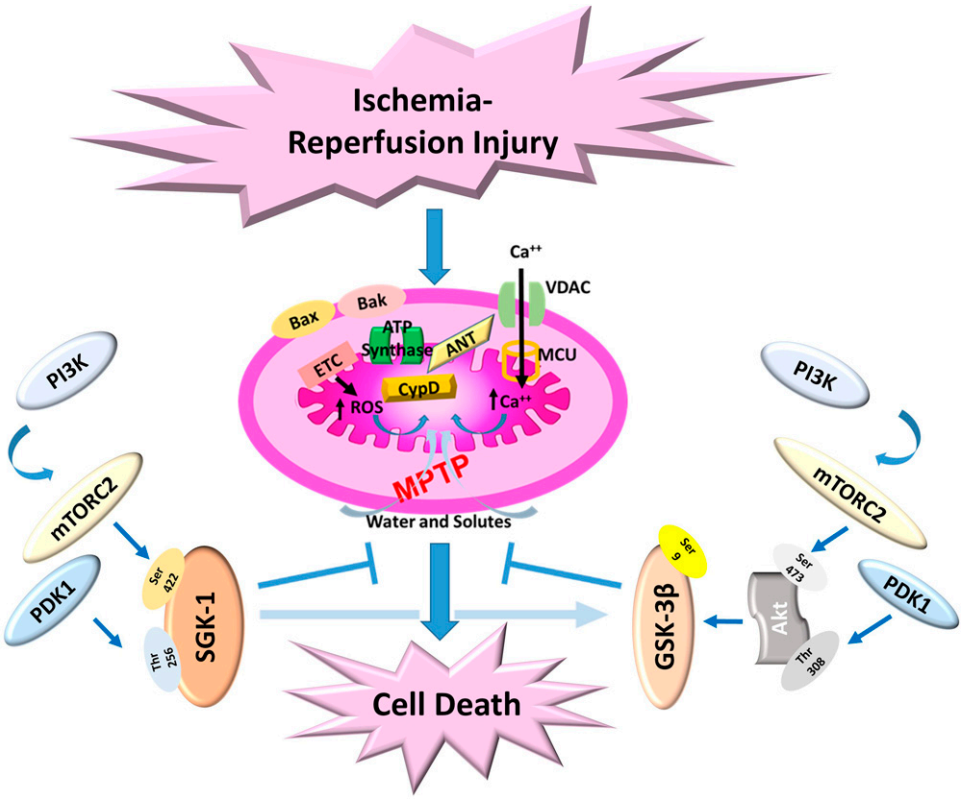

Fig. 1. Diagram depicts the potential role of SGK-1 in regulation of MPTP. The prevailing conditions of intracellular Ca^{++} overload and oxidative stress during IRI cause marked MPTP induction and cell death (e.g., apoptosis and necrosis). Accordingly, mitochondrial uptake of Ca^{++} likely occurs through VDAC and MCU located within outer and inner mitochondrial membranes, respectively. This coupled with generation of ROS (e.g., through dysfunctional electron transport chain) results in MPTP formation; putative pore forming components include ATP synthase and ANT. Induction of MPTP causes marked influx of water and solutes across the inner mitochondrial membrane, ultimately causing disruption of mitochondrial integrity, resulting in cell death. A variety of cytoprotective agents and maneuvers, via signaling mechanisms, regulate the MPTP, including the PI3K/Akt/GSK-3β pathway; Akt-mediated Ser9 phosphorylation of GSK-3β results in inhibition of the MPTP and protection against cell death. The PI3K/SGK-1 signaling is emerging as an Akt-independent means of inhibition of MPTP and cytoprotection not only via GSK-3β phosphorylation but also likely via interaction with pore forming and/or regulating components of the MPTP.

chronic kidney disease has been explored in mice but AKI was induced by means other than IRI (Shu et al., 2023).

SGK-1 and the Heart

SGK-1 and Transplantation (Table 1). Myocardial infarction remains a major cause of morbidity and mortality (Jenča et al., 2021). Further, restoration of blood flow to the ischemic heart is associated with significant injury (Mozaffari et al., 2013; Heusch 2019; Popov et al., 2023). Indeed, IRI of a transplanted heart can result in serious early injury and long-term sequel thereby necessitating unraveling of the mechanisms involved and potential targets of therapy. This recognition has led to the investigation of the SGK-1 status and impact of dexamethasone treatment in a rat model of cardiac transplantation (Yang et al., 2015). The authors showed temporally-regulated SGK-1 protein expression in allogeneic and syngeneic hearts (i.e., by cardiomyocytes rather than infiltrated immune cells). Further, dexamethasone increased SGK-1 expression in cardiomyocytes of grafted hearts in association with reduced donor cardiomyocyte injury, suggesting a protective role of the SGK-1 in the transplanted heart. While SGK-1 phosphorylation/activation status was not determined, dexamethasone also increases SGK-1 phosphorylation (Rusai et al., 2013). Thus, the possibility that SGK-1 could serve as a cardioprotective kinase has been investigated under several protocols and conditions as described below.

SGK-1 and Cardioprotection (Table 1). An earlier study examined the role of SGK-1 on the effects of insulin-like growth factor (IGF) in hearts subjected to coronary artery ligation. The mIGF-1 isoform was studied which is comprised of Class 1 signal peptide and a C-terminal Ea extension peptide (Santini et al., 2007). The mIGF-1 isoform is expressed at high levels in neonatal tissues and adult liver, but its expression is reduced in extrahepatic tissues. However, with aging, its expression increases in response to injury. It was shown that transgenic mice, with persistent expression of cardiac-restricted IGF, do not manifest significant impairment of cardiac growth and physiology. However, following MI, transgenic mice displayed better restoration of cardiac function, an effect attributed to upregulation of cell survival pathways and promotion of inflammation resolution (manifested by reduced interleukin (IL)-1β and IL-6 but increased IL-4 and IL-10) accompanied by increased proliferative activity of ventricular tissue several weeks after injury. These effects were associated with upregulation of PDK1 and SGK-1 signaling in cardiac tissue of transgenic mice, without activation of Akt, mTOR and p70S6 kinase. The authors proposed that persistent expression of cardiac-restricted mIGF-1, via a pathway dependent on PDK1/SGK-1 signaling, promotes a local tissue environment conducive to efficient myocardial wall replacement following MI.

