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N-glycosylation modulates the membrane sub-domain distribution and activity of glucose transporter 2 in pancreatic beta cells

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ABSTRACT

The glucose transporter isoform, GLUT2, -mediated glucose sensing is essential for maintaining normal glucose-stimulated insulin secretion in pancreatic beta cells. We previously reported that GnT-IVa glycosyltransferase is required for the production of an *N*-glycan structure that acts as a ligand for galectins to form the glycan–galectin lattice that maintains the stable cell surface expression of GLUT2, and cellular glucose transport activity, although the functional relevance of the *N*-glycosylation of GLUT2 to its membrane sub-domain distribution is not fully understood. In the present study, we demonstrated that disruption of the GLUT2 *N*-glycan–galectin lattice by the genetic inactivation of GnT-IVa, or by treatment of pancreatic beta cells with competitive glycan mimetics, induced the re-distribution of GLUT2 into the lipid-raft microdomain. This subsequently resulted in the binding of Stomatin to GLUT2 and an attenuation of cellular glucose transport activity. Moreover, disruption of the lipid-raft microdomain by treatment with methyl-β-cyclodextrin caused the GLUT2 to be released from lipid-rafts and reactivation of the cellular glucose transport activity in GnT-IVa deficient beta cells. These results indicate that the membrane sub-domain distribution of GLUT2 is associated with the glucose transport activity of beta cells, in which the GnT-IVa-dependent formation of the *N*-glycan–galectin lattice plays an important role. This provides a novel pathophysiological insight into the mechanism of beta cell failure in the pathogenesis of type 2 diabetes.

1. Introduction

In mammalian cells, glucose is a major source for energy production in the form of ATP and for the synthesis of proteins, lipids, and nucleotide-sugars through cellular metabolism and homeostasis. In mammals, blood glucose levels are maintained within a narrow range by endocrinological regulation. Cells uptake extracellular glucose from interstitial fluid by a passive and facilitative transport process along with the downward gradient concentration of glucose across the cellular plasma membrane [1]. The plasma membrane possesses a glucose transport system facilitating diffusion either into or out of the cells. This system referred to as the "glucose transporter" (GLUT). GLUT consists of 13 members, of which 11 are specific for sugar transport without any energy-requirements, such as ATP hydrolysis or a H+ gradient [2,3]. The GLUT-dependent cellular glucose uptake is a physiologically mandatory process. GLUT2 is involved in glucose sensing for insulin secretion in pancreatic beta cells, the net glucose release into the blood stream by hepatic gluconeogenesis, and transepithelial glucose transport in the kidney and intestine. GLUT4 is involved in the acute insulin-responsive glucose absorption in adipose tissue and muscle for rapid removal of blood glucose into energy stores such as glycogen and triacylglycerol. GLUT1 is ubiquitously expressed and is involved in whole-body glucose homeostasis [4]. Members of the GLUT family proteins are structurally conserved and share a structure that includes 12 membrane-spanning regions and a single *N*-glycan attached in either the first or the fifth extracellular loop domain [3,5]. Previous studies have reported that *N*-glycosylation is

Abbreviations: ATP, adenosine tri-phosphate; GLUT, glucose transporter; GnT, *N*-acetylglucosaminyltransferase; PBS, phosphate buffered saline; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; KRH, Krebs–Ringer HEPES buffer; DTSSP, 3,3'-dithiobis[sulfosuccinimidylpropionate]; DMSO, dimethyl sulfoxide; DSP, dithiobis[succinimidyl propionate]; HBSS, Hank's balanced salt solution; PKA, protein kinase A; MβCD, methyl-β-cyclodextrin; 2-NBDG, 2-[*N*-(7-nitrobenz-2-oxadiazol-4-yl)amino]-2-deoxy D-glucose.

