Study of interactions between tumor cells and cancer-associated fibroblasts in pancreatic ductal adenocarcinoma using 3D models

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Abstract: The tumor microenvironment (TME) is a complex and continuously evolving entity, the study of which becomes increasingly important in the search for new anti-cancer therapies. TME includes, in addition to the extracellular matrix (ECM), a cellular component consisting of: immune cells, blood vessels and cancer-associated fibroblast (CAFs). These components regulate oncogenic functions such as tumor progression, metastasis, angiogenesis and resistance to chemoterapy. Within TME, CAFs have been identified as critical regulators of the malignat phenotype in several metastatic desmoplastic tumors.

To investigate the interaction between CAFs and cancer cells in the highly aggressive pancreatic ductal adenocarcinoma (PDAC) we have chosen the human pancreatic cell line PANC-1 and the human MRC-5 fibroblasts co-culture for 7 days in two different 3D cell models: spheroids (direct contact) and co-culture on transwell (indirect contact). First, we evaluated the expression of a typical CAFs marker, α-SMA, confirming its increased expression in activated MRC-5 and the role of the growth factor TGF-β released by cancer cells in this expression modification. The TGF-β-mediated transition from normal fibroblasts into CAFs was also proved by hyperproliferation of MRC-5 cells, while the release of the cytokine IL-6 from activated fibroblasts, that is another functional response of activated fibroblasts is not clearly elucidated: an higher release of the cytokin from MRC-5 was observed after co-culture with PANC-1 cells in transwell model, whereas in spheroid the co-culture did not have a significant effect. It has been previously demonstrated in other desmoplastic tumors that IL-6 released by CAFs is involved in the aggressive phenotype of these cancers, since it is involved in their chemoresistance and increased proliferation and migration, due to the epithelial-mesenchimal transition. PANC-1 proliferation stimulated by IL-6 released by MRC-5 was demonstrated, while a resistance to the chemotherapeutic drugs doxorubicin and gemcitabine was not observed, so as no effect was obtained on tumor cells migration. We can conclude that in PDAC models, the interaction between CAFs and cancer cells is a complex issue that still need to be investigated. Moreover, the integration of different experimental approaches, based on different 3D culture models, proved to be important to disclose a so complex scenario.