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Reserach Article

Phosphatase and Tensin Homologue (PTEN)-Induced Putative Kinase 1 Promotes Pancreatic B-Cells Proliferation in Glucotoxicity Through Activation of Akt/Mtor/Hif-1α Pathway

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Abstract

Sustained high glucose is harmful to pancreatic β-cells, resulting in impaired pancreatic β-cells proliferation. Understanding the molecular mechanisms related to β-cells proliferation is pivotal for the prevention of β-cells injury caused by glucotoxicity. The role of Phosphatase and tensin homologue (PTEN)-induced putative kinase 1 (PINK1) in the proliferation of pancreatic β-cells constantly exposed to high glucose was studied. Sustained high glucose decreased Akt/mTOR/HIF-1α proteins expression in INS-1 β-cells, and that this reduction can be further prompted by PINK1 silencing and conversely enhanced by PINK1 over-expression. PINK1 deficiency aggravated glucotoxicity-induced pancreatic β-cells proliferation and inhibition of Akt/mTOR/HIF-1α pathway whereas PINK1 over-expression could reverse these adverse effects. This study provides fundamental data supporting the potential protective role of PINK1 as a new therapeutic target necessary to preserve β-cells proliferation under non-physiological hyperglycemia conditions.

Keywords: Phosphatase and tensin homologue (PTEN); Induced putative kinase 1, β-cells proliferation; High glucose; Akt/mTOR/HIF-1α

Introduction

Type 2 diabetes mellitus (T2DM) is the common metabolic disorder that affects more than 2.56 million adults worldwide focusing on the relative shortage of insulin secretion in liver, muscle and adipose tissue of peripheral metabolities [1]. Under normal circumstances, pancreatic α and β-cells monitor blood glucose level, and when blood glucose rises, these cells absorb glucose through glucose transporter (GLUT) 2, which promotes glucose metabolism, followed by increased mitochondrial substrates and electron transport chain drive with increasing intracellular adenosine triphosphate (ATP) levels and closing membrane-related ATP-sensitive potassium channels (K +-ATP) accompanied by voltage-dependent calcium channel opening and calcium influx. Intracellular calcium ([Ca2+]) concentration immediately increases stimulation of insulin secretion and activation of insulin-sensitive cells glucose transporter, allowing cells and tissues to absorb glucose in the body as energy source [2-4]. However, high glucose can directly damage pancreatic β-cells by increasing insulin resistance in vivo and prompting the body to raise blood glucose level with the formation of the vicious cycle known as "glucotoxicity" which leads to mitochondrial damage of pancreatic β-cells, and ultimately decreases the number of pancreatic β-cells proliferation and promotes the occurrence and development of diabetes [4]. Pathophysiological changes in pancreatic β-cells during glucotoxicity were not fully elucidated. Recent studies have shown that protein kinase B (Akt) related pathway is critical to the maintenance of pancreatic β-cells numbers, structures and functions [5,6].

The most well known function of Akt is its key role in glucose metabolism. Akt-deficient mice are characterized by impaired glucose uptake and inhibition of glucose output in muscle and adipose tissue, ultimately leading to glucose intolerance, insulin resistance, and development of severe diabetes associated with β-cells failure [7]. In the population of patients with severe hyperinsulinemia and family history of diabetes, the Akt gene mutation has been identified [8,9]. It is well known that activated Akt phosphorylates broadly distributed substrates[10-13]. For example, Akt phosphorylates glycogen synthase kinase-3β (GSK-3β) and inhibits its activity, thereby promoting glucose metabolism and regulating cell cycle [14]. Activation of Akt phosphorylates mammalian target of rapamycin (mTOR) complex [12]. Studies have shown that Akt/mTOR plays an important role in the regulation of β-cells functional activity [11]. Glucose tolerance is impaired in Rictor/mTORC2 deficient β-cells, while insulin content in pancreas is reduced and glucose secretion by glucose stimulation is impaired [13]. Studies have also shown that mTORC1 can positively regulate the expression of hypoxia inducible factor-1α (HIF-1α) and further promote cell growth and ribosomal protein biosynthesis [15].