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required for achieving stable cell surface expression and for the transporter activity of GLUT1 and GLUT2 [6–11]. Generally, newly synthesized plasmalemmal proteins and secretory proteins are transported to the Golgi apparatus, where they undergo maturation of their *N*-glycans by sequential enzymatic reactions of Golgi-residing glycosyltransferases. This process consequently produces diverse *N*-glycan structures and confers various functions on proteins. The biological significance of protein *N*-glycosylation has been recently established. *N*-acetylglucosaminyltransferase (GnT)-IV and GnT-V are essential glycosyltransferases cooperatively catalyzing the formation of multi-antennary *N*-glycans (Supplemental Fig. 1), bearing various glycan epitopes that enable the carrier proteins to interact with other molecules on the cell surface. Galectins are a family of lectins that selectively bind to the Gal-GlcNAc moieties of *N*-glycan branches with relatively weak affinities [12]. The apparent binding affinity depends on the intrinsic multivalency, and oligomeric state of the galectin, and on the multivalency of the glycan ligands. As a result, interactions among oligomers of galectins and multivalent glycans promote the formation of glycan–galectin lattice structures on the cell surface that have a great influence on the functions of membrane proteins [13]. It has recently been established that multi-antennary *N*-glycan production facilitates *N*-glycan–galectin lattice formation that restricts the diffusive mobility of the cell surface membrane proteins and is involved in their conversion into clusters, a process consequently regulates molecular and cellular functions [14,15]. Cell surface membrane proteins form homotypic and heterotypic clusters in various membrane sub-domains, are dynamically exchanged and are redistributed among them in response to signaling reflecting cellular microenvironments [16–21]. It has been established that the glucose transport activity of GLUT1 is regulated by membrane sub-domain localization [22,23], as well as an *N*-glycosylation step, which implies the presence of a functional linkage between membrane sub-domain distribution and *N*-glycosylation for controlling glucose transport activity.

The present study was undertaken to elucidate the regulation of GLUT2 activity by its membrane sub-domain localization and *N*-glycosylation using primary isolated pancreatic beta cells that must contribute to better understand the physiological regulation of the glucose sensor function of pancreatic beta cells and furthermore provide a novel molecular insight into the pathogenesis of type 2 diabetes.

2. Materials and methods

2.1. Reagents and antibodies

Collagenase type-V from clostridium histolyticum and DNase were purchased from Sigma. Complete proteinase inhibitor cocktails (EDTA+, or free) were purchased from Roche. Hank's balanced salt solution (HBSS) with 5.6 mM glucose was purchased from Invitrogen. Dispase was purchased from Calbiochem. Ficoll PM400 was purchased from GE healthcare. 3,3′-Dithiobis[sulfosuccinimidyl propionate] (DTSSP) and Dithiobis[succinimidyl propionate] (DSP, Loman's reagent) were purchased from Thermo scientific. GLUT2 antibody was purchased from Millipore, and Galectin9 and Stomatin antibodies were purchased from Santa Cruz Biotechnology.

2.2. Isolation of primary mouse islets

Primary pancreatic islet cells were prepared as previously described [10]. Briefly, 1 ml of collagenase solution (3 mg/ml collagenase type-V, 5 μg/ml DNase, 2× complete proteinase inhibitor (EDTA free) in HBSS with 5.6 mM glucose) was injected into the distally ligated pancreatic duct of a euthanized mouse, and the excised pancreas was then incubated with additional 2 ml of collagenase solution at 37 °C with shaking (200 strokes/min) until a homogenous mixture was obtained. Following centrifugation of the digestive solution at 200*g* for 5 min, the pellet was resuspended in 3 ml of 25% Ficoll PM400/HBSS solution, which was thenoverlaid with 3 ml of 23%, and 2 ml of 20% and 2 ml of 11% Ficoll PM400/HBSS solution to form discontinuous gradients. Following centrifugation at 800*g* for 15 min, islets were collected from the top two boundaries of gradients. To obtain higher purity of islets, islets were hand-picked under a stereomicroscope using a micropipette. Single cell suspension was obtained by disruption of islets by incubation with dispase solution (0.5 U/ml dispase, and 5 μg/ml DNase in HBSS with 5.6 mM glucose) at 37 °C and consecutive washing with HBSS.