Other investigators have explored the role of SGK-1 in urocortin-1-induced cytoprotection (Cong et al., (2014). Using neonatal cardiomyocytes subjected to hypoxia-reoxygenation (HR) injury, it was reported that treatment with urocortin-1 increased cell viability but decreased lactate dehydrogenase release and cleaved caspase 3 level, effects attenuated by knockdown of SGK-1. Further, authors reported concentration- and time-dependent increases in urocortin-1-induced SGK-1 mRNA and protein expressions as well as its phosphorylated form via the PI3K-dependent pathway; nonetheless, these studies were seemingly carried out in cardiomyocytes not subjected to HR but serving as control. Since urocortin-1 reportedly increases in cardiomyocytes subjected to HR, the authors conjectured that HR-induced upregulation of endogenous urocortin-1 regulates SGK-1 expression and/or phosphorylation. However, HR did not affect SGK-1 and phosphoSGK-1 levels in cardiomyocytes. A follow-up study reported that estrogen regulates SGK-1 expression via increasing urocortin-1 action in cardiac cells subjected to HR injury (Cong et al., 2015).

More recently, the impact of microRNAs in pathogenesis of cardiovascular disorders has received considerable attention. Accordingly, effects of miR-145, in the context of assessment of SGK-1, has been examined in hypoxic cardiomyocytes (Sun et al., 2018). Results indicated upregulation of miR-145 expression in hypoxic H9c2 and HL-1 cells, an effect associated with expression of hypoxia-inducible factor-1α. Further, miR-145 mimetic increased cell viability and migration of H9c2 cells under normoxia, while hypoxic cells with upregulation of miR-145 exhibited reduced reactive oxygen species (ROS) and apoptosis but increased cell viability. Based on Western blot studies (without demonstrable semi-quantitative analyses), authors reported that miR-145 overexpression inhibited activation of apoptotic factors but promoted SGK-1 upregulation (via PI3K) in H9c2 cells. Further, rat hearts subjected to MI displayed increased levels of both miR-145 and SGK-1 mRNA expression (and protein expression albeit based on sample size of 1 for sham versus MI), leading to the conclusion that miR-145-induced cardioprotection is mediated via SGK-1.

The recognition of hydrogen sulfide as a cardioprotective substance has led to investigation of the role of PI3K/SGK-1/GSK-3β in its cytoprotective effects in the context of assessment of autophagy; these studies were based on recognition of anti-autophagy effects of hydrogen sulfide in hearts subjected to in vivo IRI (Jiang et al., 2016). It is noteworthy that phosphorylation of GSK-3β (Ser9), via PI3K/Akt and/or SGK-1, results in its inactivation and consequent cytoprotection via inhibition of mitochondrial permeability transition pore (MPTP) opening (Mozaffari et al., 2013; Tanaka et al., 2018; Zheng et al., 2020) (Fig. 1). Thus, the impact of pharmacologic inhibition of PI3K and GSK-3β or knockdown of SGK-1 on neonatal cardiomyocytes subjected to HR, with or without hydrogen sulfide treatment, were determined on autophagy-related genes, namely ATG5, Beclin1 and Atg9 (Jiang et al., 2016). Hypoxia-reoxygenation significantly increased mRNA expression of genes of interest, effects which were reduced by hydrogen sulfide treatment. Inhibition of PI3K or SGK-1 knockdown further increased mRNA expression of aforementioned genes, effects that were partially reduced by hydrogen sulfide. On the other hand, GSK-3β inhibition produced an opposite effect. Similar effects were reported for protein levels under these conditions. Further, hydrogen sulfide-induced cytoprotection was associated with increased PI3K and SGK-1 protein levels, and their phosphorylated forms, and also increased phosphoGSK-3β level. The effects of hydrogen sulfide on PI3K and GSK-3β were reversed by LY294002 (a PI3K inhibitor). In addition, knockdown of SGK-1 reversed hydrogen sulfide-induced increase in phosphoGSK-3β level in cardiomyocytes subjected to HR. Based on their collective observations, the authors proposed that hydrogen sulfide, via PI3K, stimulates SGK-1 which, in turn, inhibits GSK-3β thereby suppressing autophagy, culminating in cytoprotection against HR.

SGK-1 and Mechanical Stress (Table 1). Mechanical stress is intimately related to cardiac function and structure

TABLE 1
SGK-1 in conditions associated with cardiac injury

Model/Condition	Findings/Conclusions	Citation
Heart transplantation using Wistar and Lewis rats	• Time-dependent SGK-1 expression in transplanted hearts • Dexamethasone-induced increase in SGK-1 expression and reduced injury	Yang et al., 2015
Myocardial infarction (MI) in Friend Virus B mice; Persistent expression of cardiac-restricted insulin-like growth factor	• Better restoration of cardiac function following MI • Upregulation of PDK1/SGK-1 signaling	Santini et al., 2007
Neonatal Sprague-Dawley rat cardiomyocytes subjected to hypoxia-reoxygenation and/or control conditions	• Urocortin-1 increased cell viability and reduced cell death • Urocortin-1 increased SGK-1 expression (mRNA and protein) and phosphorylation status	Cong et al., 2014
Ovariectomized rat (± estrogen); neonatal rat cardiomyocytes	• Cytoprotective effect of estrogen related to urocortin-1-induced upregulation of SGK-1	Cong et al., 2015
Cardiomyocytes cell lines and HR; impact of miR-145	• Hypoxic cells upregulated miR-145 in association with increased expression of hypoxia-inducible factor-1α • Cytoprotective effect of miR-145, likely in association with SGK-1 upregulation	Sun et al., 2018
Sprague-Dawley rats subjected to MI	• Increased miR-145 and SGK-1 mRNA expression in rat heart subjected to MI	
Neonatal Sprague-Dawley rat cardiomyocytes subjected to HR; effects of hydrogen sulfide	• Hydrogen sulfide suppressed autophagy and protected against HR-induced cardiomyocyte injury • Hydrogen sulfide-induced cytoprotection associated with activation of PI3K/SGK-1	Jiang et al., 2016
Rat heart subjected to aortic banding	• Increased SGK-1 protein expression and phosphoSGK-1 level	Aoyama et al., 2005
Cardiomyocytes subjected to stress (e.g., hypertrophy)	• SGK-1-induced phosphorylation of GSK-3β and cytoprotection	
Mechanical stretch and inflammatory response of cardiac fibroblasts from B6/129S wild type and SGK-1 knockout mice	• Chemokine release in association with increased SGK-1 level and activation • Reduction of stretch-induced chemokine release with SGK-1 deficiency	Gan et al., 2018
Isolated Sprague-Dawley rat heart subjected to IRI; low versus high perfusion pressure	• Exacerbation of inflammatory response and cardiac injury at higher perfusion pressure • Inhibition of SGK-1 exacerbated IRI; effects more pronounced at lower perfusion pressure	Baban et al., 2014
Extract of *Potentilla reptans* given at reperfusion of the ischemic heart of Wistar rat	• Cardioprotective effect associated with decreased SGK-1 and GSK-3β protein levels	Enayat et al., 2021
Gallic acid treatment and/or SGK-1 inhibition in Wistar rat heart subjected to IRI	• Combination treatment exerted greater cardioprotection	Souri et al., 2023
SGK-1 knockout mouse, generated on a 129/SvJ background; endothelial cells in the context of MI	• SGK-1 ablation increased scarring and decreased neoangiogenesis	Zarinpashneh et al., 2013
Human intracoronary thrombus and ST-segment elevated MI	• Increased SGK-1 expression	Cai et al., 2022

