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SAD-A and AMPK kinases

The "yin and yang" regulators of mTORC1 signaling in pancreatic β cells

Jia Nie[1], Xiao Han[2], and Yuguang Shi[1,*]

[1]Department of Cellular and Molecular Physiology; Pennsylvania State University; College of Medicine; Hershey, PA USA;

[2]Key Laboratory of Human Functional Genomics of Jiangsu Province; Nanjing Medical University; Nanjing, China

SAD-A kinase is a member of the AMPK-related family of kinases, which are under the control of LKB1 kinase. In the human kinome, SAD-A is most closely related to AMPK, a key energy sensor and master regulator of metabolism. In contrast to AMPK, little is known about the physiological function of the SAD-A kinase in metabolism. Recent studies using knockout mice have revealed a striking role of the SAD-A kinase in regulating dynamic functions of islet β cells, from glucose-stimulated insulin secretion (GSIS), islet β-cell size and mass, to GLP-1 response as the first tissue-specific effector of mTORC1 signaling. These studies suggest that SAD-A and AMPK kinase may function as the positive and negative regulators of mTORC1 signaling in islet β cells. Importantly, these findings have implicated SAD-A kinase as a novel drug target for the treatment of type 2 diabetes.

Keywords: insulin secretion, LKB1, AMPK-related kinase, GLP-1, incretin, type 2 diabetes

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*Correspondence to: Yuguang Shi; Email: yus11@psu.edu

Introduction

The AMPK-related family of kinases, which consists of 13 members, plays an important role in regulating glucose and energy homeostasis.[1-8] AMPK is a key regulator of energy homeostasis, being activated in response to an increase in AMP/ATP ratio under low nutrient conditions.[1] These functions are partly mediated by its regulatory role in nutrient sensing in hypothalamic neurons.[9] AMPK is also required for GSIS and other pancreatic β-cell functions, as suggested by the phenotype of mice with targeted deletion of α1 and α2 subuits of the kinase.[10,11] Surprisingly, this phenotype directly contradicts with that of the mice with targeted deletion of LKB1 which activates AMPK and 12 other members in this family.[12,13] Accordingly, LKB1 deficiency in adult islet β cells leads to increased pancreatic β-cell mass and insulin secretion,[14-16] raising a key question of whether other members in the AMPK-related family of kinases may also regulate islet function. Furthermore, AMPK is a potent inhibitor of the mammalian target of rapamycin (mTOR) signaling, which coordinates nutritional status with protein synthesis in pancreatic β cells.[1,17] mTOR is an evolutionarily conserved serine/threonine kinase that functions in 2 complexes: mTORC1 and mTORC2. The mTORC1 complex functions as a sensor of nutritional status and responds by altering metabolic processes, whereas mTORC2 complex is involved in the regulation of cytoskeletal organization.[1,32] Thus, targeted deletion of LKB1 in mice also leads to mTORC1 activation.[14,16] Recent studies using knockout mice has revealed a surprising role of SAD-A in regulating islet β-cell functions as the first tissue-specific effector kinase of mTORC1 signaling in islet β cells.

SAD-A and Insulin Secretion

SAD-A, also referred to as BRSK2, is a member AMPK-related family of kinases that is most closely related AMPK[12] in the human kinome. In contrast to other members of this family, we have recently shown that SAD-A is exclusively expressed in the pancreas and brain,[18] implicating a role of the kinase in energy metabolism. Major

progress has been made in recent years in elucidating the function of SAD-A kinases in the brain, including neuronal polarity and axon specification.[19-21] By contrast, little is known about the physiological function of SAD-A in pancreas, although SAD kinases are activated by stimuli that evoke GSIS, including activation by PKA- and CamKK1-mediated signaling pathways.[22,23] Using adenoviral overexpression, our recent studies provide the first evidence for the SAD-A kinase as a key regulator of GSIS.[24] We show that SAD-A promotes GSIS in part by activating the p21-activated kinase-1 (PAK1) through phosphorylation of PAK1 at Thr423. PAK1 is an effector of Rho GTPases, and is activated in response to the onset of GSIS through phosphorylation at Thr423. Additionally, SAD-A stimulates cytoskeletal remodeling of F-actin, which is required for the trafficking and fusion of insulin secretory granules to the plasma membrane.

