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Development of humanized 3D liver metastasis of pancreatic origin: The role of tissue-specific extracellular matrix in tumor progression and chemoresistance

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Background & Aim: Over 50% of patients with pancreatic cancer are diagnosed at the metastatic stage and die because of the debilitating metabolic effects of their unrestrained growth. Despite efforts in the past 50 years, conventional treatment approaches have had little impact on the course of this aggressive neoplasm. Therefore, the development of new treatment strategies to control cancer metastases is of immediate urgency. Fulfillment of this difficult task relies on our knowledge of the cellular and molecular biology of both primary and metastatic pancreatic cancer and the use of relevant 3D extracellular matrix models will certainly help define individual and collective aspects of this complicated process.

Aim: To study the role of tissue-specific extracellular matrix in tumor progression and chemoresistance based on the utilization of decellularized human livers and pancreas.

Methods: Our model is based on the utilization of decellularized human livers (n=4) and pancreas (n=4) that have previously been characterized for cellular material elimination and preservation of extracellular matrix (ECM) proteins and micro-architecture. Both metastatic tumor cells (PK1, derived from a liver metastasis from pancreatic origin) and primary pancreatic tumor cells (PANC1) were seeded onto 5 mm³ liver and pancreas scaffolds, as well as 2D culture systems. Histological analyses were used to confirm cell attachment and migration. Further, gene expression after 7 and 14 days was evaluated by qRT-PCR. Additionally, alamarBlue assay was performed to test chemo-resistance in both 2D and in 3D scaffolds upon treatment with 0.5 µM of doxorubicin and gemcitabine.

Results: Behavioural and molecular differences were observed between cancer cell lines in the different decellularized tissues. PK1 metastatic cancer cells were able to exclusively migrate and invade the liver scaffolds, and only attached superficially onto the pancreatic scaffolds. Whereas, PANC1 primary cancer cells were able to migrate and invade the pancreas scaffolds but only attached superficially onto the liver scaffolds. These differences were corroborated by significant deregulations in gene expression, for MMP9, COL1A1, TIMP1, WNT1 and β-CATENIN between 3D scaffolds and 2D cultures. Interestingly, both primary and metastatic cells were found significantly more resistant to treatment with doxorubicin and gemcitabine in the 3D models when compared to the same treatment on 2D cultures (n=4, p<0.001).

Conclusion: Our results suggest that primary and metastatic pancreatic cancer cells manifest a conserved invasive behavior depending on the 3D ECM structure of origin. Moreover, there is an evident alteration in cell response to different cancer chemotherapy in the presence of a natural ECM niche. These observations provide a proof of concept for the development of an effective bio-engineered model characterized by a well-defined 3D ECM microenvironment.

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