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Response of cancer-associated fibroblasts (CAF) to Targeted Radionuclide Therapy of pancreatic cancer microenvironment

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Pancreatic ductal adenocarcinoma (PDAC) is an aggressive cancer associated with a poor prognosis. Current treatments, such as chemotherapy and radiotherapy, fail to improve patient survival. This failure can be explained by PDAC high desmoplasia where cancer associated fibroblasts (CAFs) are the main contributor. Indeed, after conventional X-rays radiotherapy (X-RT), CAFs adopt a senescent phenotype associated with numerous soluble and insoluble factors secretion/release, referred as senescence-associated secretory phenotype (SASP). Through paracrine effects, SASP will also induce tumor cells aggressiveness (e.g. increased invasion and proliferation). However, unlike X-RT, targeted radionuclide therapy (TRT) delivers low doses at low dose rates and over several days. Therefore specific radiobiology of CAFS exposed to TRT must be addressed.
In this project, we exposed CAFs to TRT and investigated their biological response considering SASP induction. Immortalized human CAFs (iCAF136) were treated to TRT, using a CAF's specific/non-specific antibody fragment radiolabeled with lutetium-177 at different volumic activities (MBq/mL), or to X-RT at different doses (0, 2, 4, 8 Gy, Xenx Xstrahl™). Clonogenic survival of iCAF136 decreased in an activity/dose-dependent manner after TRT and X-RT. Moreover, for TRT it was target specific. While screening different senescence biomarkers (prolonged cell cycle arrest, senescence-associated β-galactosidase activity, persistent DNA damage and lamin B1 expression), we observed that X-RT, but not TRT, induce senescence of iCAF136. These results are confirmed in primary CAF cell line derived from patient biopsies.
Therefore, CAFs response to X-RT differs from TRT. We will next investigate SASP effects of X-RT or TRT treated CAFs on PDAC tumor cells.

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