2.3. Membrane fractionation

Lipid rafts and non-lipid raft (detergent-soluble) proteins were separated by sucrose-gradient centrifugation. In subsequent steps, solutions and samples were kept at 4 °C. Islet cells were washed twice with PBS and lysed in KRH (Krebs–Ringer HEPES buffer; 136 mM NaCl, 20 mM HEPES, 4.7 mM KCl, 1.25 mM $MgSO_4$, and 1.25 mM $CaCl_2$, pH 7.4) supplemented with 5 mM EDTA, 0.5% Triton X-100, and 1× complete proteinase inhibitor cocktail, by passage through a 21 gauge needle. The lysed cells were centrifuged at 800*g* for 10 min to remove unbroken cells and nuclear debris. 500 μl of the cell homogenate was mixed with an equal volume of 80% sucrose/KRH containing 5 mM EDTA and place on the bottom of an ultra-clear centrifuge tube (Beckman, 344057). On the resulting 40% sucrose homogenate solution, 2 ml each of 35% and 5% sucrose/KRH containing 5 mM EDTA was overlaid. The gradient was then centrifuged at 200,000*g* (42,000 rpm, in a Beckman SW55Ti rotor) for 18 h and 10 fractions (500 μl each) were collected from the gradient. 1 ml of ice-cold ethanol was added to each of the samples, and the mixtures were then centrifuged at 13,000*g* for 30 min. The resultant protein precipitates were dried and dissolved in 50 μl of 1× SDS–PAGE sample buffer. Non-solubilized membrane proteins, including lipid rafts, float toward the lighter surface fractions, and are thus separated from the soluble proteins remaining in the bottom-loading zone.

2.4. Glucose uptake assay

Cellular glucose transport activity was measured as previously described [10,24]. Briefly, islet cells were pre-incubated in KRH for 20 min at 37 °C and then incubated with 200 μM of 2-NBDG in KRH containing 10 mM glucose at 37 °C for 5 min. Glucose transport was terminated by addition of 2 mM cytochalasin B in KRH then cells were washed with KRH twice. Cellular uptaken 2-NBDG was measured by cell fluorescence using fluorescent plate microplate reader (MTP-650FA, Corona electric).

2.5. Cell surface protein cross-link, and immunoprecipitation

Islet cell surface proteins were cross-linked by DTSSP as previously described [10] and intracellular proteins were cross-linked by DSP. To analyze the glycan-mediated membrane sub-domain distribution of GLUT2 and galectin binding, islet cells were washed twice with HBSS and then incubated with glycans in RPMI 1640 medium for 2 h at 4 °C. The cells were washed twice with ice-cold PBS, and then incubated with 2 mM DTSSP in PBS for 2 h on ice. Crosslinking was terminated by the addition of 1 M Tris–HCl (pH 7.5) to a final concentration of 10 mM. To evaluate the interaction between GLUT2 and Stomatin, DSP was used instead of DTSSP. Briefly, DSP was first dissolved in DMSO at 20 mM and then mixed

with cell suspension in PBS at 2 mM. The cells were then lysed in lysis buffer (20 mM Tris–HCl (pH 7.5), 150 mM NaCl, 1% Triton X-100, 1× Complete proteinase inhibitor cocktail), and GLUT2 was precipitated using specific antibody. Co-immunoprecipitation of Galectin9 and Stomatin were detected by immunoblotting using specific antibodies.