Our previous study showed that PINK1 can protect pancreatic β-cells from glucotoxicity and reduce β-cells apoptosis by enhancement of PINK1 expression [16]. It has reported that PINK1 can

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phosphorylate parkin and regulate its translocation to mitochondria and maintain parkin's ligase activity by identifying ubiquitination of mitochondrial outer membrane proteins and next cause impaired mitochondria to be degraded and cleared in healthy mitochondrial pools by mitonchondrial-dependent autophagy mechanisms [17]. It has also reported that PINK1 can mediate selective mitochondrial autophagy by interacting with the Beclin1 gene to maintain an effective mitochondrial dynamic balance [18]. It has reported that PINK1 can also directly activate mitochondrial autophagy by using the highly selective autophagic receptors such as Optineurin and nuclear dot protein 52-kDa (NDP52) through non-parkin-dependent pathways [19]. In addition, studies have found that PINK1 protects SH-SY5Y neuroblastoma cells from a variety of cytotoxic agents including oxidative stress damage by the mechanism of PINK1/Aktser473/mTORC2 to play a protective role on cells. Studies have also found that under hypoxic conditions, PINK1 knockout can reduce HIF-1α induction and transcriptional activity suggesting that PINK1/HIF-1α pathway may also play a protective role in cell metabolism [20]. So far, the accurate effect of PINK1 on pancreatic β-cells proliferation under non-physiological glucotoxic conditions has never been reported and relevant aspects need further investigation. In this study, we clarified the roles of PINK1 on pancreatic β-cells proliferation under continuous high glucose and explored whether PINK1 regulates Akt/mTOR/HIF-1α activity in pancreatic β-cells.

Materials and Methods

Plasmids, reagents, and cells preparation

The small interfering RNA (siRNA) reagents targeting rat PINK1 and Scrambled siRNA were purchased from GenePharma Co., Ltd. (China, Shanghai). The construct pcDNA3.1 plasmids expressing PINK1 and Scramble were purchased from ShengGong Co., Ltd. (China, Shanghai). Rat insulinoma INS-1 cells were purchased from Biotech Co., Ltd.(Shanghai, China). INS-1 cells were maintained in RPMI 1640 medium with 11.1mM glucose supplemented with 10% fetal bovine serum, 10mM HEPES, 2mM L-glutamine, 1mM sodium pyruvate, 50μM β-mercaptoethanol, 100U/ml penicillin and 100mg/ml streptomycin as described previously. Cell culture reagents were all purchased from Invitrogen.

DNA transfection

Cells were transfected with or without indicated siRNA, plasmid DNA constructs using lipofectamine 3000 following the manufacturer's instructions.

Western blotting

Total proteins were extracted from the INS-1 cells using protein extraction kits (KeyGEN BioTECH, China) following the manufacturer's instructions. For total protein extraction, every 10uL 100mM PMSF was added to each 1mL of cold RIPA lysates buffer (strong) and mixed and kept on ice for several minutes. After collecting adherent cultured INS-1 cells and aspirating the medium, they were washed with 1mL cold PBS twice and shaken several times to remove the culture medium. After adding 120uL above prepared RIPA lysis (strong) to sufficiently lysate, the homogenate was transferred to pre-chilled centrifuge tube to be centrifuged at 4˚C for 5min at 10, 000 r/min, then the supernatant was transferred to a new pre-chilled centrifuge tube to accept protein quantitation (BCA method) and then aliquots were stored at -70˚C to avoid repeated freezing and thawing. Proteins (50μg) were separated in 6-12% crite-rion precast gels and 5% polyacrylamide gels and transferred onto polyvinylidene fluoride membranes. The membranes were incubated with primary anti-PINK1 antibodies (1:200, Santa Cruz), anti-Akt (1:800, Proteintech), anti-p-Akt(ser473) (1:1000, Cell signaling), anti-GSK-3β (1:800, Proteintech), anti-mTOR (1:800, Proteintech), anti- p-mTOR(ser2448) (1:1000, Cell signaling), anti-HIF-1α (1:800, Proteintech), or anti-GAPDH (1:1000, Proteintech) and visualized with horseradish peroxidase-conjugated secondary antibodies (1:4000, Proteintech) using chemiluminescence detection reagent (advansta, USA). The membranes were scanned and analyzed using Scion Image software (Scion Corp., Frederick, MD, USA).

Cell proliferation assay

Cell proliferation was observed by MTT proliferation detection kit following the manufacturer's instructions. All kits were obtained from Beyotime Institute of Biotechnology (Haimen, China).

Statistical analysis

Comparisons were made using the unpaired Student's t-test. Values represent the mean ± standard error of the mean (SEM). Statistical significance is as indicated.