leading to investigation of the role of SGK-1 in mechanical stress-related cardiac outcomes. Accordingly, marked increases in both SGK-1 and phosphoSGK-1 were reported for rat hearts subjected to aortic banding (Aoyama et al., 2005). Additional in vitro studies, under various conditions, indicated that the protective effect of SGK-1 on cardiomyocytes subjected to stress relates to phosphorylation of downstream effectors such as GSK-3β. More recently, it was reported that SGK-1 (but not SGK-2 or SGK-3) plays a pivotal role in mechanical-stretch-induced inflammatory response of cardiac fibroblasts (Gan et al., 2018). These studies were based on the observation that cardiac fibroblasts of wild-type mice subjected to mechanical stretch displayed increased chemokine release in association with increased SGK-1 level and activation, whereas stretch-induced chemokine release was reduced in cardiac fibroblasts of SGK-1 knockout mice. These observations led to the conclusion that SGK-1 may be a promising therapeutic target for cardiac fibrosis and HF. Given regulation of SGK-1 by mechanical stress, our group examined its role in the isolated rat heart subjected to global IRI, at low and high perfusion pressures (Baban et al., 2014). Accordingly, Langendorff-perfused hearts were subjected to an ischemia-reperfusion insult, at either 80 or 160 cm of H2O, with the perfusion buffer lacking or containing the SGK-1 inhibitor, GSK650394A, while normoxic hearts served as controls. We found that IRI reduced phosphoSGK-1 accompanied by disruption of mitochondrial membrane potential and increased apoptosis and necrosis. Further, IRI increased expression of growth-arrest and DNA damage-associated protein 153 (a determinant of inflammation and cell death) and the proinflammatory cytokine-IL-17. These

effects were greater at higher perfusion pressure. On the other hand, the anti-inflammatory cytokines, IL-10 and IL-27, increased more in ischemic-reperfused hearts subjected to lower pressure. Pharmacological inhibition of SGK-1 further reduced phosphoSGK-1, increased growth-arrest and DNA damage-associated protein 153 and IL-17, but reduced IL-10 and IL-27, in association with augmented disruption of mitochondrial membrane potential, and exacerbated cell death. These effects were greater at lower pressure. Thus, it appears that SGK-1 in a pressure/mechanical stress-dependent manner acutely regulates inflammation and cell fate in the ischemic-reperfused heart, aspects that are of relevance to systemic hypertension and associated increase in myocardial load/mechanical stress.

The aforementioned studies generally support a role for SGK-1 as a cardioprotective kinase. Nonetheless, it is noteworthy that two other studies do not seemingly support this contention. Enayati et al. (2021) examined the postconditioning effect of an ethyl acetate fraction of *Potentilla reptans* (a perennial plant in Eurasia and North Africa) in the isolated rat heart subjected to regional IR insult; postconditioning refers to interventions instituted immediately at reperfusion of the ischemic tissue (Mozaffari et al., 2010; de Miranda et al., 2021). Aside from assessing various parameters related to cardiac function, oxidative stress and apoptosis, the authors reported that the cardioprotection of Potentilla reptans' extract, introduced immediately at reperfusion, was associated with significant decreases in SGK-1 and GSK-3β proteins; however, the phosphorylation/activation status of these proteins was not determined, thereby making it difficult to appreciate their roles in this study. A more recent study examined the impact of gallic acid (an anti-oxidant) and inhibition of SGK-1 (using GSK650394) in the isolated heart subjected to global IRI. Animals were pretreated with gallic acid for 10 days while the SGK-1 inhibitor was added to the perfusate 5 minutes before induction of ischemia (Souri et al., 2023). While each treatment alone reduced various oxidative stress and cardiac enzyme markers in association with attenuation of infarct size, combination treatment exerted more marked protective effects. The protective versus exacerbating effect of SGK-1 inhibition may relate to differences in experimental protocols such as the use of peristaltic pump for constant flow perfusion versus adjusting the perfusion pressure as well as the SGK-1 inhibitor being administered 5 minutes before ischemia versus it being present throughout the IR protocol in the studies of Souri et al. (2023) versus Baban et al. (2014). The timing and duration of exposure to the SGK-1 inhibitor (or other modalities/maneuvers) is an important consideration since reperfusion of the ischemic heart is known to mobilize diverse signaling pathways, immediately following reperfusion, culminating in reperfusion-induced injury (Mozaffari et al., 2013; Popov et al., 2023).

