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Endothelial progenitor and dendritic cells as probes for cellular MRI and gene delivery vehicles

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INTRODUCTION: Gene therapy holds enormous therapeutic potential for breast cancer treatment. However, the infiltrative nature of breast cancer poses a problem for successful delivery of needed genes to the sites of invading tumor cells, when administered locally. In addition, lack of an efficient vector and delivery system itself limit the effectiveness of systemically delivered genes. Recently, stem/progenitor cells have been considered as delivery vehicles for corrective genes to the site of interest and it is outmost necessary to monitor the migration and homing of the genetically modified administered cells. Current *in vivo* imaging techniques lack the ability to track the real time cell migration and homing with the acceptable resolution to the cancer tissue. The purpose of this study was to determine if endothelial progenitor (EPCs) and/or dendritic cells (DCs) can be used as gene delivery vehicles as well as cellular probes for magnetic resonance imaging (MRI).

METHODS: Human breast cancer MDA-MB-231 cells were subcutaneously implanted in the right flank of nude mice. EPCs (isolated from fresh human cord blood) and DCs (differentiated from the cord blood CD34+ or CD14+ cells) were genetically transformed to carry hNIS gene using adenoviral vectors and magnetically labeled with ferumoxides-protamine sulfate (FePro) complexes. To confirm transfection, technetium-99m pertechnetate (Tc-99m) uptake study was performed and the radioactivity was determined by a gamma counter. Mean intracellular iron was determined by UV/VIS spectrophotometric method using hydrochloric acid and potassium ferrocyanide. Cells were administered intravenously in tumor bearing mice when tumors grew to 0.5 cm in sizes. MRIs were acquired 7 days after cell injection and SPECT images were acquired within the 24 hours of performing the MRI. T2, T2* and 3D GRE images were obtained using a 7 Tesla, 20 cm bore superconducting magnet interfaced to a BRUKER console. After SPECT, whole tumors were collected for the *ex vivo* measurement of radioactivity, and immuno and histochemical staining to confirm the presence of administered, genetically transformed cells.

RESULTS: More than 90% cells were labeled. Transfected cells exhibited significantly increased radioactivity as compared to the non-transfected cells. MRI images showing low signal intensity areas around the tumors in mice that received iron labeled cells indicated the accumulation of administered cells, also confirmed by Prussian blue tissue staining. In addition, SPECT images showed significantly higher radioactivity in tumors (compared to background activity) in animals that received transfected cells.

CONCLUSION: Our study indicates that both EPCs and DCs can be used to deliver genes by systemic administration. Genetically transformed, magnetically labeled DCs or EPCs can be used both as delivery vehicles and as cellular probes for detecting *in vivo* migration and homing of cells by MRI. This method can be used in the future development of gene therapy approaches where genetically modified cells can be tracked by real time *in vivo* MR scanning in different disease processes.