Results

Surplus high glucose inhibits Akt/mTOR/HIF-1α pathway

To examine Akt/mTOR/HIF-1α pathway responsiveness to surplus high glucose in pancreatic β-cells, we monitored the relative enrichment of p-Akt/Akt in total proteins of INS-1 cells exposed to surplus high glucose. When INS-1 cells were treated with 33.3mM glucose, we got remarkable decreases in the ratio of p-Akt to Akt at 72h compared with control cells treated with 11.1mM glucose and cells treated with 11.1mM glucose plus 22.2mM mannitol, demonstrating that p-Akt/Akt is suppressed by surplus high glucose (Figure 1). Further, the relative enrichment of p-mTOR/mTOR, showed as its p-mTOR/mTOR ratio, was remarkably reduced after exposure of surplus high glucose (Figure 1). Besides, there were remarkable increments of GSK-3β (Figure 1), with concomitant reductions of HIF-1α (Figure 1). Overall, these results demonstrated that Akt/mTOR/HIF-1α pathway is inhibited in pancreatic β-cells under surplus high glucose conditions.

Activation of PINK1 promotes β-cells proliferation

To investigate the effect of PINK1 on INS-1 cells proliferation quantified by Optical Density (OD) values under the condition of 11.1mM or 33.3mM glucose for 72h, the cell proliferation was measured by MTT assay. The results showed that the cell proliferation of PINK1siRNA group was lower than that of untransfected group and negative control group (P<0.01) under 11.1mM glucose for 72h (Ta-

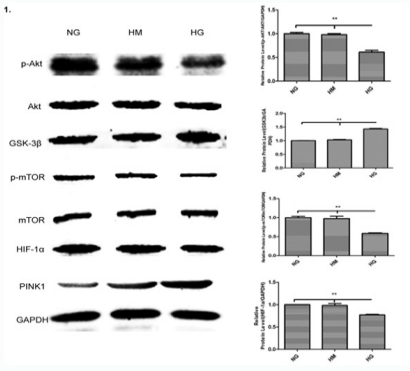

Figure 1: Detection of Akt/mTOR/HIF-1α pathway in pancreatic β-cells. (A) Detection of p-Akt/Akt, p-mTOR/mTOR , GSK-3β, HIF-1α in INS-1 cells. INS-1 cells cultured with 11.1mM glucose alone (NG) or 33.3mM glucose alone (HG) or 11.1mM glucose plus 22.2mM mannitol (HM) for 72h (n = 3; **P < 0.01). Mean ± SEM.

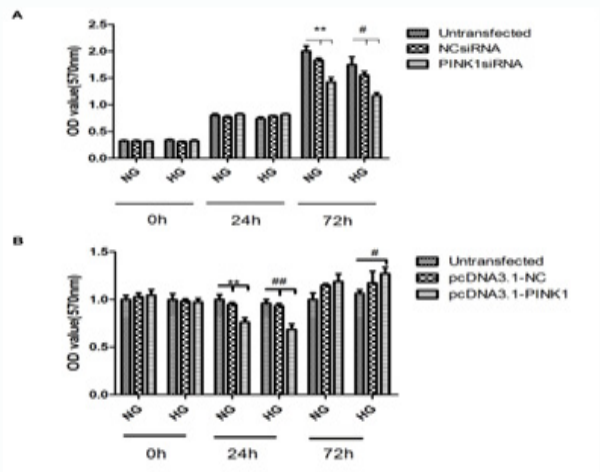

Figure 2: PINK1 and cell proliferation in INS-1 cells. (A) and (B) Cell proliferation in INS-1 cells was detected using the MTT staining assay (n = 5; *P<0.05; **P<0.01; #P<0.05; ##P<0.01). Mean ± SEM.

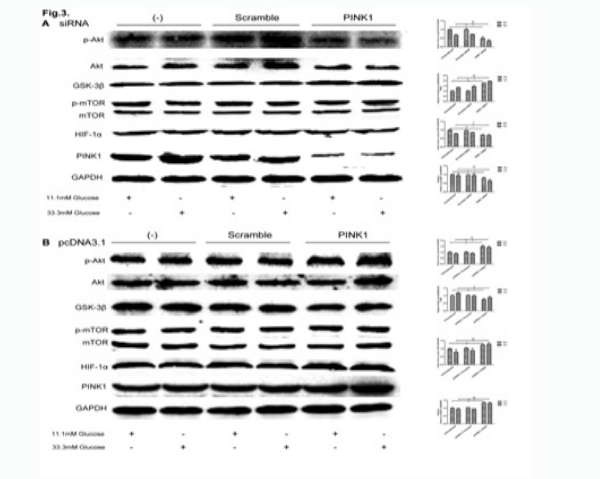

Figure 3: PINK1 and Akt/mTOR/HIF-1α pathway in INS-1 cells. (A) and (B) Western blot detection of p-Akt/Akt, p-mTOR/mTOR, HIF-1α and GSK-3β in INS-1 cells (n = 3; *P<0.05; **P<0.01; #P<0.05; ##P<0.01).

