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Pancreatic Ductal Cells and the Biology of Regeneration: From Mechanisms to Therapeutic Translation

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ADMINISTRATIVE INFORMATION

Support - Not Applicable.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2025110088

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 November 2025 and was last updated on 26 November 2025.

INTRODUCTION

Review question / Objective To what extent do pancreatic ductal cells contribute to β-cell regeneration or endocrine differentiation in mammalian models and humans, and what molecular, cellular, and environmental factors regulate this regenerative process?

Rationale Pancreatic ductal cells, once considered terminally differentiated, are now recognized to possess latent progenitor potential and can contribute to β-cell regeneration under injury, cytokine stimulation, or pharmacologic signals. Emerging evidence shows that ductal cells can reactivate developmental regulators (Ngn3, Sox9, Pdx1) and generate insulin-producing cells.

Condition being studied Type 1 Diabetes.

METHODS

Participant or population This review will include studies involving mammalian pancreatic ductal cells or duct-derived epithelial structures, regardless of species or disease status. Eligible populations include:Animal models (mouse, rat, and other mammals) in which pancreatic ductal cells (e.g., Sox9$^+$, HNF1β$^+$, CK19$^+$ epithelium) are assessed for plasticity, progenitor activity, or endocrine differentiation.Human pancreatic tissue (healthy, diabetic, injured, or surgically resected) examining ductal activation, co-expression of endocrine markers, or ductal involvement in β-cell regeneration.Ex vivo and in vitro ductal systems, including isolated ductal cells, pancreatic duct glands, and duct-derived organoids.The population is therefore defined at the cellular/tissue level, focusing specifically on pancreatic ductal epithelium as a potential progenitor source for endocrine or β-cell neogenesis.

Intervention Interventions include any experimental, physiological, or pharmacologic stimuli applied to pancreatic ductal cells that aim to modulate plasticity, progenitor activation, or endocrine differentiation.

Comparator Comparators will include any reported control conditions such as untreated or sham-operated groups, vehicle or placebo treatments, alternative stimuli or dose conditions, genetic control groups, and standard versus modified in vitro culture environments. Studies lacking explicit comparators, including descriptive human tissue analyses, will still be included if they provide relevant information on ductal–endocrine differentiation.

Study designs to be included This review will include mammalian in vivo experiments, ex vivo and in vitro ductal or organoid studies, and human observational or histological studies that report ductal activation or endocrine differentiation. Interventional and non-interventional designs are eligible if they provide relevant mechanistic or lineage evidence. Reviews and non-original studies will be excluded.

Eligibility criteria Studies will be eligible if they investigate mammalian pancreatic ductal cells and report evidence of ductal activation, progenitor marker expression, endocrine differentiation, or β-cell formation. In vivo, ex vivo, in vitro, and human histological studies will be included when they provide original data relevant to ductal plasticity. Studies will be excluded if they lack ductal analysis, do not report endocrine or progenitor outcomes, or are reviews, commentaries, or conference abstracts.

Information sources A comprehensive search will be conducted in PubMed/MEDLINE, Embase, Scopus, and Web of Science from inception to June 2025 to identify all relevant studies on pancreatic ductal cell plasticity and β-cell regeneration.

Main outcome(s) The main outcomes will be evidence of pancreatic ductal cell plasticity and endocrine differentiation, including the emergence of insulin-producing β-like cells, activation of key progenitor markers such as NGN3, SOX9, and PDX1, and quantifiable changes in β-cell mass or insulin expression.

Additional outcome(s) Additional primary outcomes include functional assessment of newly formed β-like cells, such as glucose-stimulated insulin secretion, and validated lineage-tracing evidence confirming ductal origin of endocrine cells.

Quality assessment / Risk of bias analysis Quality assessment will be conducted independently by two reviewers using tools appropriate to each study design. Animal and in vivo experimental studies will be evaluated with the SYRCLE Risk of Bias tool Human studies will be appraised using the Joanna Briggs Institute (JBI) critical appraisal checklist. Each study will be rated across domains relevant to selection, performance, detection, attrition, and reporting bias, and classified as low, unclear, or high risk of bias. Any disagreements will be resolved through consensus or by consulting a third reviewer.

Strategy of data synthesis Data will be synthesized narratively because of expected heterogeneity in study designs and outcomes. Findings will be grouped by key themes related to ductal cell plasticity and β-cell regeneration, and similarities or differences across studies will be described.

Subgroup analysis Not Applicable.

Sensitivity analysis Not applicable.

Country(ies) involved United States.

Keywords Pancreatic ductal cells; β-cell regeneration; endocrine differentiation; cellular reprogramming; pancreatic ductal plasticity.

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