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Glucose enhances collectrin protein expression in insulin-producing MIN6 β cells

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ABSTRACT

Collectrin is a novel target gene of hepatocyte nuclear factor-1α in pancreatic β-cells and controls insulin exocytosis. Although glucose is known to stimulate the expression of genes of the insulin secretory pathway, there is no information on how glucose regulates collectrin expression. We investigated the effects of glucose on the expression of collectrin in MIN6 β-cell line. Glucose, in a dose-dependent manner, increased collectrin protein levels without changing collectrin mRNA levels and protein stability, indicating that glucose stimulation of collectrin protein expression is primarily mediated at a translational level. Although mannose and pyruvate also increased collectrin protein expression level, neither 2-deoxyglucose, mitochondrial fuels leucine and glutamate, sulphonylurea nor Ca^{2+} channel blockers, mimicked the effects of glucose. These data indicate the involvement of mitochondrial TCA cycle intermediates, distal to pyruvate, in the regulation of collectrin protein expression in β-cells.

Introduction

Hepatocyte nuclear factor (HNF)-1α is a homeodomain-containing transcription factor expressed in the liver, kidney, intestine, and pancreas [1]. Heterozygous mutations in the HNF-1α gene cause a monogenic form of diabetes (maturity-onset diabetes of the young: MODY3) characterized by impaired insulin secretion by pancreatic β-cells [2]. Recently, we reported that HNF-1α controls the transcription of collectrin/TMEM27 in pancreatic β-cells [3,4]. Collectrin was originally identified as a kidney-specific type I membrane protein sharing significant homology with the C-terminal domain of angiotensin-converting enzyme-2 (ACE2) [5], but it is also highly expressed in pancreatic β-cells [3,4]. We and others have reported that collectrin plays important roles in insulin secretion [3,6], pancreatic β-cell proliferation [4], and insulin sensitivity [7] for glucose metabolism.

Glucose is known to stimulate insulin biosynthesis [8], and several genes of the insulin secretory pathway including prohormone convertase 3 (PC3) [9], chromogranin A [10], glucose transporter 2 (GLUT2) [11], and insulin receptor substrate 2 (IRS-2) [12]. Since collectrin controls insulin secretion from pancreatic β-cells, we hypothesized that its expression is also regulated by glucose. To test this hypothesis, we investigated in the present study the expression of collectrin in a mouse β-cell line (MIN6) and mouse pancreatic islets. The results showed that collectrin protein expression is regulated by glucose at translational level.

Methods

Reagents. D-Glucose, D-mannitol, mannose, pyruvate, and L-leucine were obtained from Sigma (St. Louis, MO). Insulin, L-glutamine, and tolbutamide were from Wako Pure Chemical (Osaka, Japan). Cycloheximide and verapamil were from Calbiochem (San Diego, CA). Cell culture medium was from Sigma.

Cell culture. The pancreatic β-cell line MIN6 [13] was maintained in Dulbecco's modified Eagles' medium (DMEM) (25 mM glucose) containing 10% (v/v) fetal bovine serum, 1% (v/v) penicillin/streptomycin, and 100 μM β-mercaptoethanol and incubated at 37 °C in 5% CO_2. Upon reaching 80% density, MIN6 cells were detached and plated onto 6-well plates at a density of 2.5×10^5 cells per well and incubated 48 h. Prior to the glucose regulation experiments, MIN6 cells were incubated in DMEM medium containing 5.5 mM glucose for 16 h.

Isolation of pancreatic islets. Pancreatic islets were isolated from C57BL/6 mice by the collagenase digestion method [14]. Before experiments, islet cells were incubated in RPMI 1640 medium containing 11 mM glucose for 16 h, then cultured in the presence of 3 mM or 20 mM glucose for 24 h.

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Western blotting. MIN6 cells and pancreatic islet cells were lysed in extraction buffer [50 mM Tris–HCl, 20 mM ethylenediaminetetraacetic acid (EDTA), 1% sodium dodecyl sulfate, and 100 mM NaCl], and Western blotting was performed as described [15]. Briefly, 10 μg of proteins were subjected to 10% SDS–PAGE and transferred by electroblotting to an Immobilon-P Transfer Membrane (Millipore, Bedford, MA). The membranes were incubated overnight at 4 °C with either rabbit anti-collectrin antibody [3], mouse anti-GAPDH antibody (Promega, Madison, WI), mouse anti-β-actin monoclonal antibody (Sigma), or mouse anti-HNF-1α monoclonal antibody (BD Biosciences, Palo Alto, CA). After incubation with horseradish peroxidase-conjugated second antibodies, the proteins were visualized using ECL enhanced chemiluminescence detection system (Amersham Biosciences, Piscataway, NJ).