SAD-A Controls GLP-1 Response in Islet β Cells

GLP-1 is an incretin hormone that improves glucose responsiveness or sensing of islet β cells. GLP-1 is secreted in response to oral ingestion of nutrients and strongly enhances GSIS through activation of the adenylate cyclase coupled with incretin receptors, leading to increased production of cAMP.[25,26] The increase in $[cAMP]_i$ exerts its powerful potentiating effect on GSIS through both PKA-independent and PKA-dependent mechanisms, the former involving activation of Epac2 (cAMP-GEFII) pathways.[27,28] Long-acting GLP-1 analogs, such as Byetta and Liraglutide, are used in the clinic worldwide for the treatment of type 2 diabetes by improving multiple β-cell functions.[25] Increased GLP-1 action is also attributed to the complete remission of type 2 diabetes in obese patients who undergo a gastric bypass surgery.[29-31] However, the distal signaling pathways that mediate GLP-1 effects in islet β cells remain poorly defined. We have recently identified SAD-A as a pancreas-specific regulator of GLP-1 effect in islet β cells.[18] We show that SAD-A is activated in islet β cells in response to treatment with GLP-1 and forskolin, and that overexpression of SAD-A greatly enhances GLP-1 effect on GSIS from isolated mouse islets. Consequently, targeted deletion of SAD-A from the pancreas causes glucose intolerance from impaired incretin response in SAD-A knockout mice.[18] Furthermore, we identified Thr443 of SAD-A as a novel auto-inhibitory phosphorylation site, which negatively regulates GLP-1 effect. Thus, ablation of Thr443 significantly enhances SAD-A activity and incretin effect on GSIS .

SAD-A as a Tissue-Specific Mediator of mTORC1 Signaling

Cumulative evidence suggests a critical role of mTORC1 in regulating pancreatic β cells' mass and function, which is highlighted by the phenotypes of multiple mouse models of constitutive activation or inhibition of mTORC1 signaling. Accordingly, targeted deletion of TSC1 and TSC2, repressors of mTORC1, leads to increased islet β-cell mass and enhanced GSIS.[33-35] Conversely, targeted deletion of S6K1, an effector of mTORC1 signaling, or ablation of S6K1 phosphorylation site in ribosomal protein S6, leads to hypoinsulinemia, defective GSIS, and reduction in islet β-cell size.[36,37] Furthermore, inhibition of mTORC1 with rapamycin also causes reduction in islet mass and insulin content, leading to exacerbation of type 2 diabetes.[38,39] However, the molecular mechanisms linking mTOR effect to dynamic islet β-cell functions remains elusive.