SGK-1 and Non-Cardiomyocytes (Table 1). Other studies have addressed the role of SGK-1 in cells other than cardiomyocytes in MI. Zarrinpashneh et al. (2013) explored the role of SGK-1 in endothelial cell migration and tube formation given its role in angiogenesis during embryonic development. SGK-1 ablation in mice significantly decreased phosphorylation of the target protein, N-myc downstream-regulated gene 1 in heart and endothelial cells, which correlated with alterations in nuclear factor-κB signaling cascade consistent with its activation and upregulation of its downstream effector, vascular endothelial growth factor-A. These changes were accompanied by smaller size of cardiomyocytes and reduced heart and body weights. Further, SGK-1 ablation increased scarring and decreased angiogenesis following MI. Additional in vitro studies showed that knockdown of SGK-1 resulted in defective endothelial cell migration and tube formation, effects reversed by its re-expression. Authors concluded that intact SGK-1 signaling plays a pivotal role in adult myocardial neo-angiogenesis and wound healing following an ischemic insult. Thus, given the emerging concept that, aside from infarct size reduction, attenuation of coronary microvascular injury represents a new frontier of cardioprotection (Heusch 2019), determination of the role of SGK-1 in coronary microcirculation, in hearts subjected to oxidative stress, is warranted. Interestingly, a recent study examined SGK-1 expression in intracoronary thrombus in acute ST-segment elevation MI of humans (Cai et al., 2022). Initial proteomic analyses revealed significant upregulation of SGK-1 in thrombus which was further confirmed by immunohistochemistry and Western blotting. While there is a paucity of information regarding the role of SGK-1 in platelet function, the findings of this study, despite its limitations (e.g., small sample size, unknown status of active SGK-1 form), reveals the complexity of modulation of SGK-1 activity in MI.

In summary, utilizing diverse experimental models, protocols and conditions, the preponderance of evidence suggests that upregulation of endogenous SGK-1 confers beneficial effects to cardiomyocytes or intact heart in response to HR or IRI, respectively, likely serving as a compensatory mechanism to curtail damage (Table 1). This raises the possibility that augmented SGK-1 signaling would exert even greater beneficial effects to the heart during the immediate/early phase of oxidative injury (e.g., at reperfusion of the ischemic heart). However, to the knowledge of this author, selective SGK-1 activators are not available but their development would advance research in the field. Nonetheless, major gaps remain in our understanding of the role of SGK-1 in the ischemic-reperfused heart. To provide examples, the following questions can be explored. What is the role of SGK-1 in coronary microvasculature? What is the role of SGK-1 in cardioprotective maneuvers, such as ischemic pre- or post-conditioning as well as cardioprotective agents such as mitochondrial ATP-dependent potassium channel openers? How does SGK-1 activation impact the mitochondrial death pathway, a critical determinant of cell death? How does SGK-1 activation, intended to preserve the viable portions of the myocardium, impact long-term sequel of MI – i.e., HF? Investigation of such issues should strengthen the rationale for therapeutic modulation of SGK-1 in MI.

SGK-1 and the Kidney

SGK-1 and Renoprotection (Table 2). The early recognition of SGK-1 as a stress-regulated protein led to its investigation in response to HR in HEK-293 cells, an immortalized human embryonic kidney cell line (Rusai et al., 2009). The authors reported that HR increased SGK-1 transcript, its protein, and its phosphorylation levels, effects associated with increased apoptosis, which was significantly reduced by prior SGK-1 overexpression. Further, utilizing in vivo renal IRI models, increased transcript and protein for SGK-1 were reported in association with worsened apoptosis of kidney cells, the latter effect being exacerbated in mice lacking SGK-1. The authors concluded that upregulation of SGK-1, and consequent anti-apoptotic

TABLE 2
SGK-1 in conditions associated with kidney injury

Model/Condition	Findings/Conclusions	Citation
HEK-293 cells and HR	• Increased SGK-1 expression and phosphorylation status • Increased apoptosis that was reduced by SGK-1 overexpression	Rusai et al., 2009
- Sprague-Dawley rat model of renal IRI	• Time dependent increased SGK-1 mRNA and protein expressions as well as phosphoSGK-1 level	
- Murine model of Renal IRI; SGK-1 knockout mice on 129S1/SvlmJ background	• Increased apoptosis that was exacerbated by SGK-1 knockout	
HEK-293 cells and HR	• Erythropoietin-induced cytoprotection associated with increased SGK-1 expression • Downregulation of SGK-1 reversed cytoprotection of erythropoietin	Rusai et al., 2010
Wistar rats subjected to renal IRI	• Erythropoietin-induced renoprotection in association with increased SGK-1 expression and phosphorylation	
Hypoxic HK-2 cells	• Dexamethasone reduced cell death, an effect attributed to increased SGK-1 expression	Rusai et al., 2013
Wistar rat model of renal IRI (+/− Dexamethasone)	• Renoprotection in association with increased SGK-1 expression	
HPC and HK-2 cells	• HPC-induced cytoprotection increased SGK-1 and phosphoSGK-1 levels and activated autophagy • SGK-1 knockdown worsened HR injury and reduced HPC-induced cytoprotection; SGK-1 overexpression exerted opposite effects.	Xie et al., 2018
IPC in renal IRI; Sprague-Dawley rats	• IPC-induced renoprotection, increased SGK-1 and phosphoSGK-1 as well as autophagy activation	
Sex hormones, HEK-293 cells, and HR	• Testosterone, but not 17-beta estradiol, increased SGK-1 expression	Rusai et al., 2011
Wistar rats subjected to renal IRI	• Higher SGK-1 expression and phosphorylation in male compared with female rats • Castration reduced SGK-1 protein and phosphoSGK-1 levels	
AKI secondary to lower limb IRI; C57BL/6 mice	• Significant AKI, increased mitochondrial SGK-1 activity and decreased autophagy	Packialakshmi et al., 2022
Murine model of global SGK-1 activation and DOCA/Salt hypertension; founder animals, harboring S422D point mutation, were backcrossed with C57BL/6 mice	• Worsened glomerular hypertrophy and fibrosis without affecting hypertension level	Sierra-R amos et al., 2021

effect, exerts renoprotection. A follow-up study examined the role of SGK-1 in erythropoietin-induced renoprotection (Rusai et al., 2010). Accordingly, treatment of hypoxic HEK 293 cells with erythropoietin decreased the release of lactate dehydrogenase and reduced apoptosis, effects which were accompanied by increased SGK-1 expression (and phosphorylation but data not shown). Downregulation of SGK-1 (by siRNA) reversed the protective effect of erythropoietin in hypoxic HEK-293 cells. Further, administration of erythropoietin to rats before induction of renal ischemia (50 minutes), followed by up to 24 hours of reperfusion, reduced serum creatinine and blood urea nitrogen, effects which were associated with time-dependent increase in SGK-1 expression and phosphorylation. Interestingly, the impact of dexamethasone on renal IRI in the context of assessment of SGK-1 was introduced relatively late into the literature. In 2013, Rusai et al. showed that incubation of hypoxic HK-2 cells (human proximal tubule cell line) with dexamethasone reduced cell death, an effect attributed to increased SGK-1 expression. Utilizing the rat model of unilateral renal IRI, the authors further showed that dexamethasone exerted protection (e.g., reduced blood urea nitrogen) in association with prominent upregulation of SGK-1 and its phosphorylation.