Real-time RT-PCR. Real-time quantitative RT-PCR was performed as described previously [3,16]. Briefly, RNA was isolated from MIN6 cells using Trizol according to the instructions supplied by the manufacturer. First-strand cDNA synthesis was performed using High capacity cDNA archive kit (Applied Biosystems, Foster City, CA) and real-time PCRs were performed on an ABI PRISM 7900 (Applied Biosystems). The primers and the probes for collectrin and TATA binding protein (TBP) were purchased from ABI.

Measurement of intracellular ATP levels. Intracellular ATP levels were measured using an ATP bioluminescence assay kit (Roche Applied Science, Indianapolis, IN) according to the protocol provided by the manufacturer [16].

Statistical analysis. Values were expressed as mean ± SD. Differences between groups were examined for statistical significance using the unpaired Student's *t*-test. A *p* value less than 0.05 was considered significant.

Results

Glucose increases collectrin protein levels in β-cells

MIN6 β-cell line is considered a suitable model for pancreatic β-cells in terms of glucose-regulated insulin biosynthesis [17,18]. MIN6 cells were incubated for 24 h under different glucose concentrations (2.8–25 mM), and then examined for collectrin protein expression levels. Glucose significantly increased collectrin protein levels in a dose-dependent manner (Fig. 1A); with strong expression of collectrin protein in the presence of 25 mM glucose (9.6-fold) compared with that under basal 2.8 mM glucose concentration. The expression of collectrin tended to be up-regulated at 6 h (Fig. 1B), but a significant glucose-induced increase in collectrin expression was noted at 12 h, which persisted at least for 24 h (Fig. 1B). On the other hand, glucose had no effect on control GAPDH (Fig. 1A–E) or β-actin (Fig. 1F), indicating the selective effect of glucose on collectrin expression.

To examine the effect of glucose on the expression of collectrin in normal β-cells, mouse pancreatic islets were isolated and incubated in the presence of 3 or 20 mM glucose. Similar to MIN6 β-cell line, glucose increased collectrin protein levels in pancreatic islets (Fig. 1C), suggesting that glucose regulates the protein in normal β cells as well as MIN6 cells.

