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Estimating drug delivery using hybrid system for simultaneous dynamic MRI and fluorescence tomography

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Abstract

Optical tomography is often coupled with high resolution imaging modality like MRI to provide functional information associated with specific anatomical structure noninvasively. MRI-coupled paired agent fluorescence molecular tomography (MRI-PAFT) is a hybrid imaging modality capable of noninvasively quantifying drug-target engagement in vivo utilizing a targeted and an untargeted fluorescence agent. This study compares the uptake kinetics of MRI contrast agent and fluorescence agents in tumor and normal tissue, and demonstrates the potential of utilizing MRI contrast agent kinetic and targeted fluorescence agent kinetics to quantify targeted tumor receptor concentration in glioma tumor model.

Keywords

Paired-agent imaging; fluorescence tomography; MRI-coupled optical imaging; uptake kinetic; orthotopic glioma small animal model

1. INTRODUCTION

Previously, we showed that MRI-coupled paired agent fluorescence molecular tomography (MRI-PAFT) is capable of noninvasively quantifying drug-target engagement in vivo [1–3]. However, the translation of paired-agent fluorescence tomography to clinical application is challenging. Although paired-agent imaging using receptor targeted and untargeted fluorescence imaging agent has demonstrated sensitivity at detecting tumor margin in ex vivo clinical application, the adoption of the paired-agent imaging scheme in vivo for tomography requires simultaneously administering three different imaging agents: untargeted fluorescence imaging agent, targeted fluorescence imaging agent, and MRI contrast agent, making it not ideal for clinical practice. Moreover, the utilization of MRI hybrid imaging system should not be limited to extracting anatomical information for volumetric reconstruction; the true potential exists in simultaneous imaging of both MRI and optical system for functional correlations between the two modalities. Gadolinium-based contrast agents (GBCAs) is widely used in clinical MRI imaging. Gadolinium (Gd) is a non-specific imaging agent which accumulates at tumor site [4]. This bio-distribution is similar to a non-specific fluorescence imaging agent.

Herein, this study aims at comparing MRI contrast agent uptake kinetics with paired agent fluorescence tomography readouts in tumor using dynamic MRI-PAFT. To do this, dynamic MRI and fluorescence tomography are acquired simultaneously, and the kinetic behavior of the imaging agents extracted from the two modalities are used to calculate receptor availability (RA) which is a quantitative indicator of the targeted receptor density that is available for binding.

2. METHODS

2.1 Mouse handling

The glioma cell line chosen for the experimental studies was: U251 glioma cells, moderate EGFR expressing, (provided from Dr. Israel at Dartmouth College, Lebanon, NH) [5]. Cells were maintained in DMEM culture media supplemented with 5% fetal bovine serum and 1% antibiotic at 5% CO₂, 37°C. Animal studies were conducted in accordance with protocols approved by the Institutional Animal Care and Use Committee (IACUC) at Dartmouth College. Female nude mice were purchased from Charles River Laboratories (Wilmington, MD), and were orthotopically implanted tumor cells, as detailed elsewhere [6].

2.2 Imaging agents

The paired-agent fluorescence imaging used consisted of an anti-EGFR Affibody conjugated to Licor IRDye800CW as targeted agent and Affibody negative control conjugated to Licor IRDye680RD as untargeted agents. MRI contrast agent Gadovist (.5mmol/kg) (Bayer, Leverkusen, Germany) was used for dynamic MRI imaging. Paired fluorescence imaging agents and MRI contrast agent were mixed into 200 μ l injection solution.

2.3 Paired-agent MRI-PAFT acquisition

The MRI-coupled FMT system set-up is explained extensively in previous publication [1]. Full tomography is taken with 8 optical fibers that circumscribes the mouse head at different projection. The detection system consists of Acton Research Insight spectrometers with Princeton Instruments PIXIS cameras and is used to collect spectrally resolved fluorescence data. Targeted and untargeted imaging agents' spectrum were acquired continuously for around 60 minutes after administration, at a rate of approximately 1 minutes and 40 seconds per frames for a total of 35 frames. A spectral un-mixing algorithm applies linear least square fit to extract the dye-specific fluorescence from background fluorescence.