3. Results

3.1. Dysglycosylation of GLUT2 is associated with its re-distribution to lipid-raft microdomain in pancreatic beta cells

As pancreatic beta cell function is regulated by various well-organized plasmalemmal glycoproteins, assembling functional domains for appropriate cellular responses among cells in islet tissue, we isolated intact pancreatic islet cells from mice and analyzed membrane sub-domain localization and re-distribution of GLUT2 to elucidate the glucose sensor function of pancreatic beta cells. Fractionation of detergent lysates of primary islet cells by density gradient centrifugation revealed that GLUT2 almost exclusively resides in non-lipid raft microdomains in beta cell membranes (Fig. 1A). We previously reported that GnT-IVa deficiency abolished multiantennary *N*-glycan formation that induces the rapid internalization of the dysglycosylated GLUT2 in pancreatic beta cells [10,11]. This suggests that the dysglycosylated GLUT2 might be redistributed among membrane sub-domains in the process of its internalization. To elucidate the biological relevance of the protein *N*-glycosylation to membrane sub-domain distribution, we analyzed the membrane sub-domain distribution of GLUT2 in GnT-IVa deficient mouse islet cells. We could detect a substantial proportion of GLUT2 was shifted to lipid-raft microdomains in GnT-IVa deficient beta cells (Fig. 1B). To confirm that GLUT2 in GnT-IVa deficient pancreatic beta cells was localized in lipid raft-microdomains, we treated islet cells with methyl-β-cyclodextrin (MβCD) to deplete cholesterol for disrupting lipid raft-microdomain, and analyzed the membrane sub-domain distribution of GLUT2 in the cells. The GLUT2 protein enriched in lipid-raft microdomains was disappeared by MβCD treatment in GnT-IVa deficient islet cells, and the pattern of GLUT2 distribution was altered, eventually resembling that of wild type (Fig. 1C and D). These results indicate that the dysglycosylation of GLUT2 resulted in its redistribution to the lipid raft-microdomain in beta cells.

3.2. Inhibition of the GLUT2 N-glycan–galectin lattice formation induces the redistribution of GLUT2 to lipid raft-microdomain

Since GnT-IVa produces multi-antennary *N*-glycan structures consisting of LacNAc moiety (Galβ1-4GlcNAc), the binding epitope for galectins [10], we hypothesized that GLUT2 *N*-glycan–galectin lattice formation restricts the movement of GLUT2 among membrane sub-domains and prevents the trafficking of GLUT2 to lipid raft-microdomains on beta cell surface. To confirm this, we challenged wild type islet cells with lactose (Galβ1-4Glc), mimicking a LacNAc structure, to competitively inhibit the binding between the GLUT2 *N*-glycan and Galectin9, and then analyzed membrane sub-domain distribution of GLUT2. The lactose treatment significantly reduced the binding between GLUT2 and Galectin9 (Fig. 2A) that was coincident with enrichment of a substantial proportion of GLUT2 in the lipid raft-microdomain (Fig. 2B and C). These results indicate that the binding of the GLUT2 *N*-glycan and Galectin9 anchors GLUT2 to non-lipid raft-microdomains and the disruption of the binding induces the trafficking of GLUT2 to the lipid raft-microdomain (Supplemental Fig. 2).

3.3. N-glycosylation mediated GLUT2 membrane trafficking is associated with the glucose transport activity of pancreatic beta cells

It has been well established that the re-distribution of GLUT1 among membrane sub-domains is associated with cellular glucose transport activity [22], since GLUT1 is associated with Stomatin in lipid-raft, which is an integral membrane protein residing in lipid-rafts and controls the function of ion channels and transporters [25,26]. GLUT1 and GLUT2 exhibit a high degree of sequence similarity, and their hydropathy plots are virtually superimposable, suggesting that these proteins are likely to adopt similar global structures within the membrane [4]. These findings imply that the glucose transport activity of GLUT2 is also regulated in the same