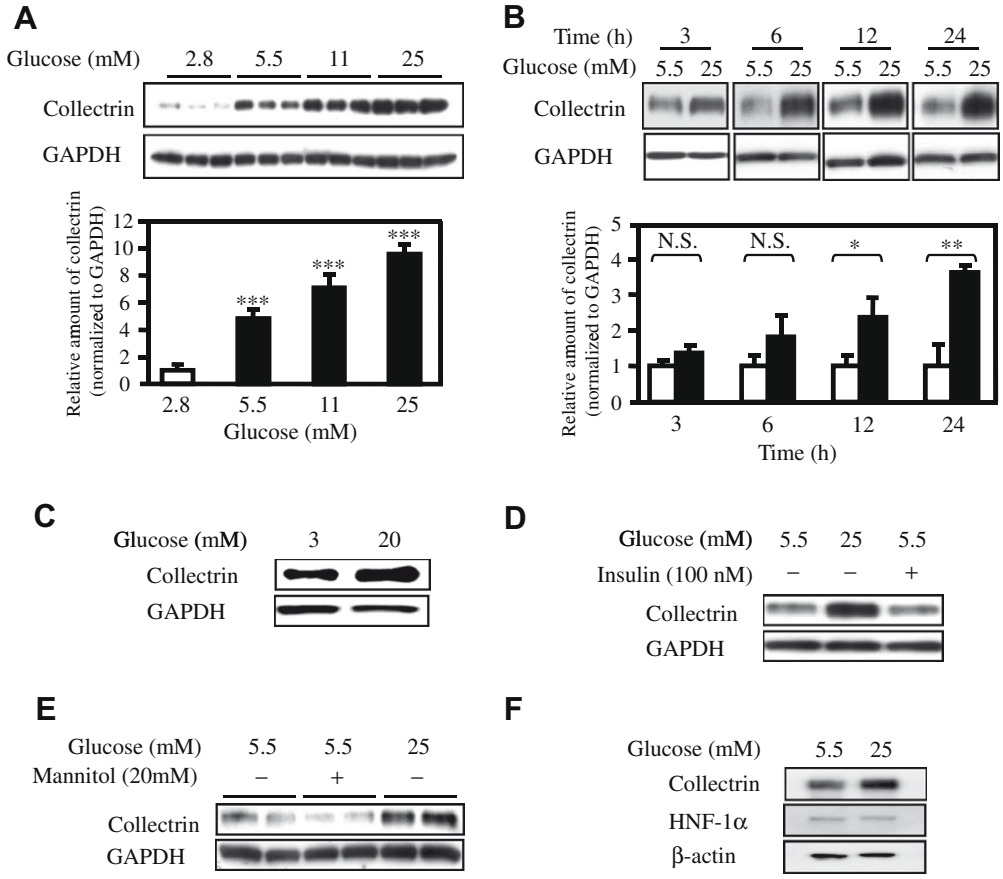

Fig. 1. Effects of glucose on collectrin protein expression. (A) MIN6 cells were cultured in the presence of 2.8, 5.5, 11, or 25 mM glucose for 24 h. Collectrin protein levels were normalized to GAPDH levels. The results are from three independent samples. Data are mean ± SD. $^{***}p < 0.005$. (B) MIN6 cells were cultured in the presence of 2.8 or 25 mM glucose for 3, 6, 12, or 24 h. The results are from three independent samples. Data are mean ± SD. $^{*}p < 0.05$, $^{**}p < 0.01$. (C) Western blot analysis of collectrin and GAPDH protein levels in mouse pancreatic islets. (D and E) MIN6 cells were cultured under 5.5 or 25 mM glucose concentration for 24 h in the presence or absence of 100 nM insulin (D) or 20 mM mannitol (E). (F) Western blot analysis of HNF-1α protein level in MIN6 cells at 5.5 or 25 mM glucose concentrations.

MIN6 cells secrete insulin in response to high glucose [13] and insulin has been reported to induce potent stimulation of insulin gene transcription [19]. Then, we examined the effect of insulin on collectrin expression. However, incubation of MIN6 cells with 100 nM insulin in the presence of 5.5 mM glucose did not affect collectrin expression level (Fig. 1D). Equimolar mannitol, used as an osmotic control for high glucose, also did not affect collectrin expression (Fig. 1E). These results indicate that secreted insulin and osmotic pressure are not involved in collectrin expression. HNF-1α regulates the transcriptional level of collectrin [3,4]. Expression of HNF-1α, however, was similar when the cells were incubated under low and high glucose conditions (Fig. 1F).

Glucose regulates collectrin expression at translational level in MIN6 cells

Glucose enhances transcription and translation of the insulin gene [20]. We examined whether the induction of collectrin protein is regulated at mRNA level. Real-time RT-PCR indicated that collectrin mRNA expression level in MIN6 cells was unaffected by 6–24 h incubation with 5.5 or 25 mM glucose (Fig. 2A). Next, we cloned a 2-kb collectrin promoter region upstream of the luciferase reporter gene. When MIN6 cells were transfected with the reporter gene and incubated with glucose at various concentrations for 24 h, glucose did not affect luciferase activity (data not shown). Thus, stimulation of collectrin gene transcription is unlikely to account for the glucose-induced increase in collectrin protein expression.

It has been reported that glucose regulates the protein stability of insulin and MafA transcription factor in β cells [8,21]. We evaluated whether collectrin protein turnover is influenced by glucose level. MIN6 cells were incubated in the presence of cycloheximide, a translational inhibitor, in the presence of 25 mM glucose. During the incubation, the expression level of collectrin protein decayed rapidly compared with that of GAPDH (Fig. 2B), indicating the relative instability of collectrin protein. MIN6 cells were also cultured with cycloheximide under 5.5 or 25 mM glucose. A similar rapid decrease in collectrin protein was found under both concentrations (Fig. 2C), indicating that augmented collectrin protein expression by high glucose is not due to increased collectrin protein stability. Collectively, these results suggest that glucose stimulation of collectrin protein expression is predominantly mediated at a translational level.