A recent study explored the role of SGK-1 in the protection conferred by hypoxic or ischemic preconditioning (HPC and IPC, respectively) in renal injury models and in the context of assessment of autophagy (Xie et al., 2018). HPC and IPC refer to brief periods of hypoxia and reoxygenation or ischemia and reperfusion before index hypoxia or ischemia, respectively. While HPC conferred protection to HK-2 cells subjected to HR (e.g., increased viability and decreased apoptosis), IPC exerted renoprotection against IRI (e.g., decreased serum creatinine and reduced renal structural damage). Further, protective effects of HPC and IPC were associated with activation of autophagy as exemplified by increased protein levels of LC3II and Beclin-1 but decreased SQSTM/p62, a selective autophagy substrate, and increased autophagic flux. In addition, HPC and IPC markedly increased levels of both SGK-1 and phosphoSGK-1. However, knockdown of SGK-1 in HK-2 cells exacerbated HR injury and reduced protection afforded by HPC, while SGK-1 overexpression caused opposite effects. Collectively, these observations suggest that upregulation of SGK-1 likely contributes to HPC- and IPC-mediated activation of autophagy and protective effects in both in vitro and in vivo models of renal injury. The conclusion of Xie and colleagues (2018) regarding the role of SGK-1 in the aforementioned renal

studies is seemingly different from that of Jiang et al. (2016), described earlier, who concluded that the protective effect of hydrogen sulfide against hypoxic injury in cardiomyocytes relates to upregulation of SGK-1 and suppression of autophagy. Nonetheless, it is noteworthy that, aside from cell/tissue type and depending on the type and/or severity of stress, autophagy can induce cell death or promote cell survival. For example, while mild autophagy can recycle damaged cellular components and exert protection under mild/moderate hypoxia, severe and prolonged hypoxia-induced excessive autophagy can cause cell death (Chen et al., 2013). Therefore, the differing observations likely result from the complex role of autophagy in the regulation of cell fate.

SGK-1 and Sex-Related Differential in Renal IRI (Table 2). Other studies have examined sexual dimorphism in SGK-1 expression in renal IRI (Rusai et al., 2011). Initial in vitro studies, using HEK-293 cells, showed that 17-beta estradiol treatment exerted no effect; however, testosterone treatment resulted in a concentration-dependent increase in SGK-1 expression. In addition, utilizing the rat model of unilateral renal IRI, SGK-1 expression and its phosphorylation level (time-dependently) increased more in male, compared with female, rats; castration decreased SGK-1 protein and phosphorylation levels in male kidneys subjected to IRI. It was concluded that testosterone-induced upregulation of SGK-1 contributes to sex-related differences in renal cell signaling pathways. In this context, it is noteworthy that renal IRI is a common complication in various conditions (such as abdominal surgery, renal graft), and female subjects are likely to be less susceptible to renal IRI or delayed graft function, effects attributed to protective effects of estrogen but detrimental effects of testosterone (Hosszu et al., 2020). Thus, the role of SGK-1 in sex-related diverse outcomes in renal IRI remains unresolved.

SGK-1 and Distant Organ Injury (Table 2). Remote organ injury, including AKI, can be a complication/consequence of limb IRI that is associated with vascular surgery on extremities or thromboembolic events. This has led to investigation of the potential role of SGK-1 in AKI that accompanies tourniquet-induced lower limb ischemia-reperfusion (TILLIR) (Packialakshmi et al., 2022). It was found that TILLIR caused significant AKI (e.g., decreased glomerular filtration rate and increased serum urea nitrogen) along with decreased renal mitochondrial content and bioenergetics without mitophagy or generation of mitochondrial ROS. These effects were associated with increased serum corticosterone. Interestingly, as opposed to reports of activation of autophagy following direct renal IRI, TILLIR decreased autophagy (represented by increased p62 protein abundance and prevention of conversion of LC3-I to LC3-II), which was associated with activation of mitochondrial SGK-1. Thus, TILLIR-induced AKI is linked to inhibition of autophagy likely due to activation of mitochondrial SGK-1.

In summary, similar to studies reported for the heart, the majority of information, relying on diverse experimental conditions and protocols, seemingly suggests that SGK-1 upregulation in conditions associated with renal oxidative stress can exert beneficial effects (Table 2). Renal IRI is associated with marked disturbances of renal structure as well as glomerular and tubular functions but the impact of SGK-1 activation on these aspects remain largely unresolved. Importantly, depending on severity/duration of renal IRI, the kidney may/can reconstitute structure and function but remains at risk for chronic injury/failure and associated sequels (Akalay and Hosgood 2023). Thus, while immediate/short-term SGK-1 activation may exert beneficial effects in AKI, following IRI, long-term outcomes remain to be established. Importantly, increased salt and fluid retention is a potential outcome of chronic SGK-1 activation, which can increase the risk of blood pressure elevation and associated consequences. Interestingly, transgenic mice with global increase in SGK-1 activity (without protein overexpression), in whom hypertension was induced by combination of uninephrectomy, deoxycorticosterone acetate, and high NaCl treatment, displayed augmented glomerular hypertrophy and fibrosis without exacerbation of hypertension (Sierra-Ramos et al., 2021). Thus, while the pro-survival outcome of SGK-1 activation in renal IRI may/can be beneficial, adverse outcomes of long-term SGK-1 activation must be seriously considered.

