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(54) Title: TRANSDIFFERENTIATION OF PANCREATIC ACINAR CELLS

(57) **Abstract:** Induction of β -cell neogenesis has been associated with ductal epithelium, however $\approx 80\%$ of the pancreas is composed of acinar cells. Surprisingly, pancreatic acinar cells contribute to β -cell neogenesis. Partial duct obstruction (PDO) of the pancreas is a known inducer of β -cell neogenesis leading to expansion of β -cell mass, and the effect appears to be mediated by INGAP, an acinar cell protein originally identified in the regenerating hamster pancreas. We examined the effects of PDO on the incorporation of tritiated thymidine by acinar and β -cells of the pancreas in female Syrian hamsters. A single dose of tritiated thymidine was administered to all animals 2 weeks after PDO. Animals were then sacrificed at 1 hr, or at 6 weeks post-injection. Tritiated thymidine incorporation into acinar cells was highest at 2 weeks after PDO and declined at 8 weeks after PDO. Incorporation of tritiated thymidine into β -cells was inversely related to that observed in acinar cells. Two weeks following PDO, β -cell tritiated thymidine uptake was relatively low and it increased significantly at 8 weeks after PDO, consistent with β -cell neogenesis from an acinar cell origin. Electron microscopy demonstrated cells with both zymogen and endocrine granules, further suggesting acinar to endocrine cell transdifferentiation. In a second experiment, hamsters were administered either a pentadecapeptide of INGAP protein or an equivalent volume of saline for 10 days. There was a 2-fold increase in the number of extra-islet acinar-associated β -cell clusters in the INGAP peptide-treated hamsters resulting in a 2.8-fold increase in the overall extra-islet β -cell mass. Acinar-to- β -cell differentiation provides an alternate pathway to β -cell neogenesis; INGAP peptide plays a significant role in this process.



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