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Pancreatic cancer-derived exosomes suppress the production of GIP and GLP-1 from STC-1 cells *in vitro* by down-regulating the PCSK1/3

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Abstract

One hallmark of pancreatic cancer (PC) is the high prevalence of pancreatic cancer-associated diabetes mellitus (PC-DM), but the mechanisms remain to be elucidated. Patients with PC who are diagnosed with new-onset diabetes/prediabetes have recently been shown to display significantly lower levels of glucose-dependent insulinotropic peptide (GIP) secreted mainly by enteroendocrine cells. We hypothesized that PC-derived exosomes are responsible for the decreased levels of incretins in patients with PC-DM. In this study, exosomes were successfully isolated from PANC-1, MIA PaCa-2 and SW620 cells and characterized. Only the exosomes from MIA PaCa-2 cells (Exo-Mia) reduce the production of GIP and glucagon-like peptide-1 (GLP-1) from STC-1 cells *in vitro* in a concentration- and time-dependent manner. Moreover, Exo-Mia increased the levels of the *Gip* and *proglucagon* mRNAs and decreased the expression of proprotein convertase subtilisin/kexin type 1/3 (PCSK1/3), which is responsible for the post-translational processing of *Gip* and *proglucagon*. Furthermore, differentially expressed exosomal miRNAs (*miR-6796-3p*, *miR-6763-5p*, *miR-4750-3p* and *miR-197-3p*) were identified and considered to be responsible for the inhibitory effects on GIP and GLP-1 production. To further determine the approach of cancer-derived exosomes reaching enteroendocrine cells, we analyzed the uptake and distribution of exosomes in animal model. It was observed that exosomes infused into the intestinal cavity were more easily internalized by the intestinal epithelium than exosomes injected into blood. In conclusion, pancreatic cancer-derived exosomes (Exo-Mia) suppress the synthesis of GIP and GLP-1 from STC-1 cells *in vitro* by down-regulating the PCSK1/3. Moreover, it may be the pancreatic juice that transport cancer-derived exosomes to target cells (K and L cells) in the gut.