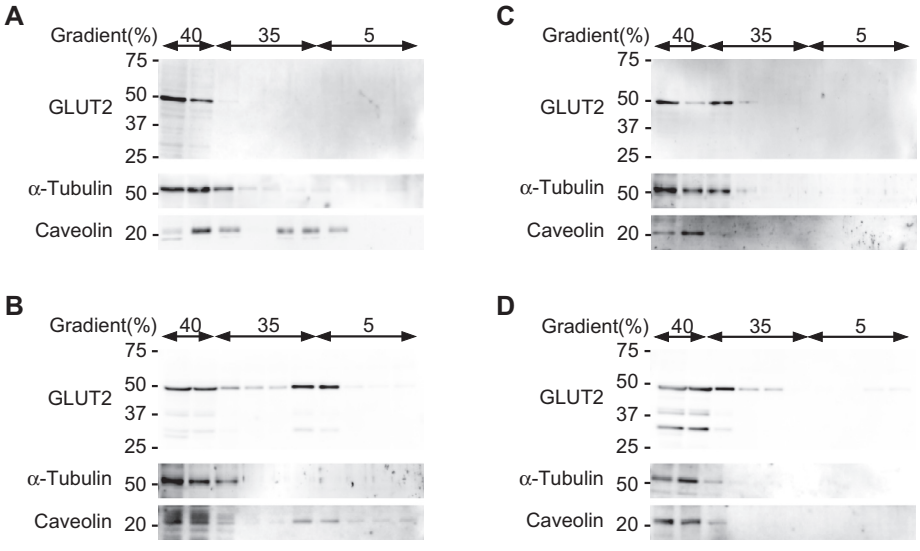

Fig. 1. Dysglycosylation of GLUT2 induces membrane re-distribution of GLUT2 into lipid-raft microdomain Immunoblots of GLUT2, α-Tubulin, and Caveolin proteins from aliquots taken from the 5–40% discontinuous sucrose gradient separation of lysates of primary isolated pancreatic islet cells. Triton X-100-resistant fractions, at the interface between 5 and 35% sucrose, denote proteins in lipid-raft microdomain. α-Tubulin, and Caveolin are marker proteins indicating the fractions of non-lipid-raft and lipid-raft microdomains, respectively. Steady state membrane distribution of GLUT2 protein in pancreatic beta cells obtained from either wild type (A) or GnT-IVa deficient (B) mice. Membrane distribution of GLUT2 protein following pretreatment with methyl-β-cyclodextrin (10 mM) in islet cells obtained from either wild type (C) or GnT-IVa deficient (D) mice.

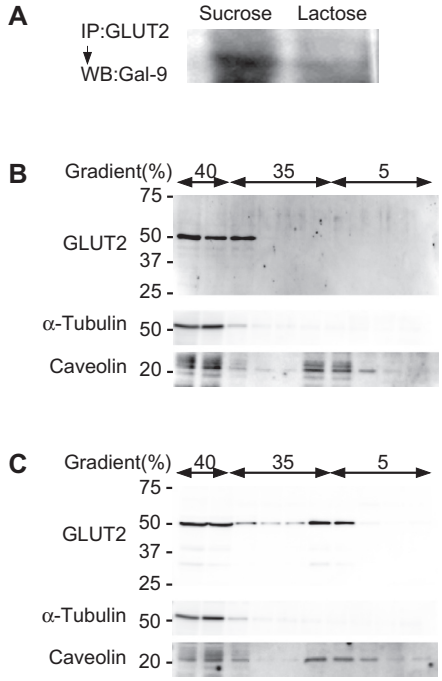

Fig. 2. Disruption of the binding between GLUT2 *N*-glycan and Galectin9 induces the membrane re-distribution of GLUT2 into lipid-raft microdomain. (A) Cell surface protein cross-linking and co-immunoprecipitation of GLUT2 with Galectin9 from wild type pancreatic beta cells either treated with sucrose (control disaccharide) or lactose (competitive inhibitory disaccharide for Galectin9 interaction). GLUT2 *N*-glycan–Galectin9 lattice can be disrupted by lactose, but not sucrose. Membrane sub-domain distribution of GLUT2 protein in beta cells treated with 10 mM of sucrose (B) or lactose (C).

manner. We examined whether GLUT2 is associated with Stomatin in lipid-raft microdomains in GnT-IVa deficient pancreatic beta cells, by intracellular protein cross-linking in conjunction with immunoprecipitation. We could detect substantial molecular interactions between GLUT2 and Stomatin in GnT-IVa deficiency, whereas wild type beta cells exhibited much less interaction (Fig. 3).