SGK-1 and Other Organs

Brain (Table 3). An earlier study reported significant increase in *SGK-1* expression in pyramidal cells (of CA2 and CA3 regions) of the hippocampus in rats subjected to transient global cerebral ischemia (10 minutes) followed by reperfusion (2 hours) (Nishida et al., 2004). A subsequent study explored the functional contribution of SGK-1 in hippocampus in response to IRI (Zhang et al., 2014). These studies used isolated rat hippocampal neurons subjected to oxygen-glucose deprivation/normoxia and the rat model of middle cerebral artery occlusion (ischemia: 2 hours; reperfusion: up to 24 hours). Both protocols caused time-dependent increase in apoptosis in association with time-dependent decreased SGK-1 protein level (i.e., 24 hours after reperfusion); SGK-1 overexpression reduced apoptosis. Further, using LY294002, authors demonstrated that the cytoprotective effect of SGK-1 is mediated by the PI3K signaling pathway.

On the other hand, others have reported beneficial impact of SGK-1 inhibition in stroke models. For example, administration of SGK-1 inhibitors (GSK650394 or EMD638683) 30 minutes before middle cerebral artery occlusion (1 hour in healthy and 45 minutes in alloxan-induced diabetic animals), followed by 24 hours of reperfusion, reduced infarct volume in healthy and diabetic mice (Inoue et al., 2016). SGK-1 inhibitors also reduced N-methyl-D-aspartate receptor-mediated neurotoxicity, a major mechanism of cell death in stroke. A more recent study addressed whether SGK-1 is involved in disruption of the blood brain barrier (BBB) that accompanies cerebral IRI (Chi et al., 2021). Accordingly, following transient middle cerebral artery occlusion (1 hour), the SGK1 inhibitor GSK650394 or vehicle was administered into the lateral brain ventricle of rats; this was followed by 2 hours of reperfusion. SGK-1 inhibition significantly reduced cortical infarct accompanied by reduced phosphorylation of N-myc downstream regulated 1 and matrix metalloproteinase 2 (MMP2) protein level in the ischemic-reperfused cortex, thereby suggesting that reduced MMP2 level contributes to reduced BBB disruption (explored using ^{14}C-α-aminoisobutyric acid coupled with use of tracer- ^{3}H-dextran). The authors concluded that SGK-1 inhibition exerts neuroprotection and reduces BBB disruption. Thus, SGK-1 inhibition, within the therapeutic window of thrombolysis, may reduce cerebral IRI.

The role of SGK-1 in brain sequel of cardiac pathology has been the focus of a study by Meissner et al. (2015). In this context, the group's earlier observations indicated a tumor necrosis factor-α (TNF-α)-dependent augmentation of posterior cerebral

TABLE 3
SGK-1 in conditions associated with injury to several organs

	Model/Condition	Findings/Conclusions	Citation
Brain	Wistar rat and transient global brain IRI	• Increased SGK-1 mRNA expression in hippocampus	Nishida et al., 2004
	Hippocampal neurons of neonatal Sprague-Dawley rats; oxygen-glucose deprivation/normoxia	• Apoptosis in association with decreased SGK-1 protein; SGK-1 overexpression reduced apoptosis	Zhang et al., 2014
	Middle cerebral artery occlusion of Sprague-Dawley rats	• Apoptosis in association with decreased SGK-1 protein; SGK-1 overexpression reduced apoptosis	
	Middle cerebral artery occlusion in C57BL6 mice (± alloxan-induced diabetes)	• SGK-1 inhibition reduced infarct volume and neurotoxicity	Inoue et al., 2016
	Middle cerebral artery occlusion in Fischer 344 rats	• SGK-1 inhibition conferred neuroprotection and reduced blood brain barrier disruption.	Chi et al., 2021
	Impact of MI-induced HF on the brain; C57BL/6N mice; TNF-α knockout mice	• Increased brain level of SGK-1 mRNA that was not reversed by etanercept (TNF-α scavenger) • Increased SGK-1 and phosphoSGK-1 in brain lysates in association with decreased dendritic spin density • TNF-α knockout mice did not manifest changes in brain SGK-1 following MI-induced HF	Meissner et al., 2015
Liver	Liver-specific SGK-1 knockout mice and IRI	• Exacerbated hepatocyte autophagy, MPTP pore opening, inflammation, and cell death	Zhou et al., 2019
	Liver-specific total SGK knockout mice and IRI	• Changes similar to those observed for SGK-1 knockdown, following liver IRI, that were inhibited by cyclosporine A	
	Liver IRI in the context of CRLM; C57/BL6 mice	• Hepatic SGK-1 activation accompanies liver IRI and may contribute to CRLM recurrence	Li et al., 2023
Lung	Murine model of acute lung injury; C57BL/6J mice	• Rosiglitazone promoted alveolar fluid clearance in association with increased expressions of SGK-1 and ENaC	He et al., 2019
	Lung epithelial cell line and rosiglitazone treatment	• Increased mRNA expressions for SGK-1 and αENaC as well as their protein levels and phosphoSGK-1	
	Murine model of acute lung injury; BALB/c mice	• Pulmonary edema in association with reduction of aldosterone synthesis encoding gene and αENaC expressions • Aldosterone-induced relief of pulmonary edema and upregulation of αENaC likely mediated via PI3K/Akt/SGK-1 signaling	Fei et al., 2021

artery tone with accompanying reduced cerebral blood flow in a mouse model of early HF that minimally affects blood pressure. HF is often associated with cognitive impairments (e.g., memory deficits), although pathogenic mechanisms remain elusive. Accordingly, using the MI-induced model of HF, authors reported increased brain expression of TNF-α, neuroinflammation, and decreased cortical dendritic spines density. Genetic deletion of TNF-α or treatment with etanercept (a soluble TNFα receptor which scavenges TNF-α) partially reversed or ameliorated, respectively, the impact of HF on density of cortical dendritic spines. Interestingly, HF mice displayed increased mRNA, protein, and activation for SGK-1. However, etanercept treatment reversed phosphoSGK-1 level without affecting SGK-1 mRNA or protein levels. In addition, HF had no impact on SGK-1 mRNA, protein expression or its phosphorylation in TNF-α knockout mice. Based on their collective observations, the authors asserted that TNF-α is a pivotal player in HF-mediated neuroinflammation and associated alterations of cortical dendritic spine density. It was suggested that modulation of SGK-1 and/or TNF-α could serve as therapeutic target(s) for memory deficits associated with HF.