ble 1 and Figure 2A). Compared to untransfected group and negative control group, no significant changes were observed in pcDNA3.1-PINK1 group with regard to cell proliferation (P>0.05) (Table 2 and Figure 2B). The cell proliferation of PINK1siRNA group was lower than that of untransfected group and negative control group (P<0.05) under 33.3mM glucose for 72h (Table 1 and Figure 2A). However, compared to untransfected group and negative control group, the cell proliferation was enhanced in pcDNA3.1-PINK1 group (P<0.05) (Table 2 and Figure 2B). Overall, these results showed that silencing of PINK1 could significantly inhibit the proliferation of INS-1 cells (normal glucose: P<0.01, high glucose: P<0.05) after 72h of normal glucose and high glucose incubation (Table 1 and Figure 2A). Overexpression of PINK1 could significantly improve INS-1 cells proliferation after 72h of high glucose incubation (P<0.05), but had no significant effect on the proliferation of INS-1 cells after 72h of normal glucose incubation (P>0.05) (Table 2 and Figure 2B).

PINK1 evokes Akt/mTOR/HIF-1α pathway in INS-1 cells under surplus high glucose conditions.

Emerging evidence implicates PINK1-mediated Akt/mTOR/HIF-1α pathway can participate in various cell functions including growth, proliferation, migration and survival [13,20]. Akt/mTOR pathway acts as a binding site for intracellular and extracellular environments and regulates a range of cellular functions: phosphorylation inactivation of GSK-3β can promote cell proliferation after activation of Akt [14]; mTOR can phosphorylate Akt serine 473 site to activate Akt; mTOR can positively regulate HIF-1α expression and positive regulation of HIF-1α target gene can promote cell growth and ribosomal protein biosynthesis. In view of this, we investigated the proliferation mechanisms of PINK1 in INS-1 cells by measuring above-mentioned proliferation-related proteins utilizing the Western blot assays under surplus high glucose conditions. The results showed down regulated p-Akt/Akt, p-mTOR/mTOR, HIF-1α proteins in PINK1 siRNAs transfected INS-1 cells compared with cells untransfected or transfected with Scramble siRNAs under 33.3mM glucose conditions for 72h (P<0.05) accompanied by upregulated GSK-3β (P<0.01) (Figure 3A). Conversely, we observed upregulated p-Akt/Akt, p-mTOR/mTOR, HIF-1α proteins in pcDNA3.1-PINK1 transfected INS-1 cells compared with cells untransfected or transfected with pcDNA3.1-Scramble under 33.3mM glucose conditions for 72h (P<0.05) accompanied by downregulated GSK-3β (P<0.05) (Figure 3B). Combined with this proliferation role of PINK1, these results indicated that PINK1 most likely evokes Akt/mTOR/HIF-1α pathway to promote INS-1 cells proliferation.

Discussion

PINK1 has received striking attention as a potential mechanism of cell survival. It has reported that PINK1 can protect SH-SY5Y neuroblastoma cells from various cytotoxic agents, including oxidative stress damage through Aktser473/mTORC2 mechanism. It has also reported that PINK1 knockout can reduce the induction and transcriptional activity of HIF-1α under hypoxic condition suggesting PINK1/HIF-1α pathway may play a protective role in cell metabolism. Of note, our previous study showed that PINK1 reduces pancreatic β-cells apoptosis in glucotoxicity [16]. However, little is known about the high-glucose-induced PINK1 function on pancreatic β-cells proliferation. By genetical modulation of PINK1, we demonstrated that PINK1 inhibition negatively modulates and jeopardizes INS-1 β-cells proliferation with exposure from high glucose surplus whereas PINK1 activation reverses the genetical effects. These findings coincide with the well-known PINK1-modulated cell survival.

