Study of the cross-talk between CAFs and metastatic breast cancer in 3D cell model

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Abstract: The study of the tumor microenvironment (TME) becomes increasingly important in the development for 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 is continuously stimulated creating a loop of paracrine signals in both directions. This cross-talk leads to a high tumor progression and invasiveness, and to an increased resistance to therapy.

We investigated this cross-talk between CAFs and cancer cells in triple negative metastatic cancer models, choosing the murine cell line, 4T1, and the murine embryonic fibroblasts NIH-3T3, we developed two different 3D models, representative of a direct and indirect contact between the two cell types: the spheroid and the co-colture on Transwell. These two models were used to analyse some of the soluble mediators that have been seen to be most involved in the cross-talk CAF-epithelial cells in previously studies: the growth factors (such as TGF-β and PDGF), produced by cancer cells, that have been shown to be able to activate fibroblast into CAFs; the interleukin 6 (IL6), which is itself released by the fibroblasts converted in CAFs, and that is involved in the chemoresistance of cancer cells.

We demonstrated that the fibroblasts co-coltured for 7 days with 4T1 cells in Transwell or as spheroids did not express the typical CAF marker, α-SMA. On the other hand, these cells showed all the typical functional features of CAFs, such as iper-proliferation and an enhanced production of IL6, activated under the action of the growth factor released by tumor cells. The high amount of IL6 released by CAFs was able to induce resistance to the effect of the chemotherapeutic Doxorubicin on cancer cells and an increased proliferation and migration of cancer cells, due to the epithelial-mesenchimal transition, in line with the role of this cytokine in the aggressive phenotype of this cancer model.

Therefore, in this study it has been confirmed that the interaction between CAFs and cancer cells into TME is extremly complex and includes several factors which contribute to provide these tumors their typical phenotype. The study of this complexity is also important for the development of new therapies, aimed to target the differnt pathways involved in this cross-talk, and therefore to limit the aggressive behaviour of these tumors.