Liver (Table 3). Hepatic IRI can cause serious impairment of liver function, even irreversible injury, and adversely impact multiple organs and tissues; it accompanies liver transplantation and surgical modalities for intrahepatic lesions (Cannistrà et al., 2016). Utilizing a liver-specific SGK-1 knockdown mouse model, Zhou et al. (2019) reported exacerbated hepatocyte autophagy (e.g., increased LC3A/B II), increased mRNA expressions for IL-6 and IL-1β, cell injury, and death [e.g., increased serum alanine transaminase and aspartate transaminase, cleaved caspase 3] in response to ischemia (45 minutes)-reperfusion (6 hours) injury. Further, mice with hepatic knockdown of the three SGK paralogs, showed generally similar but exacerbated outcomes compared with liver-specific SGK-1 knockout mice in response to hepatic IRI, effects which were abrogated by pre-treatment with cyclosporine A, which binds to cyclophilin D (CypD) and inhibits MPTP. Collectively, these observations may suggest functional redundancy in SGK paralogs and that induction of MPTP contributes importantly to cell death under these conditions. A more recent study explored SGK-1 status in the murine model of liver IRI in relation to colorectal liver metastasis (CRLM) recurrence; IRI is an unavoidable outcome of liver surgery for resection of liver metastasis in colorectal cancer, a procedure that increases long-term survival of patients with CRLM (Li et al., 2023). The authors reported that hepatic warm ischemia (90 minutes)-reperfusion (3 to 48 hours) resulted in increased SGK-1 mRNA and protein expressions which were mainly confined to hepatocytes. SGK-1 deficiency ameliorated liver IRI (e.g., reduced hepatocyte edema, sinusoidal congestion, and cell death, among other effects). Further, using a murine model of liver metastasis

coupled with hepatic IRI, the authors reported that inhibition of SGK-1 (siRNA targeting hepatocytes) reduced the progression of liver metastatic nodules in association with increased survival. The authors proposed that hepatic SGK-1 activation that accompanies IRI to this organ conveys molecular signals contributing to CRLM recurrence. Systemic administration of the SGK-1 inhibitor GSK-650394 revealed reduction in extracellular signal-regulated kinase-related neutrophil extracellular traps formation and polymorphonuclear myeloid-derived suppressor cells infiltration in association with reduction of CRLM burden and improved survival in the context of hepatic IRI. These effects were more pronounced when compared with hepatocyte SGK-1 knockdown. Based on their collective observation, the authors concluded that hepatocyte and immune cell SGK-1 synergistically promote postoperative CRLM recurrence following hepatic IRI, thereby serving as a translational target that may improve postoperative CRLM.

Lung (Table 3). Pulmonary edema, also associated with lung IRI, is a characteristic feature of acute respiratory distress syndrome. The epithelial sodium channel (ENaC), which is regulated by SGK-1, is the rate-limiting step for alveolar fluid clearance during pulmonary edema. Thus, the mechanism of rosiglitazone-induced clearance of alveolar fluid has been explored in the context of assessment of SGK-1 status (He et al., 2019); rosiglitazone is a selective agonist of peroxisome proliferator activated receptors, which is also expressed in the lung. Accordingly, using the murine model of lipopolysaccharide-induced acute lung injury (ALI), the authors reported that rosiglitazone promoted alveolar fluid clearance and ameliorated ALI (e.g., via reducing inflammatory mediators- TNF-α and IL-1β) in association with increased mRNA and protein expressions of SGK-1 and ENaC as well as phosphoSGK-1, effects which were abrogated by the peroxisome proliferator activated receptors-γ antagonist- GW9662. Additional in vitro studies using AT II cells (a lung epithelial cell line) also showed rosiglitazone-induced upregulation of mRNA expressions of SGK-1 and αENaC as well as expressions of SGK-1, phosphoSGK-1 and membrane αENaC, effects which were also blocked by GW9662. Thus, upregulation of SGK-1 exerts beneficial effects in ALI. Another study explored the role of ENaC, in the context of SGK-1, in aldosterone-mediated amelioration of lipopolysaccharide -induced ALI in mice (Fei et al., 2021). While aldosterone synthesis encoding gene (*CYP11B2*) and ENaC expressions were reduced in lipopolysaccharide -induced ALI, aldosterone ameliorated ALI by increasing the expression of αENaC in association with relief of pulmonary edema; αENaC upregulation was mediated via PI3K/Akt/SGK-1 pathway (albeit Western blotting did not include semi-quantitative analyses) leading the authors to suggest that aldosterone might be a promising adjuvant drug for ALI treatment.

In summary, compared with the heart and the kidney, relatively fewer studies have examined the role of SGK-1 in relation to IRI in other major organs (Table 3). Nonetheless, the few studies focused on the brain do not support a clear role for SGK-1 activation in limiting tissue injury due to oxidative stress. However, SGK-1 upregulation appears beneficial with respect to liver and lung injuries, but its activation during hepatic surgery, and associated IRI, may contribute to recurrent CRLM. Given such varied observations, it is difficult at this time to appreciate a clear role for SGK-1 as a protective kinase in conditions associated with oxidative stress to brain, lung, and liver.

The Role of SGK-1 in the Regulation of MPTP

The focus of this review on the status and role of SGK-1 in IRI makes it inevitable to address the contribution of mitochondria to the ultimate outcome of IRI- cell death. Since its initial description by Haworth and Hunter (1979), the contribution of MPTP to the mitochondrial death pathway has received considerable attention. The MPTP is a non-selective pore, presumably within the inner mitochondrial membrane, that is permeable to water and solutes of <1.5 kDa. While low pH (e.g., prevailing during ischemia) inhibits MPTP induction, reperfusion and associated events (i.e., increased cellular pH, marked intracellular calcium (Ca^{++}) overload and ROS generation) cause severe/permanent opening of the MPTP. Cell death via necrosis is a primary event during IRI to an organ/tissue. However, MPTP induction, depending on its severity and duration, can also cause other forms of cell death, including apoptosis, parthanatos, pyroptosis, and autophagy (Robichaux et al., 2023) (Fig. 1). Nonetheless, it is important to also note that transient MPTP opening plays physiologic roles, such as cardiomyocyte development, calcium efflux, ROS signaling, and energy metabolism (Kwong and Molkentin 2015; Pérez and Quintanilla 2017).