Our most recent study identifies a key role SAD-A kinase in regulating islet β-cell function and size as the first tissue-specific mediator of mTORC1 signaling in islet β cells.[40] We demonstrate that global SAD-A deletion causes multiple defects in islet β-cell function, which are highly reminiscent of defects observed in mice with global deletion of S6K1, including growth retardation, hypoinsulinemia, insulin deficiency, petite islets, and diminished β-cell mass.[36] These findings are further supported by the phenotype of mice with selective deletion of SAD-A in pancreas.[40] These mice exhibit significantly decreased islet β-cell size, islet mass, and a defective incretin response, leading to glucose intolerance. Conversely, SAD-A overexpression significantly increases the size of MIN6 β cells. In direct support of SAD-A as a novel mediator of mTORC1 signaling in islet β cells, glucose dramatically stimulates SAD-A protein translation in isolated mouse islets, which are potently inhibited by rapamycin. The results suggest that mTORC1 regulates SAD-A protein expression primarily at translational level. Indeed, we further demonstrate that the 5′-untranslated region (5′-UTR) of SAD-A mRNA is highly structured and requires mTORC1 signaling for its translation initiation. Accordingly, we show that the onset of GSIS greatly stimulates the SAD-A 5′-UTR luciferase reporter activity in pancreatic β cells, which is also inhibited by rapamycin. Likewise, activation of mTORC1 through overexpression of constitutively active Rheb leads to a great enhancement in the SAD-A 5′-UTR luciferase reporter activity, which is again abolished by rapamycin treatment. Our findings are consistent with previous reports that mTORC1 complex plays an important role in regulating the translation of mRNAs with highly structured 5′-UTR, including genes encoding MYC, HIF1, ODC1, cyclin D1, and VEGF.[41] mTORC1 does so through S6K1-mediated activation of eIF4A helicase activity, which is essential in unwinding a structured 5′-UTR for initiation of translation.[41]

Concluding Remarks

Both SAD-A and AMPK are under the control of LKB1 kinase, yet it is not clear how the LKB1 kinase balances its action on these 2 kinases in islet β cells. In contrast to SAD-A, which mediates mTORC1 effect, AMPK is an inhibitor of mTORC1 signaling. Consistent of LKB1 as an activator of AMPK, LKB1 deletion leads to activation of mTORC1 signaling in islet β cells.[14-16] Although other members of AMPK-related kinases may play a role in the process, it can be envisaged that AMPK and SAD-A function as the "yin and yang" of mTORC1 signaling in islet β cells (**Fig. 1**). However, conflicting results have been reported on the role of AMPK in regulating GSIS and islet function.[10,11,15-17,42,43] Key questions remain as to why targeted deletion of AMPK

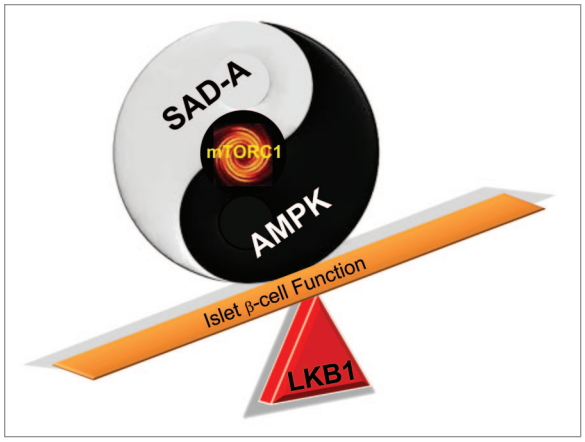

Figure 1. A hypothetic model depicting how LKB1 may balance its act on SAD-A and AMPK to regulate mTORC1 signaling and β-cell functions. Accordingly, AMPK and SAD-A function as the "yin and yang" regulators of mTORC1 activity in islet β cells, which is further fine-tuned by LKB1 kinase, a bona fide activator of both kinases.

inhibits GSIS from islet β cells in the knockout mice. Additionally, a short isoform of SAD-B kinase was recently shown to localize to centrosomes, where it controls centrosome duplication, suggesting a potential role of SAD-A in regulating cell cycle of islet β cells.[44] Therefore, future studies will reveal whether the SAD-A kinase also plays a role in regulating β-cell proliferation and survival, since GLP-1 stimulates islet β-cell regeneration in rodents and humans.[25,45] In support of this speculation, our recent studies show that SAD-A depletion causes β-cell deficiency in global SAD-A KO mice.[45] In addition to pancreas, SAD-A also expressed in brain, where it controls neuronal polarity and axon specification. It can be speculated that SAD-A may also play a role in controlling satiety, since SAD-A is exclusively expressed in the primary targeting tissue of GLP-1, which causes weight loss in part by suppressing appetite.[25,26,45-48]

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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