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P02.04.B CANCER-ASSOCIATED FIBROBLASTS IN LUNG CANCER BRAIN METASTASES: EFFECT ON CANCER CELL MIGRATION AND INVASION, AND MONOCYTE RECRUITMENT AND DIFFERENTIATION.

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BACKGROUND: Brain metastases (BrM) are a frequent complication of lung cancer with dismal prognosis. The presence of cancer associated fibroblasts (CAF) was recently described in the BrM microenvironment, but their engagement in BrM biology is largely unknown. In this study, we evaluated the effect of CAF derived from lung cancer brain metastases (BrM-CAF) on cancer cells and the recruitment and differentiation of monocytes. MATERIAL AND METHODS: Patient-derived BrM-CAF and cancer cells (BrM-CC) were isolated from lung cancer BrM. Normal fibroblasts were isolated from subgalear connective tissue. Monocytes were isolated from healthy donors' peripheral blood. Patient-derived cell cultures were characterized using immunocytochemistry and RNA expression profiling. A transwell assay and a 3D spheroid-based assay were used to assess migration and invasion, respectively; cell growth was quantified using a kinetic label-free cell counting assay. Monocyte differentiation was evaluated by flow cytometry. RESULTS: BrM-CAF expressed canonical fibroblast markers and their fibroblast-like phenotype was verified by RNA expression profiling. BrM-CC expressed epithelial markers. Conditioned media from BrM-CAF stimulated the migration of BrM-CC more than conditioned media from normal fibroblasts. In the invasion assay, the cancer cell invasive area was bigger in the presence of BrM-CAF; in addition, we observed a different pattern of invasion in BrM-CAF-containing spheroids, with more protrusions being formed. Direct co-culture with BrM-CAF diminished cancer cell proliferation. BrM-CAF conditioned media induced migration of monocytes. In direct co-culture with BrM-CAF, monocytes acquired a differentiated phenotype with both M1-like and M2-like features similar to that of tumor associated macrophages. CONCLUSION: Using patient-derived cultures, we show that BrM-CAF promote cancer cell migration and invasion but decrease their proliferation. Moreover, BrM-CAF can contribute to the recruitment of peripheral monocytes and their differentiation into tumor-associated macrophages. Taken together, these results demonstrate the role of BrM-CAF in shaping the brain metastatic microenvironment. FUNDING: This research was funded by the Charles University grant 342522; project NU22-03-00318 of Ministry of Health of the Czech Republic, Program Cooperatio, research area,,Oncology and Haematology"; Ministry of Education, Youth and Sports of the Czech Republic - LM2023053 of EATRIS-CZ and project National Institute for Cancer Research (Programme EXCELES, ID Project No. LX22NPO5102) by the European Union - Next Generation EU.