Structure effect of biodegradable macromolecular MRI contrast agents on tumor MR imaging in an animal tumor model

Y. Zong[1], E-K. Jeong[2], D. Parker[2], and Z-R. Lu[1]

[1]Pharmaceutics, University of Utah, Salt Lake City, UT, United States, [2]Radiology, University of Utah, UT, United States

Introduction

Macromolecular gadolinium (III) complexes are advantageous in contrast enhanced cancer MR imaging because of their long plasma retention time. However, slow clearance of these macromolecular agents is the main safety concern that impedes their clinical development. Recently, we have designed and developed a novel class of biodegradable macromolecular gadolinium (III) complexes based on polydisulfides[(1)] to alleviate the safety concern. We have shown that the disulfide bonds in polymer backbones can be readily degraded in vivo to facilitate rapid clearance of the contrast agents after contrast enhanced MR imaging. These biodegradable macromolecular MRI contrast agents can result in strong blood pool contrast enhancement with minimal long-term tissue accumulation comparable to currently available clinical MRI contrast agents. In this study, we investigated the structure effect of the biodegradable macromolecular MRI contrast agents on tumor MR imaging in a mouse tumor model.

Materials and Methods

Biodegradable macromolecular MRI contrast agents GDCP and GDGP were synthesized by condensation polymerization of cystine or glutathione (oxidized form) and DTPA dianhydride, followed by complexation with $Gd(OAc)_3$. The contrast agents with different molecular weights (ca. 21, 43 and 108 KDa) and narrow molecular weight distributions were prepared by fractionation using size exclusion chromatography. The contrast agents were administered at a dose of 0.1 mmol-Gd/kg to nude mice bearing MDA-MB-231 human breast carcinoma xenografts via a tail vein after a standard sedation procedure. T1-weighted axial images of tumors were acquired before and after contrast injection using spin echo sequence on a Siemens Trio 3T scanner with a human wrist coil. The imaging parameters were 10 ms TE, 400 ms TR, 90° RF tip angle, 2 mm axial slice thickness.

Results and Discussion

T1-weighted MR images showed strong contrast enhancement by both GDCP and GDGP of different molecular weights in the tumor periphery 2 minutes pot-injection and up to 60 minutes (Figure 1), although the enhancement in tumor inner tissue was relatively weak. The tumor peripheral enhancement patterns are similar for both agents with similar molecular weights (Figure 2). The agents with molecular weight of ca. 21 KDa showed strongest contrast enhancement in the tumor periphery 2 minutes post-injection, which gradually decreased thereafter. The agents with the medium molecular weight (43 KDa) maintained relatively strong and constant signal intensity up to 60 minutes. The agents with the highest molecular weight (ca. 108 KDa) resulted in low initial signal intensity, which gradually increased and reached to a maximum value before decreasing with 60 minutes post-injection. Since both GDCP and GDGP had a relatively slow in vivo degradation rate, the size of the contrast agents had a significant impact on in vivo tumor contrast enhancement and dynamic enhancement patterns. The size-dependent contrast enhancement may also be useful for identifying an agent with a proper size for accurate determination of tumor blood volume and tumor characterization based on tumor vascularity.

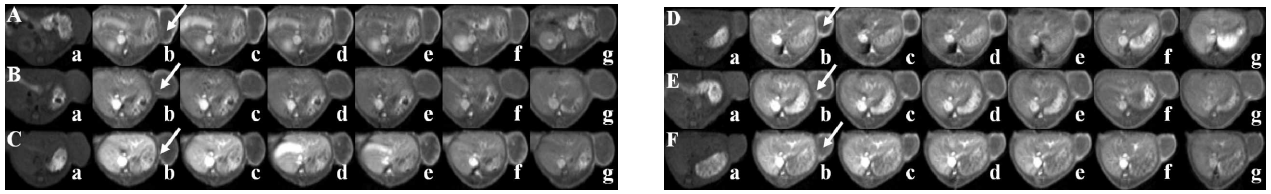

Figure 1. T1 weighted axial MR images of mice bearing MDA-MB-231 human breast cancer xenografts (arrows) before injection (a) and 2 (b), 5 (c), 10 (d), 15 (e), 30 (f) and 60 (g) min after injection of GDCP (A: 23 kDa, B: 43 kDa, C: 109 kDa) and GDGP (D: 21 kDa, E: 43 kDa, F: 108 kDa).

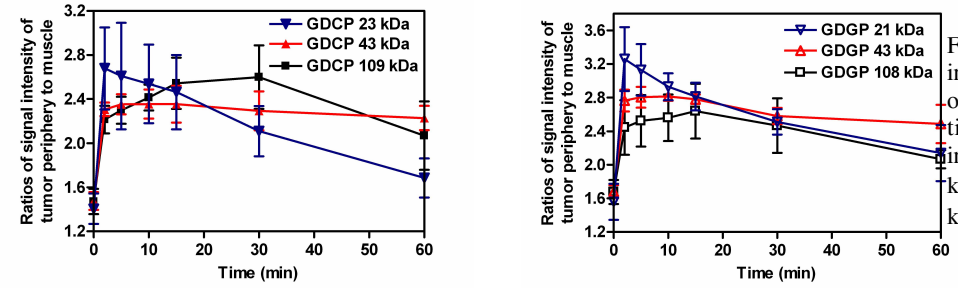

Figure 2. Relative MR signal intensities in the tumor periphery (B) of nude mice before and at various time points after the intravenous injection of GDCP (23 kDa, ▼; 43 kDa, ▲; 109 kDa, ■) and GDCP (21 kDa, ▽; 43 kDa, △; 108 kDa, □).

Conclusion. Biodegradable macromolecular MRI contrast agents GDCP and GDGP with different molecular weights showed strong tumor enhancement. Dynamic patterns of tumor enhancement were significantly affected by the size of the contrast agents. These biodegradable macromolecular MRI contrast agents have a potential for accurate tumor detection and characterization in contrast enhanced MRI.

References. (1) Lu, et al. Extracellular biodegradable macromolecular gadolinium(III) complexes for magnetic resonance imaging. MRM, 51,27-34.(2004). Wang, et al. Pharmacokinetics and tissue retention of (Gd-DTPA)-cystamine copolymers, a biodegradable macromolecular magnetic resonance imaging contrast agent. Pharm Res. 2005, 22, 596-602.