To confirm the functional relevance of the membrane localization of GLUT2 to its glucose transport activity, we analyzed glucose transport activities of GnT-IVa deficient pancreatic islet cells and chemically treated primary isolated islet cells. The GnT-IVa deficient islet cells exhibited significantly reduced glucose transport

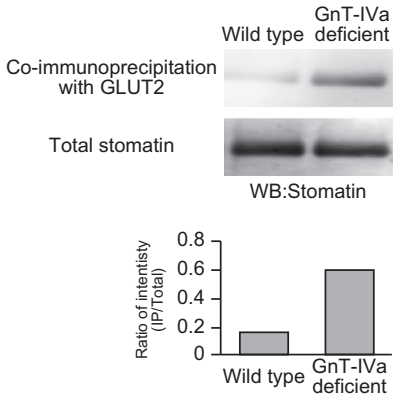

Fig. 3. Dysglycosylation of GLUT2 elevates the molecular interaction with lipid-raft residing Stomatin GLUT2-stomatin complex was immunoprecipitated from either wild type or GnT-IVa deficient mouse islet cells using antibodies against GLUT2 protein following intracellular protein cross-linking. The ratio of Stomatin band intensity (co-immunoprecipitated with GLUT2/total lysate) is graphed.

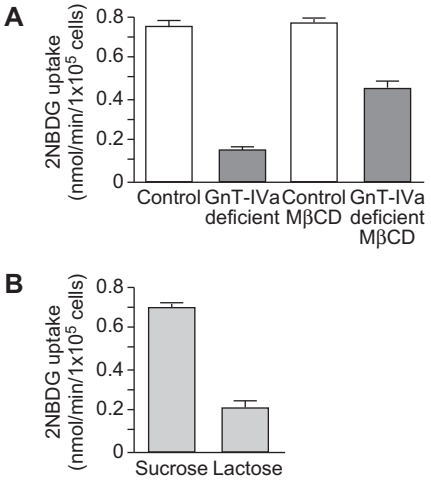

Fig. 4. Influence of the impaired GLUT2 *N*-glycan–galectin lattice formation on glucose transport activity of islet cells. (A) Cellular glucose transport activity of wild type and GnT-IVa deficient pancreatic islet cells either non-pretreatment or pretreated with 10 mM methyl-β-cyclodextrin at 37 °C for 30 min. (B) Cellular glucose transport activity of wild type pancreatic islet cells pretreated with either 50 mM sucrose or lactose at 37 °C for 2 h.

activity that was ameliorated by MβCD treatment (Fig. 4A). Furthermore, cellular glucose transport activity was also significantly reduced as the result of the disruption of the GLUT2 *N*-glycan–galectin lattice by treating wild type islet cells with lactose (Fig. 4B). These collective findings indicate that the presence of GLUT2 in a lipid raft-microdomain causes Stomatin interactions, thereby suppresses the transport activity of GLUT2, and further suggest that the glycosylation-mediated membrane sub-domain distribution of GLUT2 is important for the regulation of glucose sensor function for glucose stimulated-insulin secretion of pancreatic beta cells. Indeed, the glucose stimulated insulin secretion response of pancreatic beta cells were significantly reduced by the lactose treatment (sucrose treatment, 29.28 ± 2.39 pg/min/1×10^5 cells; lactose treatment, 16.38 ± 0.99 pg/min/1×10^5 cells), as well as GnT-IVa deficiency [10].

