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DEVELOPING A NOVEL PANCREATIC ADENOCARCINOMA ORGANOID MODEL USING CRISPR-CAS9 EDITED WITH HUMAN PANCREATIC ORGANOIDS

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Background : Pancreatic adenocarcinoma, one of the deadliest solid tumors, has a two-year survival rate below 5%. Limited progress in effective treatments stems from the lack of scalable disease models that replicate tumor characteristics for studying pathophysiology and drug evaluation. Organoids offer a promising solution by enabling the study of mechanisms and therapeutic responses. In pancreatic cancer research, organoids facilitate drug testing, while CRISPR-Cas9 introduces cancer-associated mutations to mimic disease conditions. This study aims to develop a pancreatic cancer organoid model by genetically editing normal human pancreatic organoids with prevalent driver mutations, representing over 95% of cases. Using human-derived organoids ensures a more physiologically relevant and scalable platform compared to animal models or stem-cell-derived systems.

Methods : Normal human pancreatic organoids were established from tissue samples and validated through qPCR and histological analysis. CRISPR-Cas9 was employed to introduce mutations linked to pancreatic cancer, beginning with TP53 knockout (KO).

Results : The normal human pancreatic organoids retained structural and functional characteristics, closely mimicking the original tissue. The organoids demonstrated robust viability across passages, and could be cryopreserved without loss of functionality. Initially, we targeted the TP53 gene, a well-known tumor suppressor, to create TP53-knockout (KO) organoids using CRISPR-Cas9. The resulting TP53 KO organoids exhibited increased proliferation and cancer-like traits, providing a physiologically relevant pancreatic cancer model.

Conclusions : TP53 KO organoids, generated using CRISPR-Cas9, lay the groundwork for further genetic modifications to create a comprehensive pancreatic cancer model. This platform offers significant potential for advancing disease understanding and therapeutic development.

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