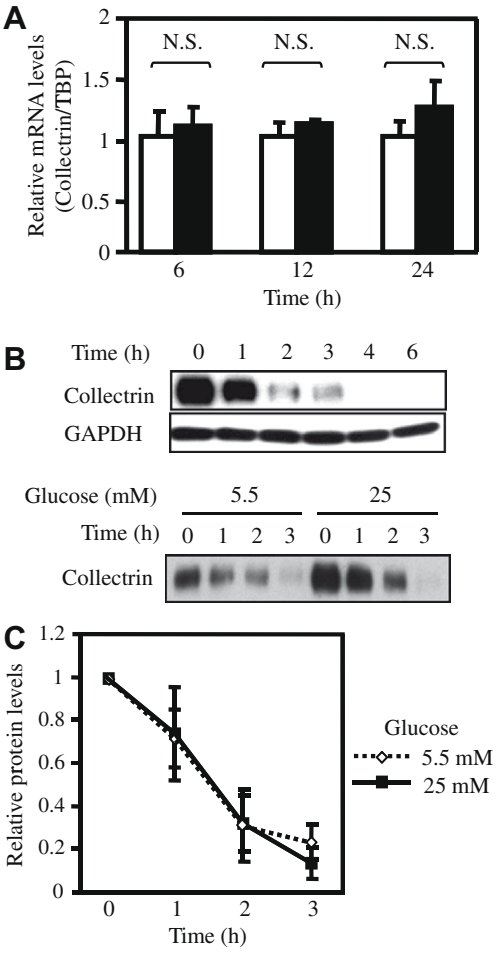

Fig. 2. Effects of glucose on collectrin mRNA levels and collectrin protein degradation. (A) MIN6 cells were cultured under 5.5 or 25 mM glucose for 6–24 h and then collectrin and TATA binding protein (TBP) (control) mRNA levels were measured by real-time PCR. The results are from three independent samples. Data are mean ± SD. N.S.; not significant. (B) MIN6 cells were cultured in the presence of 25 mM glucose and cycloheximide (10 μg/ml) for 6 h, and collectrin levels were analyzed by western blot. (C) MIN6 cells were cultured in the presence of 5.5 or 25 mM glucose in the presence of cycloheximide for 0–3 h ($n = 3$). Data are presented as a-fold decrease of collectrin protein (mean ± SD).

Glucose-stimulated collectrin expression requires glucose metabolism in MIN6 cells

To determine whether glucose uptake and phosphorylation can generate adequate signals that induce collectrin protein expression, we treated MIN6 cells with 30 mM 2-deoxyglucose. 2-deoxyglucose is phosphorylated to form 2-deoxy-D-glucose-6-phosphate, which cannot be further metabolized *via* glycolysis [22]. Incubation of MIN6 cells with 2-deoxyglucose failed to increase collectrin expression (Fig. 3A). These results indicate that glucose metabolism is necessary for glucose-stimulated collectrin expression. Glucose is metabolized to pyruvate through glycolysis. Pyruvate enters the TCA cycle and generates ATP. In pancreatic β-cells, an increase of ATP/ADP ratio closes ATP-sensitive potassium channels, leading to membrane depolarization and calcium influx. We next tested whether substrates related to glucose metabolism regulate collectrin protein level. Mannose is metabolized to fructose 6-phosphate, which is an intermediate of glycolysis [23]. At 25 mM, mannose increased the expression of collectrin (Fig. 3B). Furthermore, incubation of MIN6 cells with 20 mM pyruvate for 24 h also increased collectrin expression (Fig. 3C). We next examined the effect of TCA cycle intermediates on collectrin expression. Leucine is about one-third as potent an insulin secretagogue as glucose [24]. Leucine allosterically activates glutamate dehydrogenase, thus enhancing conversion of glutamate to α-ketoglutarate, an intermediate of TCA cycle [24]. The combination of leucine and glutamine stimulates insulin release more strongly [25]. However, leucine alone, or the combination of leucine and glutamine failed to increase the expression of collectrin (Fig. 3D). The combination of leucine and glutamine produced as much ATP as 25 mM glucose in MIN6 cells (Fig. 3E), indicating that augmented collectrin expression is independent of ATP levels.

