Examination of Wnt signaling as a therapeutic target for pancreatic ductal adenocarcinoma using a pancreatic tumor organoid library.

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INTRODUCTION

• Pancreatic ductal adenocarcinoma (PDAC) 4th leading cause of cancer deaths.
• PDAC presents at late stage and is refractory to most treatment modalities.
• Low tumor cellularity and high desmoplastic response makes in vitro study difficult, but several mutations have been identified.
• Wnt signaling, activated by pancreatic ductal ligation injury, plays a critical role in proliferation and chemotherapeutic resistance. Wnt signaling, therefore, may serve as a potential therapeutic target.
• Pancreatic tumor organoid libraries (PTOL) allow for accurate investigation of other therapies.

MATERIALS AND METHODS

• Seven PDAC organoids grown in Human Pancreatic Stem Cell medium.
• Minimal media conditions required to maintain growth assessed with depletion of the various niche factors Wnt3a, EGF, Noggin, R-spondin, ALK inhibitor, or p38 inhibitor.
• Confirmation of Wnt inhibition by growing organoids in minimal media and treating with Wnt inhibitors ICG001, ETC159, C59.
• Growth assessed with CellTiter Glo 3D.
• Tumors injected into athymic nude mice and treated for 30 days with assessment of growth rate and tumor regrowth following removal of drug.
• Gene signatures for respective organoid and PDX models were determined through RNA-seq
• RT-PCR performed for human Wnt genes

OBJECTIVE

• Subclassify PDAC organoids based on Wnt dependency to determine if combinatorial treatment with Wnt inhibitors and chemotherapy would serve as a feasible treatment.

PATHWAYS

CONCLUSIONS

• Each organoid demonstrated different niche factor dependencies, providing an avenue for targeted therapy, particularly Wnt inhibition.
• Combinatorial treatment with Wnt inhibition and chemotherapy in vitro and in patient-derived xenograft models suggests beneficial application of combinatorial treatment.
• Gene signature and expression analysis of each organoid suggests correlation between genotype and Wnt (in)dependency observed in vitro.

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References