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Mesenchymal stem cells (MSCs) and TRAIL-induced apoptosis in pancreatic and prostate carcinomas

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1 Introduction

Homing of manipulated mesenchymal stem cells (MSCs) to glioma xenograft models has been demonstrated in recent reports. MSCs may contribute to the formation of tumor stroma and tumor blood vessels and thus may be ideal vehicles for the targeted transfer of therapeutic genes.

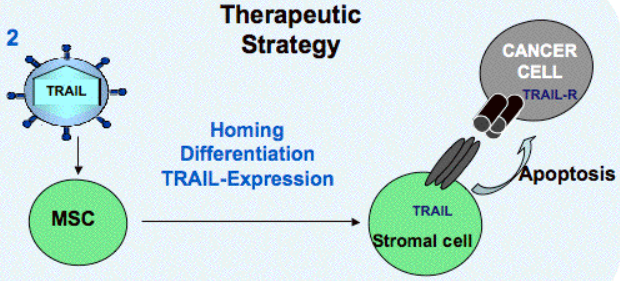
The death ligand tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is a potent inducer of apoptosis in transformed cells, while sparing most normal cell types. Lentiviral transduction of MSCs with TRAIL may result in TRAIL-overexpressing tumor stroma and endothelial cells which in turn induce paracrine programmed cell death in surrounding tumor cells.

Methods

-TRAIL sensitivity of established and freshly isolated human prostate carcinoma cells towards recombinant TRAIL was tested by MTT assays and annexin-staining followed by flow cytometry.

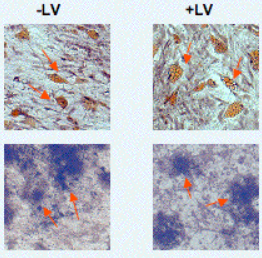
-For therapeutic intervention, lentiviral vectors are constructed for expression of TRAIL. MSCs are selected from intraoperatively harvested bone marrow. Migration to cancer cells was detected in a transwell-assay. To detect homing towards cancer cell spheroids MSCs were stained with CellTracker Red and spheroids with CellTracker Green.

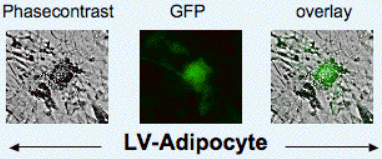
2 Therapeutic Strategy



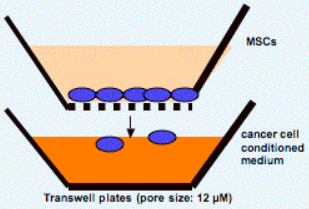
3 Potential of lentivirus (LV) infected MSCs to differentiate

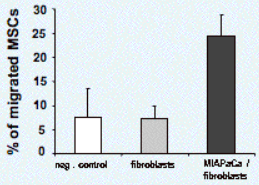
MSCs maintain the potential to differentiate into adipocytes (a, Oil-Red-O staining) and osteoblasts (b, van Kossa staining) following lentiviral infection



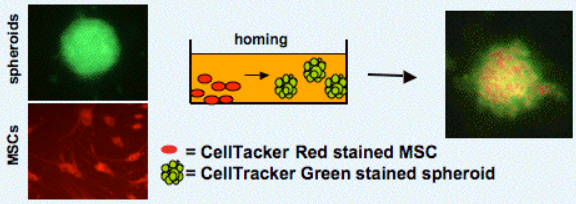


4 Specific *in vitro* homing of MSCs to tumor cells



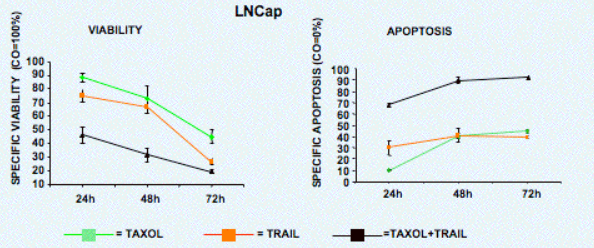


Homing of MSCs towards cancer cell spheroids

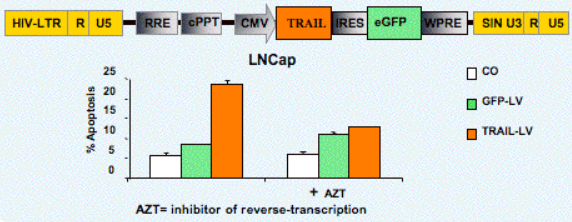


MSCs homed into cancer cell spheroids composed of pancreatic cancer cells (MIA PaCa), fibroblasts and endothelial cells (HUVEC)

5 Recombinant TRAIL induces apoptosis and sensitizes tumor cells for chemotherapy (Taxol)



Lentiviral TRAIL is cloned and specifically induces apoptosis



AZT= inhibitor of reverse-transcription

6 Conclusion /Take home message

Autologous MSCs may be a powerful tool for the transfer of therapeutic genes into tumors, e.g. for specific induction of tumor apoptosis

Outlook

-Co-culture of cancer cells with MSCs infected with lentiviral TRAIL (Donor/Target Kill Assays)

-Transfer of therapeutic genes via MSCs in pancreas and prostate xenograft models and analysis of tumor growth and tumor apoptosis