Novel Epac2 isoforms and their roles in pancreatic β-cell functions

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We have previously clarified the physiological roles of Epac2 (exchange protein directly activated by cAMP 2)-mediated signaling in insulin secretion induced by incretin and sulfonylureas. There have been three Epac2 isoforms identified to date: a full length Epac2A, Epac2B lacking N-terminus cAMP binding domain, and Epac2C, the shortest isoform predominantly expressed in the liver. To further investigate the cellular functions of Epac2 in pancreatic β-cell, we first intended to ablate both Epac2A and Epac2B in insulin-secreting MIN6-K8 cells by the CRISPR/Cas9 system (KO-1 cells). In the KO-1 cells, although protein expression of Epac2A was ablated, the expressions of multiple Epac2B-like isoforms were still detected. We then ablated all these isoforms and established the Epac2-null cell lines (KO-2 cells). While relatively weak activation of Rap1, a downstream molecule of Epac2, by cAMP was found in the KO-1 cells, no Rap1 activation was observed upon cAMP stimulation in the KO-2 cells. Interestingly, insulin secretion in response to Epac-selective cAMP analog and GLP-1, an incretin, was reduced in both KO-1 and KO-2 cells to the same extent, compared to the parental MIN6-K8 cells. These results indicate that Rap1 activation through newly identified Epac2B-like isoforms is not involved in insulin secretion, suggesting their roles mediating the cellular functions different from insulin secretion in pancreatic β-cells.