To date, feasible strategy by which PINK1 regulates β-cells proliferation remains poorly elucidated. Of note, our findings specify that the expression of Akt, phosphorylated Aktser473, mTOR and phosphorylated mTOR proteins in INS-1 cells were all decreased and the expression of GSK-3β protein was increased in high glucose state. PINK1 silencing could further inhibit the expression of Akt, phosphorylated Aktser473, mTOR, phosphorylated mTORser2448 proteins accompanied by further increased GSK-3β protein expression whereas PINK1 over-expression could reverse the genetical effects. It has reported that PINK1 can activate mTORC2 to protect SH-SY5Y neurons from dopaminergic neurotoxins and other cytotoxic agents by phosphorylation of Akt. In view of this, we considered whether PINK1 could also protect INS-1 cells from carbohydrate damage by Akt/mTOR pathway. Activated Akt phosphorylates a wide range of substrates to participate in related physiological activities and plays an important role in regulating cell growth, insulin signaling, and glucose metabolism. Murine β-cells Rictor/mTORC2 deficiency is expressed as impaired glucose tolerance while insulin secretion in the pancreas is reduced and insulin secretion by glucose stimulation is impaired. Consistently, our results uphold the hypothesis that sustained high glucose can induce PINK1 to promote pancreatic β-cells proliferation against surplus high glucose via Akt/mTOR signaling.

Table1 1:PINK1 and cell proliferation in INS-1 cells. Cell proliferation in INS-1 cells was detected using the MTT staining assay (n = 5; *P<0.05; **P<0.01; #P<0.05; ##P<0.01). Mean ± SEM.

Group	0h		24h		72h	
	NG	HG	NG	HG	NG	HG
Untransfected	0.325±0.021	0.338±0.028	0.802±0.069	0.740±0.067	2.002±0.211	1.748±0.328
NCsiRNA	0.323±0.026	0.310±0.021	0.767±0.045	0.786±0.031	1.901±0.084	1.551±0.155
PINK1siRNA	0.315±0.019	0.323±0.044	0.818±0.040	0.817±0.035	1.424±0.183**	1.168±0.126#

Table1 2: PINK1 and cell proliferation in INS-1 cells. Cell proliferation in INS-1 cells was detected using the MTT staining assay (n = 5; *P<0.05; **P<0.01; #P<0.05; ##P<0.01). Mean ± SEM.

Group	0h		24h		72h	
	NG	HG	NG	HG	NG	HG
Untransfected	1.000±0.098	0.997±0.441	1.000±0.109	0.959±0.094	1.000±0.150	1.063±0.081
pcDNA3.1-NC	1.028±0.087	0.982±0.051	0.948±0.043	0.932±0.060	1.148±0.040	1.174±0.273
pcDNA3.1-PINK1	1.046±0.127	0.973±0.081	0.762±0.098**	0.686±0.126##	1.189±0.176	1.270±0.152#

Our findings specify that the expression of HIF-1α protein in INS-1 cells was decreased and PINK1 silencing could further inhibit the expression of HIF-1α protein expression whereas PINK1 over-expression could reverse the genetical effects. Studies have reported that HIF-1α expression in PINK1 +/+ cells is significantly higher than that in PINK1 -/-; silencing of PINK1 can reduce the induction and transcription of HIF-1α; HIF-1α related pathway can be positively regulated by PINK1 to protect primary cortical neurons or mouse embryonic fibroblasts and other cells from hypoxia to survive, suggesting that PINK1/ HIF-1α may play a protective role under cell metabolism stress. In view of this, we hypothesized whether PINK1 could promote INS-1 cells proliferation under high glucose by targeting HIF-1α. Consistently, our results uphold the hypothesis that sustained high glucose can induce PINK1 to promote pancreatic β-cells proliferation against surplus high glucose via HIF-1α.

In this study, we clarified that pcDNA3.1-mediated activation of PINK1 accelerated and advanced INS-1 cells proliferation suggesting that notable sufficiency or positive intervention of PINK1 encourages cells proliferation. We also showed that positive PINK1-mediated Akt/mTOR/HIF-1α under high glucose over-flow conditions. Future studies should address the particularly subtle interplay among PINK1 and potential Akt/mTOR/HIF-1α components implicated in pancreatic β-cells fate suffering from unfavorable high glucose. It would also be valuable to explore further in diabetic animal models and then in humans. These will provide the foundation for systematic and comprehensive analysis of mechanisms adjusting pancreatic β-cells proliferation.

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