Polydisulfide based biodegradable macromolecular MRI contrast agents

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Introduction. Macromolecular Gd(III) complexes with high molecular weights have demonstrated superior MR contrast enhancement to lower molecular weight contrast agents in animal models. However, the clinical development of these agents is limited by the safety concerns deriving from their slow excretion after the MRI examinations. To alleviate the safety concerns, we have recently developed novel biodegradable macromolecular Gd(III) complexes using biodegradable disulfide bonds. Disulfide bonds have been incorporated into backbone of the macromolecular Gd(III) complexes or used as spacers to conjugate Gd(III) chelates into biomedical polymers. The cleavage of the disulfide bonds results in the breakdown of the macromolecular complexes into smaller excretable Gd complexes or the release of Gd chelates from polymeric carriers. The novel biodegradable macromolecular contrast agents have demonstrated prolonged contrast enhancement for cardiovascular and cancer MR imaging in animal models. Here, we report the physicochemical and biological properties in vivo contrast enhancement novel polydisulfide based biodegradable macromolecular contrast agents and how their structures affect in vivo contrast enhancement.

Materials and Methods. The biodegradable macromolecular contrast agents have been prepared by copolymerizing DTPA dianhydride with cystamine or cystine and its derivatives followed by complexation with Gd(III). Modified copolymers are also prepared by grafting PEG on GdDTPA cystine copolymers (GDCP). The degradability of the agents has been studied both in vitro and in vivo. The in vivo contrast enhancement of these agents has been investigated in animal models for cardiovascular imaging and neoplastic imaging on a Siemens 3T trio scanner. The impact of structural characteristics including molecular weight and steric hindrance around the disulfide bonds on the in vivo contrast enhancement has been investigated. GdDTPA cystamine copolymers (GDCC) were selected for detailed study of its toxicity, pharmacokinetics, and long-term Gd tissue retention in an animal model.

Results and discussions. Biodegradable macromolecular contrast agents with various structural characteristics have been prepared and characterized. The molecular weights of the copolymers range from 10,000 to 60,000 Da (linear size). They are readily degraded in the incubation with cysteine, and the degradation rate varies based on their structures. Negative charged GdDTPA cystine copolymers (GDCP) degrade slower than neutral agents GDCC and GdDTPA cystine diester copolymers (GDCEP). Consequently, GDCP exhibits size-dependent prolonged in vivo blood pool contrast enhancement due to its relatively slow degradation rate. GDCC and GDCEP do not show similar size-dependent in vivo contrast enhancement, possible because of their rapid degradation rate. In vivo degradation products of the agents are also identified in rat urine samples by mass spectrometry. The pharmacokinetic study has shown that the increase of molecular weight of GDCC does not result in prolonged blood pool contrast enhancement. No significant contrast enhancement was observed in the blood pool for GDCC with molecular weight of 18 and 60 KDa in15 minutes in rats. The Gd complexes were rapidly excreted from the body and tissue Gd retention for both GDCC-18 and GDCC-60 was at the same level as a low molecular weight control agent Gd(DTPA-BMA) 10 days after the injection. GDCC also demonstrated lower toxicity than GdDTPA. The modification of GDCP with PEG further alters the in vivo contrast enhancement of the agent. The in vivo contrast enhancement of modified agents also depends on the length of PEG. Longer PEG results in more prolonged blood pool contrast enhancement.

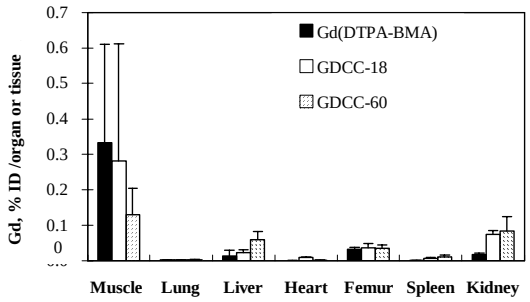

Figure. Tissue Gd accumulation in rats 10 days after injection of Gd(DTPA-BMA), GDCC-18, and GDCC-60 at a dose of 0.1 mmol-Gd/kg.

The study has shown that the polydisulfide based biodegradable macromolecular contrast agents can provide prolonged in vivo contrast enhanced and can be excreted rapidly with minimal Gd tissue accumulation. Their in vivo contrast enhancement may be tuned by the structural modification of the agents for different applications.

Conclusion. The novel biodegradable macromolecular MRI contrast agents have a great potential for further clinical development in cardiovascular and cancer imaging.