TGF-β signaling loop in adeno pancreatic cancer: activation of TME fibroblasts and effects on tumor cells

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Abstract: The study of the tumor microenvironment (TME) becomes increasingly important in the development of new anti-cancer therapies. Within TME, cancer-associated fibroblasts (CAFs) have been identified as critical regulators of the malignant phenotype in several aggressive and desmoplastic tumors. CAFs pleiotropic actions on cancer cells are continuously stimulated, creating a loop of paracrine signals in both directions. This crosstalk leads to a high tumor progression, invasiveness and to an increased resistance against the recommended therapy.

We investigated crosstalk between CAF-like fibroblasts and pancreatic ductal adenocarcinoma cancer model, choosing the human tumoral cell line PANC-1 and the human fibroblast line MRC-5, using two different 3D models, representative respectively of direct and indirect contact between the two cell types: the heterospheroid and the co-culture on transwell. These two models were used to analyze the TGF-β involvement in the crosstalk between CAF-like fibroblasts and pancreatic cancer cells.

We demonstrated that the fibroblasts co-cultured for 5 days with PANC-1 cells in transwell, overexpress the typical marker of myofibrotic CAFs (myCAFs), α-SMA, and acquire a hyperproliferative phenotype in both transwell cultures and spheroids. TGF-β signaling pathway inhibitors reduce MRC-5 proliferation, highlighting the key role of this soluble factor, detected in the supernatant of tumor cells, on fibroblasts activation. TGF-β, detectable in the supernatant of MRC-5 cells on transwell, without significant variations between mono- and co-culture conditions, was proved to be enough for inducing a hyperproliferative effect and resistance the antineoplastic drug gemcitabine in PANC-1. Co-culture with MRC-5 did not show any effect on PANC-1 migration, which is a functional response typical of the epithelial-mesenchymal transition (EMT) of cancer cells. Nevertheless, the expression of the epithelial marker E-cadherin, is reduced in PANC-1 co-cultured with MRC-5 in transwell model. So, even if TGF-β released by activated fibroblasts seems to not be sufficient to exert the functional responses of EMT in PANC-1, this is confirmed by the decrease of the E-cadherin.

In this study it has been confirmed the importance of TME TGF-β in the complex interaction between CAFs and cancer cells. Moreover, the study of this crosstalk can be important for the development of new therapies, aimed to target the TGF-β pathway, and therefore to limit the aggressive behavior of these desmoplastic tumors.