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Wharton's jelly-derived mesenchymal stem cell: Conditioned media induces apoptosis of pancreatic cancer

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Pancreatic cancer has an extremely poor prognosis, due to not only being a highly complex and aggressive malignancy (higher invasion and metastasis) but also is resistant to most therapies. Stem cell based treatments are being increasingly explored especially for those cancers that cannot be treated with targeted therapy. In the last decade, Mesenchymal Stem Cells (MSCs) have attracted significant attention as a result of their accessibility, tumor-oriented homing capacity and the transplantation feasibility. We propose a novel strategy of using MSCs as a cell-based anticancer therapeutic option. Till date, MSC-based therapy for pancreatic cancer has not been demonstrated. Our study demonstrates the feasibility using the pancreatic cell-line-based model (MiaPaCa-2 and PanC1). Expression of classical pancreatic cancer stem-cell markers i.e., CD44+/CD24+ in MiaPaCa-2 was 71.7±5.5% and PanC-1 showed 64.6±5.2% as compared to fibroblast cell line NIH-3T3 (19.1±1.4%) ($p=0.0001$). Sensitivity (IC50 dose response) towards Gemcitabine (Gem) and 5-Fluorouracil (5FU) was derived from MTT assay. PanC-1 showed relatively more resistance than MiaPaCa-2 (Gem-600 nM vs. 350 nM and 5-FU ≥1000 nM vs. 400 nM) respectively suggesting PanC1 is more resistant. To study the interaction between human Wharton's Jelly-derived Mesenchymal Stem Cells (hWJMSCs) and pancreatic cancer cells, co-culture assays were performed (ratio of 1:1; 48 hours). Markers of pro-apoptosis (Bax) and proliferation (Ki-67) were assessed by immunofluorescence. An inverse proportionate expression of Bax and Ki67 was observed when MiaPaCa-2/PanC-1 was treated with hWJMSCs (32.5% and 13% respectively). To verify these results, PKH-26-labeled hWJMSCs were overlaid on pancreatic tumor cells (1D). It was observed microscopically that PKH-26-labeled hWJMSCs proliferated two-fold in comparison to tumor cells. The effect of MSCs directly affecting the pancreatic tumor cell was reconfirmed with a proliferative marker Ki67. Functional properties EpCAM/CXCR4 (metastatic markers), Vimentin and E-cadherin (EMT markers) were evaluated using flow cytometry and qPCR. EpCAM was significantly ($p=0.0002$) decreased when treated with hWJMSCs in comparison to untreated tumor cells (MiaPaCa-2-23% vs. 37%; PanC1-20% vs. 50%). However, no significant change in CXCR4 expression was observed. To understand the cellular cross-talk between hWJMSCs and pancreatic tumor cells, the conditioned media derived from hWJMSC (CM) was studied. Expression of Bax was significantly further increased (58%) when treated with CM in comparison to hWJMSCs alone (32.5%). However, inhibition of EpCAM expression did not differ from hWJMSCs alone treatment. Migration and invasion potential of tumor cells were inhibited when treated with CM (MiapaCa-2-2.2 vs. 9 cells/field; PanC-1-5 vs. 10.5 cells/field), compared to untreated tumor cells. On frequency distribution histograms (flow cytometry) apoptotic events were characterized by a distinctive sub-G1 peak that represents oligonucleosomal DNA fragments. MiaPaCa-2 and PanC1 cells treated with CM showed significant ($p<0.005$) reduced number of cells entering G1 phase of the cell cycle i.e., at G0 M phase. This result was also evident as per DNA-fragmentation assay. Thus, our results suggest that Wharton's jelly-derived mesenchymal stem cells secretome can modulate the proliferation and migratory (oncogenic) capabilities of pancreatic tumor cells. In other words, paracrine factors released by hWJMSC might act as a cytotoxic biological agent. Hence, CM could be a novel cell-free therapeutic candidate. Presently, under investigation is the proteomic analysis of CM treated pancreatic tumor cells using 2D and MALDI/MS techniques.

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