An In Vitro Inflammation-induced Acinar-to-ductal Metaplasia Model for Primary Human Pancreatic Acinar Cells

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Background: Pancreatic ductal carcinoma (PDAC) is one of the most deadly human malignancies, largely due to the lack of methods for early diagnosis and intervention. Development of human PDAC tumorigenesis models would be critical to design new strategies for improving PDAC diagnosis, prevention and treatment. Pancreatitis-induced acinar-to-ductal metaplasia (ADM) has been found to be a key event for KRAS-driven tumorigenesis in PDAC development. Thus, understanding the molecular mechanisms for inflammation-induced ADM in human pancreatic tissue would pave the way to engineer human PDAC tumorigenesis models. **Methods:** To understand the underlying mechanisms of pancreatitis-induced ADM in human tissues, an Ulex europaeus lectin (UEA) and CD133 staining-based method was developed for lineage tracing of human primary pancreatic acinar cells in vitro. BD-matrigel-based 3D culture was established to identify pancreatitis-associated cytokines and growth factors that induced ADM of human primary pancreatic acinar cells. **Results:** The human primary pancreatic acinar and duct cells were defined by the UEA^+ $CD133^-$ and UEA^- $CD133^+$ surface staining pattern, respectively. Under 3D culture condition, TGF-β1, a growth factor significantly up-regulated during chronic pancreatitis, efficiently promoted ADM-associated alterations in human primary pancreatic tissues, characterized by the generation of acinar-derived duct-like cells with UEA^+ $CD133^+$ surface staining and sphere formation ability. Blocking TGFBR1/ALK5 completely abolished TGF-β1 induced ADM. **Conclusion:** TGF-β1 might play important roles in pancreatitis-induced ADM via activation of the canonical SMAD pathway and non-canonic pathways. The model established in our current study will setup a platform to develop human PDAC tumorigenesis models and screen targets for early diagnosis and intervention.