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Advanced 3D preclinical models of pancreatic neuroendocrine tumors: from bioprinting to precision-cut tumor slices

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BACKGROUND

Current pancreatic neuroendocrine tumors (PanNETs) in vitro models struggle to accurately replicate the tumor's biology and microenvironment, limiting insights into disease mechanisms and drug response. This project aims to develop: 1) 3D bioprinted PanNETs models that replicate tumor-stroma interactions and support studies on tumor biology and 2) precision-cut tumor slices for personalized drug testing.

METHODS

Bioprinted models were generated using PanNET cell lines and HUVECs (human umbilical vein endothelial cells), embedded in a hydrogel-based bioink. Both simple (mono-culture) and complex (co-culture) models were generated, and cultured under static or dynamic (100 µL/min flow rate) conditions. Immunofluorescence was used to assess morphology, viability, and functional marker expression. PanNET slices (350µm in thickness) were obtained from surgical specimens (n=15) using a vibratome. Viability, tissue architecture, and drug responses to Everolimus and Sunitinib were assessed.

RESULTS

1) Both simple and complex bioprinted scaffolds remained viable for up to 21 days. PanNET cell lines and HUVEC retained physiological morphology and marker expression (PanNET: CgA, SYN; endothelial cells: CD31). Homo- and hetero-cellular crosstalk was observed, including aggregation of PanNET cells into islet-like structures, cobblestone-like morphology and network formation by endothelial cells, and direct interactions between the two cell types. Distinct in vitro behaviors were observed depending on the aggressiveness of the PanNET cell lines, mirroring their in vivocharacteristics.

2) Around 40 PanNET slices per patient were generated. The slices remained viable for up to 10 days post-vibratome cutting, assessed through metabolic assay. Histologically, PanNET slices retained the tissue original architecture and the cellular complexity and heterogeneity of the tumour and

tumor microenvironment during the culture period. Specifically, tumor slices retained key cellular populations, including tumor cells, endothelial cells, fibroblasts, and immune cells. PanNETs slices displayed distinct responses to each drug tested.

CONCLUSIONS

3D bioprinting is a feasible and effective method for generating PanNETs models potentially replicating tumor and microenvironment, on which to perform functional studies. Patient-derived vibratome slices demonstrated to be a valid and promising approach for tailored drug testing.

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