PO1-3

APPL2 deficiency suppresses glucose-stimulated insulin secretion by disrupting F-actin remodeling in pancreatic β cells

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Defective glucose-stimulated insulin secretion (GSIS) is a key characteristic of type 2 diabetes at late stage. Previous studies have shown that the adaptor protein APPL1 potentiates first-phase GSIS by modulating the exocytotic machinery SNARE proteins in an Akt-dependent manner, whereas the role of its close homolog APPL2 in pancreatic β cells remains obscure. Here, we show that APPL2 regulates GSIS in a distinct mechanism from APPL1. Mice lacking APPL2 in pancreatic β cells displayed a dramatic reduction of first-phase and second-phase GSIS, resulting in glucose intolerance. APPL2 deficiency had no effect on glucose metabolism, calcium signaling and SNARE protein expression but impaired glucose-stimulated F-actin (Filamentous actin) remodeling in pancreatic islets. Defective GSIS in the islets lacking APPL2 was reserved by the F-actin depolymerizing drug Latrunculin A. Further analysis revealed that RNAi-mediated knockdown of APPL2 largely abolishes glucose-stimulated activation of Rac1, a small GTPase is known to regulate F-actin remodeling in pancreatic β cells. Therefore, deciphering the role of APPL2 in F-actin remodeling might provide a potential therapeutic target for type 2 diabetes by continuously evoking first- and second-phase GSIS.

PO3-3

Correlation between IGF-II and Foxo1 in pancreatic adult stem cell differentiation

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To investigate the mechanism of rapamycin inhibiting the differentiation and proliferation of newborn porcine pancreatic adult stem cells and to explore the therapeutic methods that can effectively reduce the side effects of rapamycin.

Porcine NPCCs were treated with rapamycin alone or in combination with IGF-II, and the caspase-3 and H3-thymidine uptake assays were performed to detect apoptosis and proliferation. The expression of Insulin, PDX-1,NeuroD/Beta2 and Foxo1, a downstream transcription factor of IGFII, was analyzed by RT-PCR and Western blot to evaluate the differentiation ability of pancreatic adult stem cells.

The NPCCs treated with rapamycin inhibited the proliferation of β cells, increased the apoptosis, reduced the insulin secretion, inhibited the expression of PDX-1 and NeuroD/Beta2, and decreased the expression of IGF-II Foxol expression and induction of Foxol from the cytoplasm to the nucleus of the ectopic. The combined treatment of rapamycin and IGF-II can reduce the side effects of rapamycin, inhibit the decrease of β-cell number and insulin content, repair the expression of insulin, PDX-1, NeuroD/Beta2, inhibit Foxo1 expression and intracellular ectopic.

Aberrant expression of IGF-II and Foxol genes is the key inducing factor of rapamycin inhibiting the proliferation and differentiation of NPCCs, and IGF-II treatment can effectively reduce the side effects of rapamycin on NPCC differentiation.

PO1-4

Downregulation of HuD by lower zinc in diabetic pancreatic β cells

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Pancreatic β-cell failure is the major pathophysiologic abnormalities of type 2 diabetes (T2DM).

HuD is a RNA-binding protein expressed in neuron and pancreatic β cells and plays diverse roles in regulations of insulin synthesis, autophagosome formation, and triglyceride (TG) synthesis.

However, the regulatory mechanism governing HuD expression has not been yet elucidated. Here, we present evidence that zinc ion is a novel upstream regulator for HuD expression in pancreatic β cells. Depletion of intracellular zinc ion using N,N,N′,N′-tetrakis(2-pyridinylmethyl)-1,2-ethanediamine (TPEN) resulted in a reduction of HuD mRNA, while zinc sulfate (ZnSO4) treatment raised HuD expression in pancreatic β cells. In silico analysis revealed that the promoter region of HuD has an element responsible for the binding of zinc-dependent transcription factors, and KLF6 was identified as a binding partner by chromatin-immunoprecipitation (ChIP) assay. KLF6 increased HuD expression in zinc-dependent manner by facilitating its transcription. Taken together, our results suggested that the zinc/KLF6 axis is a crucial role for regulating HuD expression in pancreatic β cells.

PO4-1

Bone quality in Chinese postmenopausal women with type 2 diabetes – impact of dipeptidyl peptidase-4 inhibitor usage

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Objectives: To compare the bone quality in type 2 diabetes (T2D) subjects to those without T2D and evaluate the impact of dipeptidyl peptidase-4 inhibitor (DPP4-i) usage on bone quality in T2D subjects, in view of the potential effects of DPP4 and the incretins on bone biology.

Methods: We conducted a cross-sectional study of post-menopausal women with T2D subjects recruited from the Hong Kong West Diabetes Registry and non-diabetic subjects from the Hong Kong Cardiovascular Risk Factor Prevalence Study, from November 2016 to June 2018. Subjects with fasting glucose 5.6–6.9 mmol/L, 2 hours post-load glucose 7.8–11.0 mmol/L in oral glucose tolerance test, or HbA1c 5.7–6.4% were classified as pre-diabetes and those with normal glucose tolerance as euglycaemia. Bone mineral density (BMD), vertebral fracture assessment (VFA), and trabecular bone score (TBS) were measured by dual X-ray absorptiometry. BMD and TBS in DPP4-i users and non-users with T2D were compared.

Results: Three hundred and sixty subjects were studied: 98 with euglycaemia, 154 with pre-diabetes, and 108 with T2D. Using euglycaemia subjects as reference, pre-diabetes and T2D subjects were significantly older (euglycaemia 60.0 ± 4.4, pre-diabetes 61.8 ± 5.5, and T2D 63.1 ± 5.5 years, $p < 0.001$) and heavier (euglycaemia 56.1 ± 9.2, pre-diabetes 60.1 ± 10.1, and T2D 62.0 ± 10.5 kg, $P < 0.001$). Lumbar spine (LS) BMD among T2D subjects was significantly higher than subjects with euglycaemia after adjustment for age, height and weight (0.942 g/cm2 vs 0.876 g/cm2, $P = 0.001$). TBS among T2D subjects, however, was significantly lower than those with euglycaemia after adjustment for age, height, weight and LS BMD (1.26 vs 1.30, $P < 0.001$). Among T2D subjects, 47 were DPP4-i users and 61 were non-users. Mean duration of DPP4i usage was 3.1 ± 2.4 years. Age, height, weight, fragility fracture prevalence, HbA1c, duration of diabetes, and frequency of usage of other oral anti-diabetic agents were not significantly different between the two groups. More insulin usage was found among DPP4-i non-users. After adjustment for insulin usage, there was no difference in LS BMD or TBS between DPP4-i users and non-users.

Conclusions: Hong Kong Chinese subjects with T2D had lower TBS, an indirect index of bone microarchitecture, but higher BMD when compared with those with euglycaemia. DPP4-i usage, however, did not have significant impact on BMD or TBS among T2D subjects.