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Peribiliary glands as a niche of extra-pancreatic insulin-producing cells during experimental diabetes

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Glands of biliary tree (Peribiliary Glands: PBGs) contain a niche of heterogeneous endodermal-like stem/progenitors cells (Biliary Tree Stem/progenitor Cells: BTSCs) that can be easily induced to differentiate, in vitro and in vivo, towards pancreatic islets (1,2). Whether these cells may play a role in insulin production in diabetes is unknown. The aim of this study was to evaluate, in experimental diabetes, proliferation of PBGs and differentiation of BTSCs towards insulin-producing cells. Diabetes was generated in mice by intraperitoneal injection of a single dose of 200 mg/kg (High-Dose STZ group; N=12) or 120 mg/kg of STZ (Low-Dose STZ group; N=12). Control mice (N= 17) were injected with citrate buffer (i.e. the STZ carrier). Glucose levels in blood and urine and HbA1c blood levels were measured. Liver, pancreas and extrahepatic biliary trees (EHBT) were en bloc microdissected and processed for histology, immunohistochemistry, immunofluorescence, and RT-PCR. Our results showed that PBGs proliferated in an experimental model of type-1 diabetes. Their proliferation was greatest at the hepato-pancreatic ampulla and correlated with a decreased pancreatic islets' mass. The PBG proliferation was characterized by the expansion of the compartment of Sox9+ stem/progenitor cells that gave rise to insulin-producing cells. Insulin-producing cells were mostly located in the portion of EHBT closest to the duodenum, and their appearance was associated with the up-regulation of MafA and Gli1 gene expression. PBG proliferation and the expansion of Sox-9+, insulin-producing cells were more evident after 90 than after 30 days STZ treatment. In conclusion, PBGs and associated BTSCs respond to diabetes with proliferation and differentiation towards insulin-producing cells. This indicates that PBG niche may rescue the pancreatic islet impairment in diabetes with important implications for the patho-physiology and complications of this disease.

References

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Keywords

Peribiliary glands; diabetes; stem cell; insulin; bile ducts.

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