TRACKING OF SPIO LABELED NATURAL KILLER CELLS TO EPCAM POSITIVE PROSTATE CANCER WITH MR IMAGING

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Purpose:

The purpose of our ongoing study is to develop and optimize a technique for labeling of human natural killer (NK) NK-92 cells and genetically engineered NK-92-scFv(MOC31)-zeta cells, targeted to the Ep-CAM (epithelial cell adhesion molecule) on prostate cancer cells, with superparamagnetic iron oxides (SPIO). SPIO labeled NK cells are injected intravenously into rats with implanted Ep-CAM positive prostate cancers and the accumulation of the labeled cells in these tumors is monitored with a non-invasive magnetic resonance (MR) imaging technique.

Methods:

NK-92-scFv(MOC31)-zeta cells were genetically modified by retroviral transduction in order to express a chimeric antigen receptor specific to the EP-CAM antigen, which is overexpressed on the surface of prostate cancer cells. NK-92 and NK-92-scFv(MOC31)-zeta cells were labeled with the FDA-approved SPIO Ferumoxides (Feridex, Berlex) using simple incubation and transfection (protamine and lipofectin) techniques. Labeling efficiencies were evaluated with MR imaging and spectrometry. Subsequently, SPIO labeled NK-92 (group 1, n=6) and NK-92-scFv(MOC31)-zeta cells (group 2, n=6) were intravenously injected into the tail vein of twelve rats with subcutaneously implanted EP-CAM positive DU145 prostate tumors. The accumulation of the NK cells in the tumors was monitored by MR imaging. T2-weighted MR scans were obtained before, at 1h and 24h after cell injection (p.i.). The MR signal intensity of the tumors was measured, the signal enhancement on postcontrast images was quantified as ΔSI(%) data and these MR data were correlated with the presence of NK cells in the tumor tissue, as confirmed by immunohistochemistry.

Results:

Both the NK-92 and the genetically modified NK-92-scFv(MOC31)-zeta cells showed a significant Ferumoxides uptake and a significant MR signal compared to non-labeled control cells (Figure 2). The NK cell labeling efficiency was higher after transfection with lipofectin than after labeling by simple incubation or by incubation with protamine sulfate. After intravenous injection of $15x10^6$ Ferumoxides-labeled NK-92-scFv(MOC31)-zeta cells into tumor-bearing rats, MR showed a progressive signal decline of EP-CAM-positive prostate cancers at 1h and 24h p.i. (Figure 1). By contrast, the injection of $15x10^6$ Ferumoxides-labeled parental NK-92 cells, not directed against EP-CAM receptors, did not cause significant signal intensity changes of the EP-CAM-positive tumors. Immunohistochemistry confirmed an accumulation of the genetically engineered, EP-CAM targeted, but not the non-targeted NK cells in the EP-CAM-positive prostate cancers.

Conclusion:

The human NK-92 and NK-92-scFv(MOC31)-zeta cells can be efficiently labeled with a clinically applicable SPIO contrast agent. The accumulation of SPIO labeled NK cells in prostate cancers can be monitored with MR imaging. Our MR-based NK cell tracking technique would be in principle applicable to monitor new NK-cell based immunotherapies in patients with prostate cancers.

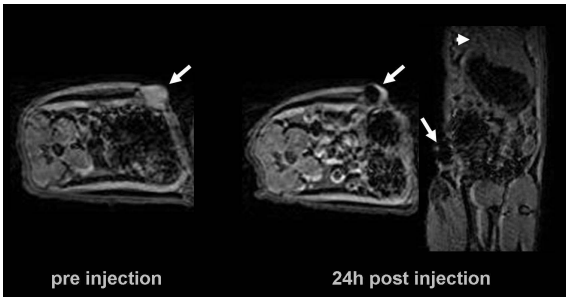

*Figure 1: T2*weighted MR images of rats with implanted EpCAM positive DU145 Prostate tumors (white arrows) show a decline in signal intensity after injection of Ferumoxides-labeled anti-EpCAM directed NK-92-scFv(MOC31)-? cells, indicating a specific NK-cell accumulation in the tumor tissue.*

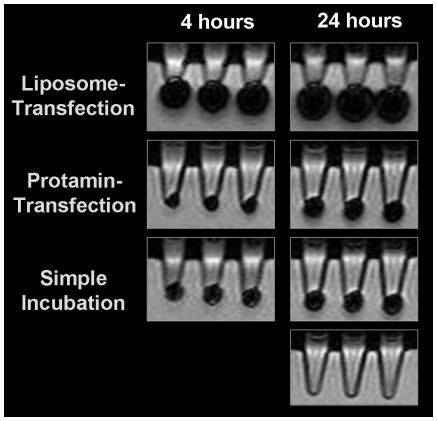

Figure 2: T2-weighted MR images of NK-92 cells in test tubes, labeled with iron oxide contrast agent by simple incubation or transfection techniques. Labeled cells show a strong T2*-signal effect.*