Extended Abstract Journal of Cell and Developmental Biology 2018
Vol.2 No.3

Cell science 2017: Bone marrow mesenchymal stem cells differentially affect the aggressiveness of cancer cell subtypes_ Tamara Lah Turnsek_ Proffesor, Inc,USA

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The most aggressive brain tumour glioblastoma multiforme is characterized by aggressive Glioblastoma (GBM) cell infiltration into surrounding brain parenchyma. We hypothesise that this invasion process is supported by Mesenchymal Stem Cells (MSCs), comprising GBM microenvironment. MSCs are recruited from bone marrow or endogenous brain tissue to the GBM tumour, but their interactions with GBM cells are still poorly understood. To elucidate the direct interaction between bone marrow-derived MSCs and two distinct GBM cell lines, U87 and U373, we tested cells' invasion in vitro, as well as in vivo, using zebrafish embryo model. Since proteases are crucial for GBM cell invasion, we focused on their role in invasion of cells in MSC/GBM direct co-cultures by analysing their expression at gene and protein levels and by applying selective protease inhibitors in the 3D-invasion model in vitro. We demonstrated that the effect of MSC/GBM cellular cross-talk on GBM cell invasion is GBM cell type specific. Namely, MSCs decreased the invasion of U87 cells, whereas they increased the invasion of U373 cells in vitro and in vivo. In contrast, both GBM cell lines increased the invasiveness of MSCs upon direct interactions. Moreover, we observed that increased U373 cell invasion in co-cultures correlated with increased expression of cathepsin B, calpain1, uPA/uPAR, MMP-9 and -14, all involved in the protease signalling cascade in GBM cells, leading to increased invasion via extracellular matrix degradation. Using selective inhibitors, we confirmed involvement of cathepsin B, MMP-9 and -14 in MSC-enhanced invasion of U373 cells. By contrast, decreased invasion of U87 upon co-culturing seemed to be independent of these proteases, implicating that the MSC regulatory potential in MSC/GBM co-cultures is dependent on GBM phenotype. Finally, we identified the genes, associated with cell response to TGF-ß that were differentially expressed in U87 vs. U373 cells that could explain different response of these cell lines to MSCs. Taken together, our findings are the first to suggest that the response of GBM cells to MSCs depends on the cancer cell's genetic subtype. This notion may be generalized to other types of stromal cells as well as to other tumours.

Conversely, direct cross-talk between MSC and the two glioblastoma cell lines improved MSC motility. MSC-enhanced invasion of U373 cells was assisted by overexpression of cathepsin B, calpain1, uPA/uPAR, MMP-2, -9 and -14, and increased activity of some of these proteases, determined by the effects of their selective inhibitors on invasion. In contrast, these proteases had no effect on U87 cell invasion under MSC co-bodying. Finally, we identified genes expressed differently in U87 and U373 cells that could explain the different response of these cell lines to MSCs. In conclusion, we demonstrated that THE cross-talk MSC/glioblastoma is different in both glioblastoma cell phenotypes, which contributes to tumor heterogeneity.

Particularly, after cell-cell interactions, chemokine CCL5 was extensively secreted from BMMSCs and a function blocking the antibody against the enhanced CCL5 cancer invasion BMMSC inhibited area. However, the antibody blocking CCL5 did not prevent the depth of the invasion. In addition, after exposure to BMMSC, expression of type I collagen mRN in CSTO cells was clearly regulated. Interestingly, also the high expression of type I collagen N-terminal propeptide (PINP) in vivo correlated with cancer-specific mortality of OTSCC patients, while there was no association between CCL5 cancerous tissue levels and clinical parameters. In conclusion, our results suggest that the interaction between BMMSC and carcinoma cells induce cytokine and matrix molecule expression, whose high level of type I collagen production is correlated with the prognosis of OTSCC patients.

This work presented at the 9th Annual Conference on Stem Cell and Regenerative Medicine September 25-26, 2017 Berlin, Germany