THERANOSTIC PROSPECTS OF GADOLINIUM-BASED MESOPOROUS SILICA NANOPARTICLE PROBES FOR FUNCTIONAL MRI

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Target audience medical professionals, oncologists; preclinical researchers in the field of contrast agent development and targeted drug delivery.

Purpose

In this work we assess the potential of a novel mesoporous nanoparticle MRI probe with theranostic prospects for targeted drug delivery. Our gadolinium-doped mesoporous silica nanoparticles (MSNPs) have a T_1 relaxivity, r_1, of 12.3 mM^{-1} s^{-1}. More importantly, our mode of Gd incorporation maintains the pores unoccupied for drug loading to keep the theranostic advantages of MSNPs for future studies, in contrast to the more conventional method of utilizing the MSNPs as carriers for Gd-chelates, equivalent to the clinically used Dotarem® (Gadoteric acid) and Magnevist® (Gadopentetic acid). In this work we demonstrate the first step of our project: targeted delivery of the probe to the tumor tissue.

Materials and Methods

For subcutaneous tumor model we used ARN8 melanoma cell line ($1x10^6$ cells mixed with Matrigel 1:0,5) injected s.c. into the right flank of NODscid-γ mice. Animals were randomly assigned to three groups, based on the injected agents: Gd-doped MSNPs (GadoNPs), pristine (non-doped) MSNPs (NPs), and Dotarem. All agents were injected intravenously, via tail-vein cannulation. The dose of GadoNPs and NPs was 20 mg/kg BW, corresponding to approximately 8 µmol Gd/kg BW, while for Dotarem it was 250 µmol Gd/kg BW.

Scanning was performed on a 7T horizontal-bore preclinical scanner (Pharmascan 70/16, *Bruker Coorporation*, Germany), using a 40 mm ID mouse-body quadrature volume resonator. T_1-weighted images (RARE, TE/TR = 9/1000, slice = 1mm, FOV = 3.5 x 3.5 cm^2, Matrix = 256 x 256, NA = 4, scan time = 3 min 12s) were collected at multiple time points: before injection, immediately after, and at 24, 48, 72, 96 and 168 hours after injection of GadoNPs; before injection, immediately after, and at 24 hours after injection of NPs and Dotarem.

To quantify signal enhancement in the tumor, we first obtained average signal intensity (SI) in ROIs within the tumor, nearby muscle tissue, kidney and noise region. We then normalized the SI in the tumor to the SI in the non-enhancing muscle tissue to account for other factors influencing SI, such as B_1 inhomogeneity, receiver gain, variations in contrast agent dose.

Results

Despite significantly lower Gd exposure per dosage with GadoNPs than Dotarem, there was a detectable increase of signal intensity on T_1 weighted images of GadoNPs treated tumors at 24 hours post-injection. At 48, 72 and 96 hours SI slightly decreased and then grew again at 168 hours (1 week) postinjection, possibly due to microstructural changes occuring during tumor growth. Pristine NPs did not affect SI in any of the selected ROIs, either immediately post-injection or at 24 hours, while Dotarem had a predictable post-contrast SI increase, which returned to pre-injection levels in 24 hours.

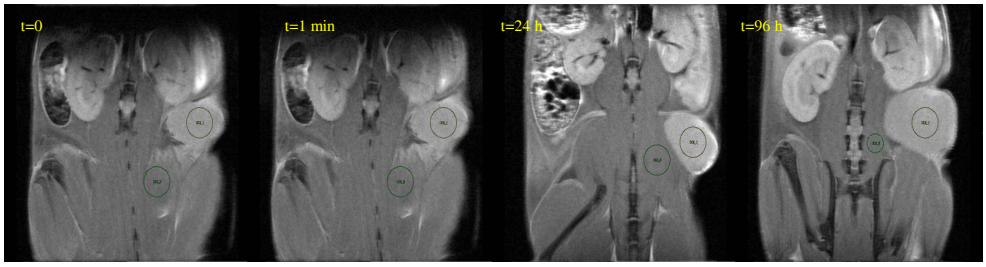

Figure 1: T_1-weighted images of the melanoma-bearing mouse before, immediately after, 24 hours and 96 hours after GadoNPs injection (ROIs from tumors and muscles shown).

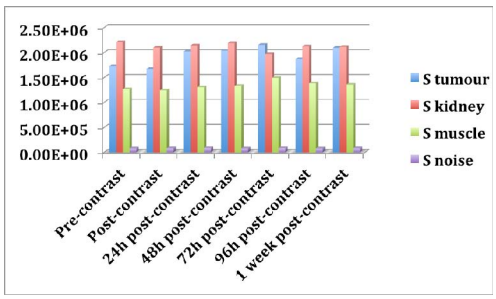

Figure 2 (left): Evaluation of longitudinal SI in tumors, kidneys and muscles in GadoNPs injected mice (n=3).

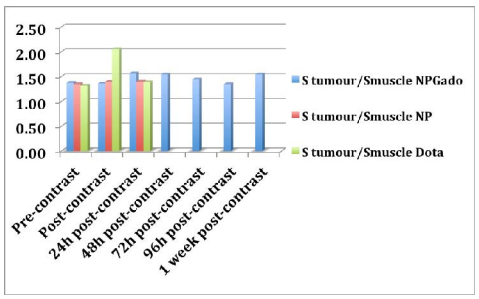

Figure 3 (right): Evaluation of longitudinal tumor-to-muscle SI in GadoNPs, pristine NPs, and Dotarem injected animals.

Conclusions

Gadolinium-doped MSNPs are retained for at least 96 hours in tumor tissue by passive tumor targeting and can be visualized by MRI, suggesting feasibility of using this NP platform for future theranostic applications. Further studies will focus on larger sample size, slower-growing tumor models, higher dose of GadoNPs, and on active tumor targeting via surface modification of nanoparticles with tumor-specific ligands.

References

1. Zhang J, et al. Synthesis and characterization of pore size-tunable magnetic mesoporous silica nanoparticles. J Colloid Interface Sci. 2011 Sep 1;361(1):16-24.
2. Rosenholm JM, et al. Nanomedicine. Nanoparticles in targeted cancer therapy: mesoporous silica nanoparticles entering preclinical development stage. 2012 Jan;7(1):111-20.
3. Wartenberg N, et al. A gadolinium complex confined in silica nanoparticles as a highly efficient T1/T2 MRI contrast agent. Chemistry. 2013 May 27;19(22):6980-3.