Treatment by sulphonylureas increases intracellular calcium levels and insulin secretion in β-cells. Tolbutamide, an ATP-sensitive potassium channel blocker, did not increase collectrin expression (Fig. 3F), suggesting that increment of calcium levels alone may not be sufficient to promote collectrin expression. Furthermore, treatment of MIN6 cells with Ca^{2+} channel blockers, nifedipine and verapamil, which inhibit any increase in intracellular Ca^{2+} level, did not result in down-regulation of the stimulated collectrin expression at high to low glucose levels (Fig. 3G). Taken together, these data indicate that glucose metabolic pathway distal to pyruvate, but proximal to α-ketoglutarate is involved in the regulation of collectrin protein expression (Fig. 4).

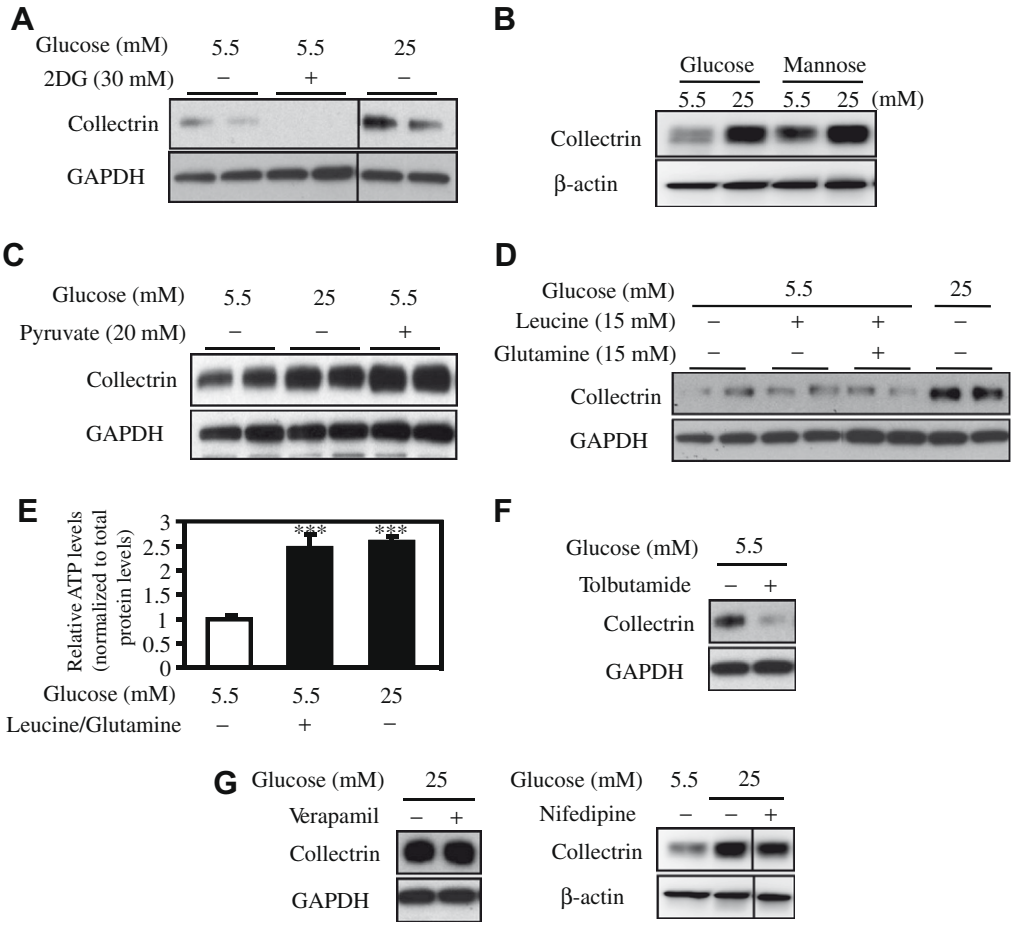

Fig. 3. Effects of insulin secretion secretagogues/inhibitors on the expression of collectrin protein. (A) MIN6 cells were cultured with 5.5 or 25 mM glucose for 24 h in the presence or absence of 30 mM 2-deoxyglucose. (B) MIN6 cells were cultured with 5.5 or 25 mM mannose for 24 h. (C–F) MIN6 cells were cultured at 5.5 or 25 mM glucose concentrations for 24 h in the presence or absence of 20 mM pyruvate (C), 15 mM leucine/glutamine (D and E), 100 μM tolbutamide (F), or 10 μM verapamil/nifedipine (G). Intracellular ATP levels were normalized to total protein levels. The results were from three independent samples. Data are mean ± SD. $^{***}p < 0.005$.

