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<th>APPL1 regulates insulin secretion in pancreatic beta cells</th>
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<td><strong>Author(s)</strong></td>
<td>Cheng, KKY; Lam, KSL; Wu, D; Xu, A</td>
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Exchange protein directly activated by cAMP 1 is involved in beta3-adrenergic induction of brown adipose tissue in white adipose tissue

YX Chen, ACP Tai, A Kai, KS Lam, SSM Chung, A Xu, SK Chung
Department of Anatomy, The University of Hong Kong, Hong Kong

Introduction: Exchange protein directly activated by cAMP (Epac1, Epac2a and Epac2b) were identified as cAMP-regulated guanine nucleotide exchange factors. Previously Epac1-deficient mice were shown to have slightly heavier body weight, higher respiratory exchange ratio, and develop more severe high-fat-diet–induced obesity and hyperglycaemia than the wild type mice, suggesting the role of Epac1 in energy expenditure and lipid metabolism. The beta3-adrenergic signalling in white adipocytes is reported to be important in lipid metabolism and energy homeostasis by induction of brown adipose tissue (BAT) in white adipose tissue (WAT).

Methods: To investigate the role of Epac1 in beta3-adrenergic induction of BAT in WAT, a beta3-adrenergic receptor agonist (CL 316,243, CL) or saline was administrated to wild type (Epac1+/+) and homozygous Epac1 knockout (Epac1-/-) mice. Peri-uterine WAT was collected for histology, immunocytochemistry, Western blots, and real time quantitative polymerase chain reaction (qPCR). Lipolytic activity was determined by glycerol released from WAT explants with or without CL treatment.

Results: After CL (1 mg/1 kg body weight/day, i.p.) treatment for 10 days, peri-uterine WAT exhibited a BAT-like phenotype with smaller eosinophilic adipocytes with multilocular lipid droplets in both Epac1+/+ and Epac1-/- mice. WAT of CL-treated Epac1-/- mice showed less typical BAT morphology compared to that of CL-treated Epac1+/+ mice. In addition, CL-induced up-regulation of uncoupled protein 1 (UCP1) seen in WAT of Epac1+/+ mice was not observed in Epac1-/- by immunocytochemical, Western blot and real-time qPCR analyses. Inductions of other genes shown to be critical for thermogenesis (Cidea, PGC1 alpha) and adipocyte differentiation (CEBP alpha and PPAR gamma) with CL treatment were also not observed in WAT of CL-treated Epac1-/- mice by real-time qPCR analysis. Concomitantly, Epac1 expression was increased in WAT of Epac1+/+ mice after CL treatment, whereas no Epac1 and no compensation of Epac2 expressions were observed in Epac1-/- WAT.

Conclusion: Epac1-mediated lipolytic activity may play an important role in beta3 adrenergic induction of UCP1 in WAT.

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APPL1 regulates insulin secretion in pancreatic beta cells

KKY Cheng1, KSL Lam1, D Wu2, A Xu1,3
1 Department of Medicine, The University of Hong Kong, Hong Kong
2 Guangzhou Institute of Biomedicine and Health, China
3 Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong

Introduction: Pancreatic beta cell dysfunction, characterised by defective glucose-stimulated insulin secretion, is a major contributor to the progression of type 2 diabetes. APPL1 has been suggested as an insulin-sensitising molecule in various insulin-responsive tissues. In this study, we aimed to investigate whether APPL1 regulates beta cell functions using genetically engineered mouse models.

Methods: APPL1 knockout and transgenic mice and their wild-type littermates were fed with standard chow or high-fat diet for a period of 24 weeks. Basic metabolic parameters and beta cell functions were examined in the above animals.

Results: In dietary obese and genetically inherited diabetic mice, expression of APPL1 in pancreatic islets is dramatically decreased, which is associated with defective insulin secretion. Genetic deletion of APPL1 leads to glucose intolerance and impaired insulin secretion, the latter due to defective exocytosis of insulin granules. By contrast, transgenic expression of APPL1 protects mice from dietary-induced glucose intolerance partly by enhancing insulin secretory capacity. Ex-vivo analysis revealed that APPL1-deficient islets exhibit a significant reduction in number of docked insulin granules accompanied with decreased exocytosis of insulin as a result of significantly decreased expression of SNARE proteins, the core components of the exocytotic machinery of eukaryotic cells. In molecular level, APPL1 enhances insulin-mediated Akt activation by suppressing the binding of Akt to TRB3, thereby up-regulating expression level of SNARE protein and insulin secretion in pancreatic beta cells.

Conclusion: APPL1 integrates the effects of insulin in peripheral target tissues and pancreatic beta cells to maintain glucose homeostasis in the body.

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