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Abstracts

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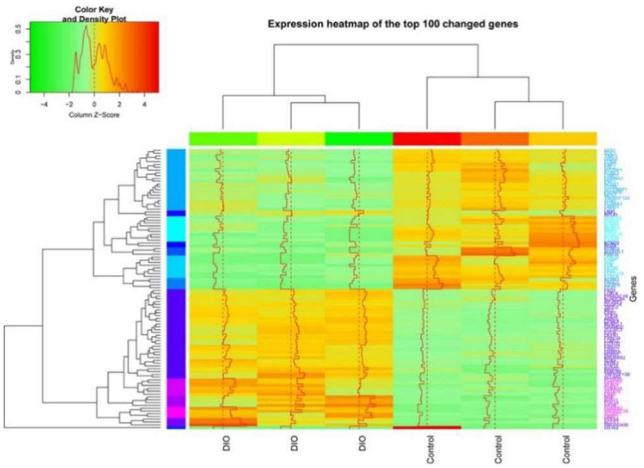
glucose homeostasis. Here we attempted to explore a new molecular mechanism mediated by Clec11a (C-type lectin domain family 11, member A) in prevention of islets disfunction during obesity.
Materials and methods: C57BL/6 mice aged 5 weeks fed a high-fad diet or standard diet for 14 weeks. Transcriptomic sequencing was performed with the islets of diet-induced obesity (DIO) C57BL/6 mice and normal food fed control mice. Differentiatial gene transcription was confirmed by real-time PCR, and protein translation was verified by western blot and immunofluorescence. The proliferation of MIN6 cells was measured by CCK8. The insulin secretion was measured by ELISA.
Results: The body weight (49.29 ± 0.79 g vs. 29.30 ± 0.54 g, $P < 0.01$, Fig 1.A), fasting blood glucose (7.58 ± 0.58 mmol/L vs. 3.90 ± 0.38 mmol/L, $P < 0.01$, Fig 1.B), and insulin level in plasma (1240.95 ± 92.30 pg/mL vs. 723.56 ± 74.33 pg/mL, $P < 0.01$, Fig 1.C) were higher in DIO mice than those of control mice. Moreover, the results of oral glucose tolerance test (OGTT) and insulin tolerance test (ITT) exhibited the impaired glucose tolerance and insulin resistance in DIO mice ($P < 0.05$, Fig. 1D,E). The mRNA of Clec11a significantly decreased in islets of DIO mice in RNA-Seq experiment by 5 folds (Fig. 1F) and confirmed by real-time PCR (Fig. 1G). The expression heatmap of the top 100 changed genes is shown in Fig. 1H. As shown in Fig. 2, Clec11a staining is localized in islets. Palmic acid (PA) treated cultured isolated islets expressed less Clec11a in a dose dependent manner (Fig. 3A,B). We then chose 0.5mM PA as the concentration in time course experiment. The protein expression of Clec11a demonstrated an waved trend with upregulated peak at 12 hours and then declined until a reversed level comparing to free fat acid (FFA-BSA) at 48h (Fig. 3C,D). The expression of Clec11a in MIN6 is also downregulated by PA in a dose dependent manner measured by real-time PCR (Fig. 4A) and western blot (Fig. 4B,C). Additionally, PA treatment inhibited the proliferation (Fig. 5A) and the secretion of insulin (Fig. 5B) in MIN6. The treatment of Clec11a protein containing medium rescrued the proliferation (0.66 ± 0.05 vs. 0.42 ± 0.04, $P < 0.01$, Fig. 5C), the secretion of insulin in high glucose (22708.16 ± 2275.08 pg/mg/h vs. 11911.69 ± 1421.1 pg/mg/h, $P < 0.01$, Fig. 5D). Moreover, the phosphorylation level of Akt was elevated by Clec11a protein containing medium in PA treated MIN6 cells by 2 folds ($P < 0.05$, Fig. 5E).
Conclusion: Clec11a might protects the islets function injured by lipotoxicity via a mechanism of regulating pancreatic beta cell proliferation and secretion.



Disclosure: **R. Shi:** None.

PS 017 Insulin secretion

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Evidence for differential role of beta-arrestin2 in GLP-1 and GIP signalling in mouse pancreatic beta cells

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Background and aims: The scaffold protein beta-arrestin2 (ARRB2) is known to uncouple G protein coupled receptors (GPCR) from G protein and to recruit new signaling pathways (such as ERK1/2) to the activated GPCR. Several groups have reported a direct interaction of the GLP-1 receptor (GLP-1R) but not of the GIP receptor (GIPR) with ARRB2 in non beta cells. Nevertheless, we and others failed to detect any differences for insulin secretion in response to 20–100 nM GLP-1 from Arrb2$^{-/-}$ mouse pancreatic islets. Our aim was to determine if ARRB2 could be involved in GLP-1R and GIPR signaling in mouse beta cells.
Materials and methods: The experiments were carried out in beta cells from four-month-old Arrb2$^{+/+}$ and Arrb2$^{-/-}$ male mice. cAMP production (CAMPS-epac), endogeneous PKA (AKAR3) and ERK1/2 (EKAR) activations were measured after adenoviral infection of cells with FRET-based sensors of interest by live microscopy. ERK1/2 phosphorylation was also determined by immunofluorescence.
Results: Compared to Arrb2$^{+/+}$ mice, Arrb2$^{-/-}$ mice displayed a better oral glucose tolerance despite an impaired i.p. glucose tolerance and a decrease in beta cell mass. This was associated with a significant increase in plasma insulin concentration after the oral glucose administration ($p < 0.05$), suggesting a greater incretin effect in Arrb2$^{-/-}$ mice. Insulin secretion was then measured from isolated islets in response to both incretin hormones: GIP and GLP-1. Unexpectedly, whereas insulin secretion from Arrb2$^{-/-}$ isolated islets was significantly reduced in response to GIP (100 pM, $p < 0.05$), insulin secretion was larger with physiological concentrations of GLP-1 (1 and 10 pM GLP-1; $p < 0.05$). By contrast, supra-physiological concentrations of GLP-1 (1 nM–10 nM) induced similar insulin secretion in Arrb2$^{+/+}$ and Arrb2$^{-/-}$ islets. The larger insulin release with physiological concentrations of GLP-1 was associated with an increased cAMP production and PKA activation in Arrb2$^{-/-}$ beta cells, while cytosolic [Ca2+] increases and emptying of the endoplasmic reticulum were both similarly affected in Arrb2$^{+/+}$ and Arrb2$^{-/-}$ beta cells. Conversely, GLP-1-induced activation of ERK1/2 was strongly decreased (~50%, $p < 0.05$) in Arrb2-/- beta cells, but the re-expression of ARRB2 in Arrb2$^{-/-}$ beta cells, using an adenovirus encoding ARRB2-GFP, completely restored ERK1/2 phophorylation induced by GLP-1 ($p < 0.01$).
Conclusion: Our study revealed in living mouse beta cells, a differential role of ARRB2 in GLP-1R and GIPR signalling. For GLP-1R, ARRB2 contributes to a partial uncoupling for the production of cAMP, the activation of PKA and consequently insulin secretion in the pM range of GLP-1, which is the physiological circulating concentration of the incretin. On the other hand, ARRB2 is required for GLP-1-induced full activation of ERK1/2. For GIPR, ARRB2 is required for GIP-induced amplification of insulin secretion. Therefore, any variation in the expression of ARRB2, as observed in diabetic states, should affect differentially the signaling of GLP-1R and GIPR.
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CB1 and CB2 antagonists stimulate insulin secretion and regulate human and mouse islet viability

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