4. Discussion

The biological significance of lipid-rafts in pancreatic beta cells has not been fully established. It has been reported that disruption of lipid-raft microdomains in beta cells by MβCD treatment induced re-distribution of ion channels and enhanced glucose-stimulated insulin secretion. This suggests that membrane compartmentalization of beta cell surface proteins is critical for regulation of the proper insulin secretion [27]. In the present study, we found that the glucose transport activity of GLUT2 is regulated by its membrane sub-domain distribution in beta cells, which is related to its molecular interaction with Stomatin, which is a lipid-raft residing protein. The cellular overexpression of Stomatin revealed the nature of the GLUT1 inhibitory mechanism, which Stomatin directly binds to the cytosolic C-terminal tail of GLUT1, where is essential for glucose transport activity [28]. Because of the high sequence similarity between GLUT1 and GLUT2, it is possible that Stomatin also binds to the cytosolic tail of GLUT2 in lipid-rafts, although the detailed molecular mechanism for the Stomatin-mediated inhibition of GLUT2 needs to be clarified in future studies.

Furthermore, it is possible that cellular metabolic stress could be involved in the membrane sub-domain re-distribution of GLUT2. It has been reported that reduced cellular ATP levels, caused by the inhibition of oxidative phosphorylation, results in the redistribu-

tion of GLUT1 to non-lipid raft-microdomains that was due to the dissociation of the GLUT1-stomatin complex and potentiated cellular glucose uptake [22,29]. It is well known that the insulin secretion function of pancreatic beta cells is linked to ATP production through cellular glucose metabolism. Under normal physiological conditions, a portion of the produced ATP is converted to cAMP and activates PKA that results in the phosphorylation of various substrate proteins and in regulation numerous cellular processes. In pancreatic beta cells, PKA-dependent GLUT2 phosphorylation attenuates glucose transport activity without alteration of the Michaelis constant [30]. This suggests that the PKA-dependent GLUT2 phosphorylation could function as a molecular switch for membrane re-distribution rather than for functional alterations. We also previously reported that cellular glucose metabolism is closely related to the pathway for producing a series of nucleotide-sugars, which are donor substrates for glycosyltransferases and, thereby, consequently modulates the formation of cellular glycan structures on glycoproteins [31]. The findings reported herein indicate that GLUT2 *N*-glycan–galectin9 lattice formation is involved in the cell surface membrane sub-domain distribution of GLUT2 that consequently regulates the cellular glucose uptake function. These findings illuminate the presence of the mechanism for integrating cellular glucose metabolism, signaling, glycosylation, and GLUT2 membrane localization in pancreatic beta cells. The production of nucleotide-sugars, as well as ATP, through glucose metabolism accommodates GLUT2 membrane localization, and consequently the cellular glucose uptake function that is conceivably a reasonable feedback mechanism for the control of the glucose sensor function and is suitable for finely regulating insulin secretion corresponding to cellular physiological conditions.

Failure of the glucose transporter function in pancreatic beta cells is associated with suppression of glucose-stimulated insulin secretion and hyperglycemia, which are early markers in the pathogenesis of diabetes in humans and rodents [32–36]. We have recently reported that high-fat diet induced transcriptional dysfunction of GnT-IVa expression impairs GLUT2 glycosylation and glucose sensor function of beta cells, and consequently evokes type 2 diabetes in mice [10,11]. It is known that rodent beta cells use GLUT2 for glucose transport, while human beta cells express much lower levels of this transporter and glucose is taken up via GLUT1 instead [37]. We demonstrated that pancreatic beta cells obtained from human type 2 diabetes donor patients were also deficient in GnT-IVa expression and GLUT1 function, and glucose stimulated insulin secretion was lost [11]. Although the detailed molecular mechanism responsible for the dysglycosylation-induced lipid-raft microdomain distribution of GLUT2 still remains unclear, it is possible that the dysregulation of the membrane sub-domain distribution of glucose transporters is involved in the failure of beta cell function in the pathogenesis of type 2 diabetes.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2013.03.076.

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