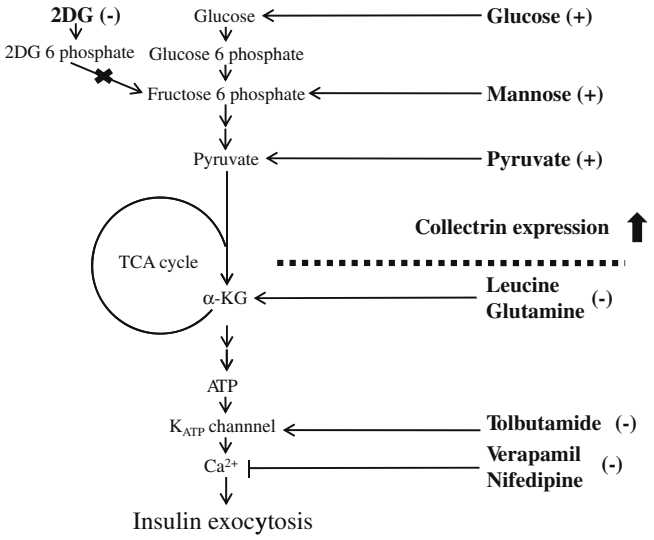

Fig. 4. Schematic representation of metabolic signaling pathways in β-cells and collectrin expression. Glucose, mannose, and pyruvate increase collectrin protein expression, whereas treatment by amino acids, tolbutamide, and Ca^{2+} channel blocker failed to mimic the effects.

Discussion

Pancreatic β cells respond to changes in blood glucose by secreting insulin and increasing the expression of many genes of the insulin secretory pathway [26]. In the present study, we found that the protein level of collectrin, a type I membrane protein involved in insulin exocytosis [3], increased in the presence of high glucose concentration in the medium. Insulin production is regulated primarily by glucose at the levels of preproinsulin mRNA translation, whereas glucose also exerts transcriptional control of the gene [26]. In contrast, the increase of collectrin expression was not mediated by changes in collectrin mRNA levels. These results indicate that glucose-stimulated collectrin expression is predominately regulated at translational levels.

The stimulatory effect of glucose was not mimicked by non-metabolizable analog of glucose, 2-deoxyglucose. Fructose is also not metabolized in pancreatic β-cells and failed to induce collectrin expression (data not shown). These findings highlight the important role of hexose sugar metabolism in collectrin protein expression. Furthermore, we showed that pyruvate, but not tolbutamide, stimulated collectrin expression. Interestingly, it has been reported that pyruvate as well as glucose stimulates proinsulin biosynthesis, but sulphonylureas have no effect on glucose-stimulated insulin expression [18,27]. In this regard, glucose regulation of collectrin and preproinsulin expression may share some mechanistic com-

monalities. Pyruvate entry into the mitochondria provides high levels of intermediates for the TCA cycle (anaplerosis). Pyruvate stimulated collectrin expression, but the combination of leucine and glutamine (increase intramitochondrial α-ketoglutarate and ATP levels) failed to mimic the effect of pyruvate, suggesting that anaplerosis by pyruvate is important for the generation of metabolic signals necessary for up-regulation of collectrin. Citrate, acetyl-CoA and/or malonyl-CoA are potential metabolic factor candidates for collectrin expression.

The results of the present study demonstrated that glucose metabolites stimulate the expression of collectrin primarily at translational level. Further studies are needed to understand the molecular mechanism(s) of glucose-stimulated collectrin expression. Since collectrin controls insulin exocytosis, a better understanding of the translational control of collectrin might be therapeutically beneficial in diabetic patients with impaired insulin secretion. Clarification of the molecular mechanism could be useful also to understand the mechanism behind proinsulin biosynthesis that has yet to be elucidated.

Acknowledgments

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