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Poster Abstract Form

Primary cancer associated fibroblasts alter PDAC tumour organoid subtype through epigenetic regulation

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Introduction

Pancreatic adenocarcinoma (PDAC) is the 3rd leading cause of cancer-related deaths in Australia with a 5-year survival rate of 13%. PDAC tumour microenvironment (TME) makes up to 80% of the tumour and is mainly composed of cancer-associated fibroblast (CAFs). TME effects on tumour growth, chemoresistance and metastasis have been established, but the mechanisms are unknown. Given the involvement of environmental cues from the TME, we suggest *epigenetic reprogramming occurs in PDAC cells in response to secreted factors from CAFs*

Methods

We established patient-derived organoids (PDO) and CAFs obtained from endoscopic ultrasound (EUS). Early-passage CAF conditioned media (CM) was mixed 1:1 with organoid media, and PDOs were cultured for up to 14 days. PDO growth and morphology were analysed through microscopy. ATAC-seq before and after CAF-CM treatment was integrated with RNA-seq to link chromatin accessibility and gene expression. To identify CAFs secreted factors responsible for PDOs changes, metabolomic was performed on CAFs-CM.

Results

Exposure of PDOs to CAF-CM resulted in altered phenotypes and increased in basal features, driven by a change in chromatin accessibility specifically at regions driving PDAC aggressivity. Metabolomic analysis on CAFs identified differential enrichment of metabolites linked to epigenetic mediators including Taurine.

Conclusion

This study shows the importance in integrating TME components when examining novel therapeutic options. In addition, we show CAFs secrete factors that enhance aggressiveness of PDOs, and these changes are driven by epigenetic reprogramming. Future experiments will identify which epigenetic factors that can be targeted to counteract PDAC aggressiveness.