MR and optical target imaging for intracranial tumors with chlorotoxin conjugated nanoprobes

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Introduction

Pediatric brain cancer is the most common malignant solid tumor and is leading cause of cancer deaths and disability in children. Target imaging is one of the important key factors in order to improve the cancer diagnosis, treatment and treatment response monitoring. Despite its high availability and usage as an important noninvasive diagnosis, MRI has not been greatly successful in target imaging for brain tumors mainly due to relatively low specificity of MRI alone and inability of contrast agent crossing the blood brain barrier. In the present study we attempted to achieve the high specificity for MR and optical imaging of pediatric brain cancer using iron oxide nanoparticles coated with polyethylene glycol(PEG)-chitosan and conjugated with targeting peptide, chlorotoxin.

Method

Nanoparticulated contrast agents were synthesized with their core materials (referred to as NPCP) of iron oxide, PEG-chitosan coating and chlorotoxin (CTX) conjugation. Pre-contrast images were obtained prior to the administrations of the nanoprobes (NPCP-CTX for MRI and NPCP–Cy5.5-CTX for optical imaging) and post-contrast time course imaging was then performed to monitor longitudinal behavior of the nanoprobe within a tumor (ND2:SmoA1 or Smo) mouse in vivo after the nanoprobe injections. The tumor type has been a mouse model of human medulloblastoma (D283). The mice were suffering from the genetically engineered small scale brain tumors developing in cerebellum with the blood brain barrier intact [1]. Transverse relaxation rate R2 maps were generated with multi-echo multi-slice images to investigate the nanoparticle uptake by brain tumor. MRI was conducted on a Bruker 4.7 T horizontal bore magnet equipped with Varian INOVA spectrometer. Custom-built mouse holders were used along with a birdcage RF coil (63 mm i.d.) for dual mouse imaging and alderman grant type RF coil (25 mm i.d.) for single mouse head imaging. In parallel fluorescence imaging was performed on a Xenogen IVIS 100 system.

Results

Base materials (NPCP: nanoparticles coated with PEG-chitosan) of our nanoprobes without CTX conjugation were synthesized in different iron concentrations to measure R2 (1/T2) values and compared to commercial Feridex IV particles as shown in Fig. 1. The increased relaxivity of NPCP over that of Feridex IV indicates greater MR contrast enhancement for NPCP. Transverse relaxation rate R2 values were measured for longitudinally acquired images as displayed in Fig.2 and colored R2 brain maps were overlaid on top of proton density weighted images. Significant R2 increase was observed for a tumor mouse injected with NPCP-CTX at 48 hours post injection in comparing with other three cases: wild type (WT) mouse injected with NPCP-CTX, tumor mouse injected with the control particles (NPCP without CTX conjugation) and WT mouse injected with NPCP particles. Figure 3 displays optical images acquired at 120 hours after administrations of NPCP-Cy5.5-CTX, NPCP-Cy5.5 and with no injection for tumor mice. Particle uptake is clearly observed for the mouse injected with targeting agent (NPCP-Cy5.5-CTX). Inset images show optical images taken for excised brain tissues after each last time point imaging.

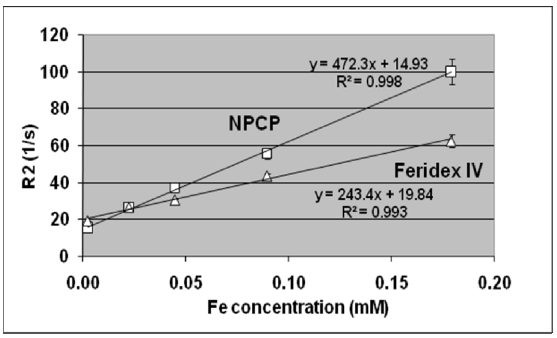

Figure 1. R2 as a function of iron concentration of NPCP and Feridex IV.

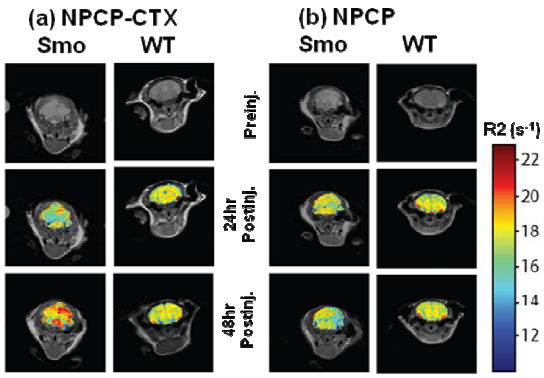

Figure 2. In vivo MR images acquired before and after administrations of target agent NPCP-CTX (a) and control particles NPCP (b) for both tumor (Smo) and wild type (WT) mice.

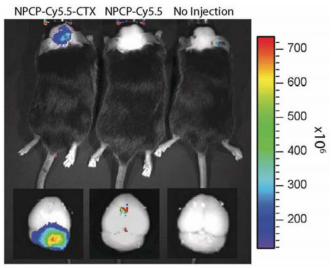

Figure 3. In vivo optical images acquired at 120 hrs post-injection.

Discussion and conclusion

We demonstrated the high specificity (through sufficient particle uptakes) of our developed targeting nanoprobe NPCP-CTX and NPCP-Cy5.5-CTX for MR and optical imaging, respectively. Furthermore, the nanoprobes synthesized for MR and optical imaging showed the ability to pass through the blood-brain-barrier (BBB) for the BBB intact mouse tumor model.

References

1. Veiseh et al. Tumor paint: a chlorotoxin: Cy5.5 bioconjugate for intraoperative visualization of cancer foci. Cancer Res 67, 6882-6888 (2007).