2.4 Dynamic MRI acquisition

A fast T1 turbo spin echo MRI scan protocol was created to capture the Gd kinetic using a clinical 3.0T Philips MRI, with sequence parameters: TR=121ms, TE=10ms, FOV=90mm², number of slice=4, and slice thickness= 1 mm. The dynamic MRI scans are collected continuously for 60 minutes at a rate of 89 seconds per acquisition. Tumor region are segmented using the contrast enhanced MRI, and Gd kinetics are extracted by measuring the signal intensity within the segmented region for the dynamic MRI acquisitions. A single frame fast T1 MRI was acquired before administration of imaging agents, and used as pre-injection Gd intensity for background signal subtraction.

2.5 Receptor availability calculation

Receptor availability is calculated using a snapshot method described in previous publication [7]. The activities of each agent measured at that time are first normalized to the activities from the first measurement: $\tilde{F}_T(t) = F_T(t)/F_T(0)$ and $\tilde{F}_{UT}(t) = F_{UT}(t)/F_{UT}(0)$, and the snapshot RA is calculated using Equation 1:

$$\text{snapshot RA}(t) = \frac{\tilde{F}_T(t) - \tilde{F}_{UT}(t)}{\tilde{F}_{UT}(t)} \quad [1]$$

Both untargeted fluorescence imaging agent and Gd contrast agent are used as untargeted agent to compute snapshot RA, and snapshot RA calculated using Gd contrast agent is compared against snapshot Ra calculated using the fluorescence paired-agent.

3. RESULTS

To confirm the approach provides a linear response to Gd contrast agent concentration, we imaged tissue-simulating liquid phantoms containing clinical Gd agent solutions of varying concentrations. Specifically, we prepared phantom solutions containing 1% intralipid in PBS, and varying concentrations of Gd contrast agent between 0 and 50 μM (0, 2, 10, 20 and 50 μM). Each phantom was imaged with the dynamic MRI protocol as described in the Methods section. The images of each phantom are plotted in Figure 1a. Mean values of MRI signal intensity inside each phantom are calculated and shown in Figure 1b. These results show a highly-linear response to changing Gd contrast agent concentration ($R^2 > 0.99$).

Gd uptake kinetics is extracted from dynamic MRI. Region of interest (ROI) is selected and the mean MRI signal of the ROI can be calculated. Figure 2a shows the MRI of a mouse shoulder in transverse plane. Gd uptake kinetics in normal tissue is shown in Figure 2b by selecting a ROI containing normal tissues. After subtracting the pre-injection MRI intensity in the ROI, Gd uptake kinetic peaked around 5 mins after injection, and is continuously cleared out.

Tumor region is segmented and mean MRI intensity for tumor is measured the same way as normal tissue. Optical untargeted agent kinetic curve measured with fluorescence tomography for the tumor region is normalized and plotted with the Gd uptake kinetics (Fig. 3a). Optical untargeted agent and Gd agent's kinetic curves show strong correlation, and the same trend in agent uptake is observed. Receptor availability is then calculated using two schemes: the tradition method using optical targeted and untargeted agents (Optical-RA), and fusion imaging method using optical targeted agent and MRI contrast agent (Gd-RA). The snapshot RAs of both methods are shown in Figure 3b. Optical-RA calculated at the end of imaging is 1.07, and Gd-RA calculated at end time point is 1.04.

4. CONCLUSION

The fast T1 MRI protocol is able to capture the Gd contrast agent uptake kinetic in normal tissue and in tumor. Similar imaging agent uptake trend is observed between Gd agent and optical untargeted agent. Using the Gd agent as untargeted agent for paired-agent imaging

scheme, snapshot RAs calculated at each time point correspond to snapshot RAs calculated using optical targeted and untargeted agent. This preliminary analysis suggests that a fusion imaging modality using MRI contrast agent as untargeted agent in paired-agent imaging scheme is possible. Work to leverage more samples for a comprehensive study are ongoing

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Figure 1: MRI Gd contrast agent phantom study. (a) Fast T1 MRI images of the tissue-simulating liquid phantoms with varying Gd concentration (0, 2, 10, 20 and 50 μM). (b) Mean values of MRI signal plotted as a function of Gd concentration with linear correlation fit.

Figure 2:

Gd uptake in normal tissue. (a) MRI image of mouse shoulder. Red dotted circle is the selected normal tissue ROI. (b) Normalized mean MRI signal intensity inside the ROI shows a fast uptake and slow clearing out of Gd contrast agent in normal tissue.

Figure 3:

Comparing Gd agent to optical agent. (a) uptake kinetics of Gd agent (red) and optical untargeted agent (blue). (b) snapshot RA calculated using optical agents' kinetics and snapshot RA (blue) calculated using combination of Gd kinetics and optical targeted agent (red).