Human bone marrow mesenchymal stromal cells (MSCs) decrease proliferation of human soft tissue sarcoma (STS) cell lines in vitro and do not affect local recurrence in xenograft models in vivo

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Background: MSCs are an attractive choice for regenerative medicine. We previously showed that MSCs enhance wound healing in animal models after radiotherapy and surgery. However, the effect of MSCs on tumor growth is not well understood. The potential use of MSCs to enhance wound healing after tumor resection in STS bearing patients is limited unless a favorable safety profile on tumor growth can be demonstrated. The purpose of this study was to evaluate in vitro the effect of MSCs on the growth of three human STS cell lines and its in vivo influence on the risk of local tumor recurrence.

Methods: Human myxofibrosarcoma and undifferentiated sarcoma primary cell lines developed using biopsy derived tumors from two patients and a commercialized human fibrosarcoma cell line (HT1080) were used. Proliferation assay of myxofibrosarcoma, undifferentiated sarcoma and fibrosarcoma cells co-cultured with MSCs was evaluated by flow cytometry (n=3) and bioluminescence emission (using eGFP/Fluc transduced myxofibrosarcoma, undifferentiated sarcoma and fibrosarcoma cells) (n=5) and compared with non-cocultured cells.

Two xenograft models were developed with male NOD/SCID γc null mice (4-8 weeks old) (n=76) harbouring the myxofibrosarcoma primary tissue line and the fibrosarcoma cell line previously transduced with eGFP/Fluc. For the myxofibrosarcoma (n=31), the patient’s original tissue sample was passaged consecutively to a minimum of 3 mouse generations before the xenograft model was used. For the fibrosarcoma xenograft model, eGFP/Fluc HT1080 (1 x10^6 cells) were injected under the dorsal skin (n=45). When tumors in both xenograft models reached 1cm in diameter, they received localized radiotherapy (single dose of 10Gy) and 48hr later were resected. MSCs (2 x10^6 cells) (n=40) or medium alone (n=36) was injected subcutaneously adjacent to the wound after tumor resection. Histological and in vivo bioluminescence analyses were performed 3 and 12 weeks after surgery.

Results: In vitro proliferation assay. The myxofibrosarcoma-MSCs co-cultures showed lower bioluminescence emission (3.9 x10^7±0.5) vs control (6.2 x10^7±1.8 p sec^{-1} cm^{-2} sr^{-1}; p<0.05) after 72 hours of co-culture. Undifferentiated Sarcoma-MSCs co-culture bioluminescence determination was lower (58.5 x10^7±17) vs control (135 x10^7±38 p sec^{-1} cm^{-2} sr^{-1}; p<0.01) after 64 hours of coculture. Fibrosarcoma-MSCs co-cultures showed diminished bioluminescence emission (18 x10^7±5.9) vs control (35.7 x10^7±10 p sec^{-1} cm^{-2} sr^{-1}; p<0.05) after 72 hours of coculture. These differences remained constant or increased up to the endpoint (120 hours). The flow cytometric proliferation assay showed an increase in mean fluorescence intensity after 4 and 6 days of myxofibrosarcoma-MSCs co-culture (335±15.5) compared with control (210±2, p<0.001). No significant differences were found in the mean fluorescence intensity in the other groups. In vivo recurrence assay. For mice bearing the fibrosarcoma cell line, in vivo bioluminescence imaging performed 3 weeks after surgery showed similar emission intensity in MSC-treated mice (543.9 x10^7±232) as controls (1378 x10^7±402 p sec^{-1} cm^{-2} sr^{-1}, p=0.08). Histological recurrence was similar in MSC-treated animals (40%) and control (70%) with a relative risk of 0.5714 (p=0.07). For mice bearing the myxofibrosarcoma tissue line, histological recurrence at 12 weeks was similar in MSC-treated animals (55.5%) and controls (60%) (p=ns).

Conclusions: We have demonstrated that MSCs decrease the proliferation of myxofibroarcoma, undifferentiated sarcoma and fibrosarcoma (HT1080) cell lines in vitro and have no effect on local fibrosarcoma or myxofibrosarcoma recurrence in vivo. Our data suggest that further studies to explore the use of MSCs in enhancing wound healing after sarcoma surgery is warranted.