Given the critical physiologic and pathologic roles of MPTP, numerous studies have explored its molecular composition and proposed several models (Kwong and Molkentin 2015; Bauer and Murphy 2020; Robichaux et al., 2023). The initial model of MPTP proposed that its principal constituents are the voltage-dependent anion carrier (VDAC), adenine nucleotide transporter (ANT), and cyclophilin D, while recruitment of other proteins (e.g., Bax) modulates its activation. However, subsequent experimental evidence has questioned the original model due to the demonstration that cyclosporine A-sensitive mitochondrial swelling persisted despite genetic deletion of ANT or VDAC. Thus, despite extensive research providing additional paradigms, the exact molecular composition of the MPTP (i.e., pore formers versus regulators) remains elusive. Nonetheless, the ever-evolving model proposes that putative pore-forming inner mitochondrial membrane components include the ANT and the F_1F_0-ATP synthase, while the outer mitochondrial membrane incorporates regulators of the MPTP, including members of the Bcl-2 family (Kwong and Molkentin 2015; Bauer and Murphy 2020; Robichaux et al., 2023) (Fig. 1).

Very few studies have addressed the role of SGK-1 in relation to MPTP. As described earlier, pharmacological inhibition or genetic ablation of SGK-1 exacerbates HR and/or IRI suggestive of greater MPTP induction. Importantly, a recent report focused on potential regulation of MPTP by SGK-1 in the context of assessment of autophagy and longevity; these studies primarily relied on the use of *Caenorhabditis elegans* (Zhou et al., 2019). Despite their expectation, authors observed that elevated autophagy shortens the lifespan of *C. elegans* devoid of SGK-1 in association with increased MPTP induction; reduction of autophagy or inhibition of MPTP opening restored normal lifespan to *SGK-1* mutants. In search of the mechanism by which SGK-1 impacts MPTP, authors reported interaction of SGK-1 with nearly the entire complement of putative MPTP proteins (e.g., VDAC1, ANT, F_1F_0-ATP synthase, etc.). Further, the relevance of interaction of mammalian SGK-1 with VDAC1 was shown by co-immunoprecipitation studies using 293T cells (derived from renal epithelial cells of a patient). Based on functional assays, it was suggested that SGK-1 maintains mitochondrial

hemostasis by promoting MPTP closure. According to the proposed model, phosphoSGK-1 impact on and/or interaction with VDAC1 ultimately causes low MPTP induction in association with normal autophagy and normal lifespan in *C. elegans*, while in SGK-1 mutants, high MPTP induction and autophagy reduce the lifespan. Moreover, using the murine model of hepatic IRI, the authors provided evidence for the collective effects of three SGK paralogs to regulate MPTP and cell death but the contribution of SGK-1 to MPTP function, per se, in this condition was not determined (Zhou et al., 2019).

The aforementioned study which highlights the role of SGK-1 in the regulation of MPTP, via a VDAC-dependent mechanism, is seemingly at odds with the evolving paradigm indicating that VDAC is dispensable with respect to MPTP function. VDAC is localized to the outer mitochondrial membrane, while putative pore-forming proteins are proposed to be within the inner mitochondrial membrane (Kwong and Molkentin 2015; Bauer and Murphy 2020; Robichaux et al., 2023) (Fig. 1). However, as indicated earlier, much of what has been reported regarding SGK-1 regulation of MPTP has emanated from studies using *C. elegans*. To the knowledge of this author, the role of SGK-1 in regulation of MPTP, and relation to putative pore forming proteins and regulators, has not been investigated in animal models of IRI involving various organs. Importantly, emerging information also indicates that mitochondrial Ca^{++} entry occurs via VDAC and the mitochondrial calcium uniporter in the outer and inner mitochondrial membranes, respectively (Sander et al., 2021; Robichaux, et al., 2023) (Fig. 1). If indeed SGK-1 functions to curtail MPTP induction, such as inhibiting mitochondrial Ca^{++} uptake (e.g., via VDAC/mitochondrial calcium uniporter), then it follows that overexpression of SGK-1 and/or its pharmacological activation should exert beneficial impact against organ injury in conditions associated with IRI. This is an important consideration since, despite optimism that cyclosporine A would evolve into a clinically-useful agent limiting MPTP induction and cell death following IRI, clinical trials have not been conclusive (Piot et al., 2008; Cung et al., 2015), thereby necessitating further research to identify novel targets to beneficially impact MPTP. While a number of SGK-1 inhibitors are available for application in the field of cancer (Sang et al., 2021; Cicenas et al., 2022), to the author's knowledge, small-molecule SGK-1 activators are not yet available. In this context, it is important to note that SGK-1 activation, while presumably beneficial with respect to in vitro IRI (e.g., cardiac or renal), its systemic administration, in animal or clinical studies, would be expected to exert "off target" effects, including renal sodium and fluid retention and risk of blood pressure elevation. Although development of SGK-1 activator(s) should facilitate investigation of their efficacy in limiting MPTP induction, thereby reducing/abrogating IRI to a given organ, consideration for systemic administration must be in the context of establishing the "therapeutic window" and incorporating strategies for more "targeted delivery", among other aspects, to reduce untoward effects.

Conclusion

The preponderance of information regarding the status and role of SGK-1 in IRI suggests that its endogenous upregulation likely serves as a compensatory mechanism to curtail tissue injury, aspects which are better established for the heart and the kidney. These observations raise the possibility that treatment with an activator of SGK-1 could accentuate its pro-survival impact, thereby conferring protection against early reperfusion-induced injury, likely reducing/preventing long-term sequels, such as heart failure or chronic renal failure. However, an impediment to such investigations is lack of availability of selective SGK-1 activator(s). Thus, introduction of small molecule activator(s) of the SGK-1 should help narrow gaps in our knowledge of highly relevant aspects, such as its role in coronary microcirculation, MPTP function and cell death, as well as whether SGK-1 activation exerts pre- and/or post-conditioning effects, among other aspects. Nonetheless, given diverse effects of SGK-1 upregulation, spatiotemporal outcomes of SGK-1 activation require careful scrutiny.

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This article contains no datasets generated or analyzed during the current study.

Authorship Contributions

Performed data analysis: Mozaffari.
Wrote or contributed to the writing of the manuscript: Mozaffari.

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Address correspondence to: Dr. Mahmood S. Mozaffari, Department of Oral Biology and Diagnostic Sciences; CL-2134, The Dental College of Georgia, Augusta University, Augusta, Georgia 30912-1128. E-mail: mmozaffa@augusta.edu