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SESSION 6 GROUP B  
3:00 PM – 4:30 PM

67

Breast Cancer Cell Ablation Using Nanoparticle-Engineered Adipose-Derived Stem Cells

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PURPOSE: Inflammatory breast cancer (IBC) is an aggressive disease characterized by the formation of tumor emboli, rapid local invasion, and lymphatic dissemination. Furthermore, IBC rapidly develops therapeutic resistance and evades immune surveillance and attack. For these reasons, the treatment of inflammatory breast cancer is extremely challenging and new therapeutic approaches are needed. Numerous studies have shown that adipose derived stem cells (ASCs), which are abundant in breast tissue, are recruited to the tumor microenvironment where they influence tumor progression. We have previously demonstrated the feasibility of using nanoparticles in conjunction with ASCs in treatment-resistant breast cancer. In this study, we show that ASCs localize to IBC tumor emboli and can be used as a targeted delivery vehicle for cancer nanotherapeutics.

METHODS: We tested the feasibility of this hypothesis by labeling ASCs with photothermal nanoparticles (GNS) and evaluating their ability to be delivered to 2D and 3D models of breast cancer cells for targeted tumor cell ablation. A panel of breast cancer cell lines [IBC (SUM149/SUM190), non-IBC (BT474M1/MD-MBA-231), and a drug-resistant isogenic variant (rSUM149)] were employed to evaluate: 1) The migratory capacity of GNS-bearing ASCs toward tumor cells; and 3) The ability of GNS-labeled ASCs (GNS-ASCs) to target and ablate tumor cells and emboli after photothermal treatment. Overall, the effects of photothermal therapy on cell viability were assessed using various laser intensities and confirmed with a live/dead fluorescent stain. In addition, tumor emboli were sectioned and imaged with MPM to demonstrate GNS penetration and distribution.

RESULTS: In the cell lines tested, GNSs displayed rapid cellular uptake in both 2D culture and in 3D tumor emboli. Furthermore, GNS-labeled ASCs displayed robust migration toward cancer cells. Live/dead staining confirmed effective photothermal treatment in all cultures, including GNS-ASC co-cultures, with a clear zone of cellular death. For tumor emboli studies, GNSs and GNS-ASCs allowed for bright fluorescent monitoring of tumor emboli using MPM, and cross-sectional imaging demonstrated nanoparticle penetration into the embolic core. GNS-labeled tumor emboli were successfully photothermally ablated following laser irradiation. Similar results were achieved with GNS-ASC and emboli co-cultures.

CONCLUSION: Taken together, these results highlight the ability of ASCs to effectively deliver nanoparticles (GNS) to inflammatory breast cancer emboli. This allows for the targeted photothermal ablation of IBC tumors. These studies demonstrate our ongoing development of a novel approach to treat therapeutically resistant breast cancers.

68

Deferoxamine Preconditioning of Irradiated Tissue Increases Fat Graft Volume Retention

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PURPOSE: Hypovascularity due to irradiation therapy causes the skin to become fibrotic and causes soft tissue to atrophy. Fat grafting has been shown to improve the quality of irradiated skin, but volume retention of the graft is significantly decreased. Deferoxamine is an FDA-approved iron-chelating medication, that has been shown to increase angiogenesis. Preconditioning of irradiated sites with this compound may reduce radiation induced ischemia and enhance fat graft survival.
METHODS: Immunocompromised nude-mice underwent external beam irradiation of the scalp. Five weeks later, mice either received seven deferoxamine treatments (1mg in 100ul) or saline subcutaneously to the irradiated area every other day. Laser Doppler analysis (LDA) was recorded prior to irradiation, following irradiation, and 24 hours following each treatment. Human fat grafts were then injected in the subcutaneous plane of the scalp and volume retention measured by CT scan over 8 weeks. Finally, skin and fat samples were evaluated histologically for vasculature, dermal thickness, and fat graft quality.

RESULTS: After 4 treatments with deferoxamine, a significant increase in microvasculature was observed using LDA. There was also significance with the development of microvasculature in the fat graft with LDA. Using microCT, we observed a significant increase in fat graft volume retention with the deferoxamine treated group compared to the saline treated group, and this was paralleled by improved histologic staining of skin and fat grafts.

CONCLUSION: Our results show increased microvasculature and increased fat graft volume retention with deferoxamine treatment. Deferoxamine treatment may also promote beneficial effects in dermal thickness and in quality scoring of the fat grafts, thus leading to a potential clinical application in radiation damaged soft tissue.

Stem Cells Harvested from Bone Marrow and Adipose Tissue Demonstrate Equivalent Healing but Through Different Mechanisms in a Murine Model of Irradiated Mandibular Fracture Healing

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PURPOSE: The difficulty of harvest and relative scarcity of bone marrow stromal cells (BMSCs) has limited the widespread use and clinical application of this technology, thereby necessitating inquiry into other therapies including adipose-derived stromal cells (ASCs). The goal of this study was to compare the ability of ASCs and BMSCs to heal mandibular defects and understand the mechanism through which this occurs. We hypothesize that ASCs will enhance fracture healing by improving vasculogenesis, while BMSCs will directly affect osteogenesis.

METHODS: Male Lewis rats were radiated (35Gy), and subsequently underwent mandibular osteotomy with external fixation with implantation of two million BMSCs (n=12) or ASCs (n=16) marked with Green fluorescent protein (GFP). After 40 days, union rates were evaluated using microCT. Confocal microscopy visualized the contribution of ASCs/BMSCs to the bone regenerate. Quantitative polymerase chain reaction of ASCs/BMSCs compared expression of osteogenic and vasculogenic genes. Coculture of ASCs (n=3) or BMSCs (n=3) with human umbilical vein endothelial cells (HUVECs) was performed in vitro in transwells to measure tubule formation as a marker of vasculogenesis.

RESULTS: ASC-implantation resulted in higher union rates than BMSC-implantation (union rate: 94% vs. 66%). These cells contribute indirectly to fracture healing, as GFP was not visualized at the site. BMSCs expressed osteogenic genes including osteopontin to a significantly greater degree than did ASCs, while ASCs expressed greater levels of vascular endothelial growth factor. This translated to greater tubule formation among HUVECs co-cultured with ASCs than with BMSCs (64.3 ± 7.3 vs. 23.3 ± 2.6, p=0.0008), and increased vasculogenesis in vivo in mandibles after ASC implantation.

CONCLUSIONS: ASCs heal fracture defects better than BMSCs. This effect is likely mediated by indirect modulation of vasculogenesis, rather than by a direct effect on osteogenesis. Clinicians interested in cell-based therapies for irradiated bone injury should consider ASCs as a promising option, given their abundance, ease of acquisition, and improved fracture healing.

Generation of Parathyroid Cells from Human Adipose Derived Stem Cells

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