

Title: Proteomic Analysis of Rap1A GTPase Signaling-Deficient C57BL/6 Mouse Pancreas and Functional Studies Identify an Essential Role of Rap1A in Pancreas Physiology

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Abstract: Ras-related Rap1A GTPase is implicated in pancreas β -cell insulin secretion and is stimulated by the cAMP sensor Epac2, a guanine exchange factor and activator of Rap1 GTPase. In this study, we examined the differential proteomic profiles of pancreata from C57BL/6 Rap1A-deficient (Null) and control wild-type (WT) mice with nanoLC-ESI-MS/MS to assess targets of Rap1A potentially involved in insulin regulation. We identified 77 overlapping identifier proteins in both groups, with 8 distinct identifier proteins in Null versus 56 distinct identifier proteins in WT mice pancreata. Functional enrichment analysis showed four of the eight Null unique proteins, ERO1-like protein β (Ero11 β), triosephosphate isomerase (TP1), 14-3-3 protein γ , and kallikrein-1, were exclusively involved in insulin biogenesis, with roles in insulin metabolism. Specifically, the mRNA expression of Ero11 β and TP1 was significantly ($p < 0.05$) increased in Null versus WT pancreata. Rap1A deficiency significantly affected glucose tolerance during the first 15-30 min of glucose challenge but showed no impact on insulin sensitivity. Ex vivo glucose-stimulated insulin secretion (GSIS) studies on isolated Null islets showed significantly impaired GSIS. Furthermore, in GSIS-impaired islets, the cAMP-Epac2-Rap1A pathway was significantly compromised compared to the WT. Altogether, these studies underscore an essential role of Rap1A GTPase in pancreas physiological function.

Key words: Ero11 β expression; Rap1A GTPase; differential expression; gene knock-out; glucose-stimulated insulin secretion; insulin tolerance test; intracellular signaling; nanoLC-ESIMS/MS; oral glucose tolerance test; pancreas.

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