Electro-nanotherapy Enhanced Delivery of Superparamagnetic Iron Oxide Nanoparticles in Liver Tumors: A Novel Means of Locoregional Drug Delivery

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Introduction

The use of functionalized superparamagnetic iron oxide nanoparticles (SPIO) as diagnostic and therapeutic agents in oncological applications is limited by their reduced tumor uptake due to sequestration by the reticuloendothelial system (RES) following systemic injection (IV) . Electroporation (EP) is a technique which can modulate the localized influx of therapeutics into cells through the rapid, reversible induction of transmembrane pores. Its clinical potential is high [1], however the lack of real time assessment of successful EP intervention reduces the therapeutic impact of the procedure. By employing EP of tissues following systemic injection of imaging and therapeutic nanoparticles one can possibly circumvent sequestration by RES and enhance the local uptake, but also monitor the actual bio-distribution of the agent in real time using non invasive MRI. Here we describe electro-nanotherapy (e-NT): the use of electroporation to enhance the local delivery of SPIOs into tumors. We hypothesized that A) e-NT would increase intra-tumoral SPIO uptake, and B) high resolution MRI T_2 and T_2* maps would provide a non-invasive means of assessing tumor SPIO distribution in a rat liver tumor model.

Methods and Materials

N1S1 liver tumors were induced in 20 Sprague-Dawley rats. Two cohorts were selected. One underwent e-NT while the second one served as control group. Both groups received doxorubicin functionalized SPIOs, serving as dual imaging and therapeutic agents, at 0.56 mg/kg body weight IV. For the e-NT group, following SPIO delivery, EP was applied directly to tumors at 500-V/cm field strength (8 pulses, 100-µs pulse duration). T_2 and T_2*maps were acquired using a Bruker 7T ClinScan MRI with multi spin echo and multi gradient echo sequences. Pre and post-treatment MRI scans s were performed for both groups to detect SPIO delivery. Both image sets were fit to monoexponential equations voxelwise to extract T_2 and T_2* maps using Matlab 7.1 (MathWorks, Natick, MA). A specific region of interest (ROI) was drawn in each T_2 and T_2* map, then averaged over the ROI to generate a mean value. After euthanasia, tumors were harvested for evaluation by ICP-MS for iron concentration. SPIO uptake between the groups was compared using ANOVA with post-hoc Tukey analysis, with $p<0.05$ considered significant.

Results and Discussion

Electro-NT significantly increased tumor SPIO uptake over IV delivery alone. Tumors that received e-NT had a 6.3 fold increase in SPIOs over controls (165 vs. 26.1 µg Fe/g, $p<0.05$). This correlated well with MRI results which exhibited significant T_2 and T_2* decreases in regions with high NP uptake (T_2 : 33.5 ms vs. 103.4 ms, $p<0.05$). Shown are two representative pre e-NT (fig 1a) and post e-NT (fig 1b) T2W images . The post-EP image shows substantial T_2 signal decay, indicating uptake of SPIOs into the hepatoma. Fig 2(a) and 2(b) show the T_2 maps depicting the regions of high (T_2 ~100 msec) and low (T_2~30 msec) SPIO uptake (color bar is in msec). Also shown in Fig 2(c) is the post contrast T_2 map, demonstrating that tumor SPIO uptake is localized to only the e-NT treated zone.

Conclusion

Electro-NT dramatically improves tumor uptake of therapeutic SPIO over conventional IV administration. Furthermore, increased uptake is specifically localized to the treated zone. 7T MRI is capable of monitoring this SPIO uptake non-invasively and also provides a tool to assess the localized e-NT response. Current work is being conducted to further exploit the potential of this loco-regional imaging and drug therapy.

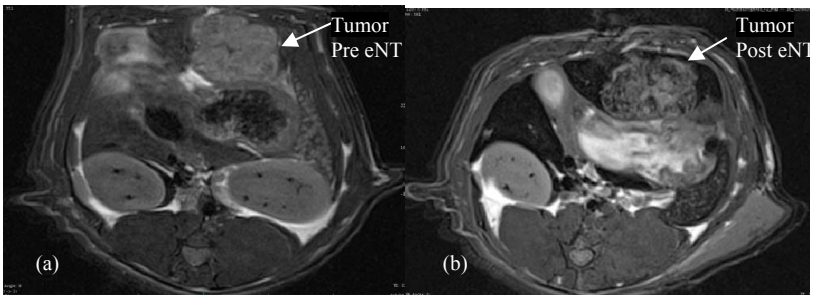
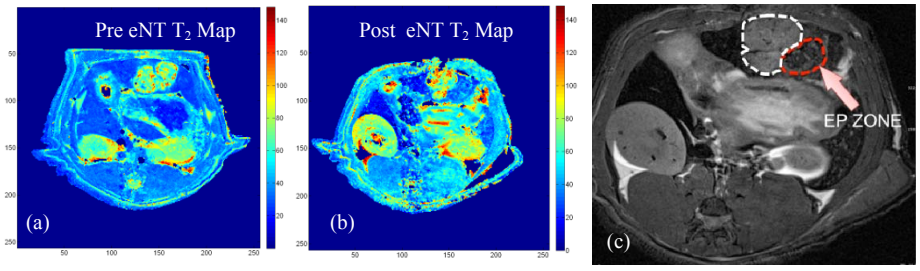


Fig 1 (a,b) *T_2-weighted GRE images of a rat hepatoma acquired before (left) and after (right) treatment with IV SPIO injection (0.56 mg/kg) and e-NT (8 pulses, 500 V/cm).*

Fig 2 (a,b) *T_2-maps with color bar* **(c)** *T2W image depicting localized SPIO uptake limited to the e-NT treated region*



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