Multivalent Gd-DOTA Decorated Starlike Amphiphilic Dextran Micelles as Sensitive MRI Probes

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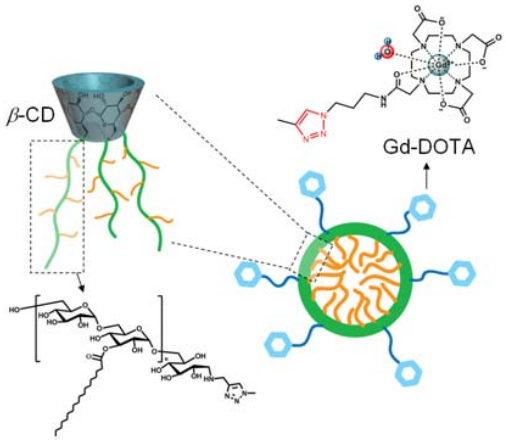
Statement of Purpose: Magnetic resonance imaging (MRI) has shown its advantages in early diagnosis, drug discovery, medical implant evaluation and other important noninvasive imaging monitoring processes.[1,2] Gadolinium(III) (Gd(III)) based complexes such as Gd-DOTA are common paramagnetic contrast agents for improving the sensitivity of MRI. However, the sensitivity of these probes are poor for cellular and molecular imaging. How to increase the sensitivity of Gd complexes will potentially improve its imaging capabilities. The rotational correlation time (τ_R) of a Gd(III) complex is closely related to its T_1 relaxivity, and longer τ_R usually leads to better sensitivity. One facile option to increase the τ_R is conjugation of Gd(III) complexes on rigid macromolecules or nanoparticles.[3] In this study, polymeric micelles of amphiphilic starlike dextran was used as nanoplatforms for conjugation of Gd-DOTA to form polymer nanoparticles with multivalent Gd-DOTA on their surface (**Scheme 1**). The T_1 relaxivity was characterized under a clinical 1.5T MRI scanner and showing much higher sensitivity than free Gd-DOTA complexes.



Scheme 1. Schematic illustration of the multivalent Gd-DOTA decorated starlike amphiphilic dextran micelles.

Methods: Starlike dextran was synthesized following a "coupling onto" approach via the click chemistry reaction between heptakis-6-azido-6-deoxy-β-cyclodextrin and alkyne dextran.[4] Amphiphilic starlike dextran β-CD-Dex-*g*-SA/alkyne with aliphatic chains and alkyne groups grafting onto the dextran backbone was synthesized by esterification reaction between the hydroxyl group (-OH) of dextran and the carboxyl group (-COOH) of stearic acid (SA) or 4-Pentynoic acid via CDI. Multiple Gd-DOTA-N_3 molecules were then grafted onto the surface of micelles of β-CD-Dex-*g*-SA/alkyne in water. T_1 relaxivities of the multivalent micelles and Gd-DOTA complexes were measured at 1.5T under a clinical MR scanner (Siemens Sonata). Macrophages and other cell lines labeled with this multivalent probes were imaged under a 3T clinical MR scanner.

Results: Amphiphilic starlike dextran β-CD-Dex-*g*-SA/alkyne was synthesized and characterized by ^{1}H NMR. SEM and DLS data shows that it can assemble into micelles with a diameter of ~100 nm. T_1 relaxivity of the resulted multivalent Gd-DOTA nanoparticles and free Gd-DOTA in water was shown in **Figure 1**, β-CD-Dex-*g*-SA/Gd-DOTA nanoparticles has a much higher T_1 relaxivity of 18.1 Gd $mM^{-1}s^{-1}$ than that of Gd-DOTA (4.0 Gd $mM^{-1}s^{-1}$). Cells labeled with this multivalent probes have shown strong contrast against unlabeled cells under a 3T clinical MR scanner.

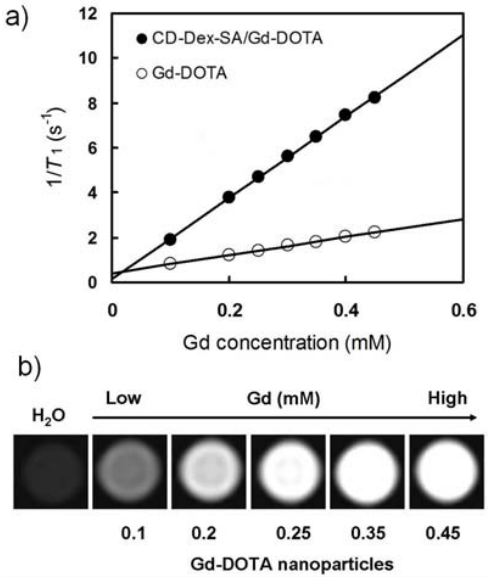


Figure 1. a) T_1 relaxation rates ($1/T_1$, s^{-1}) of multivalent Gd-DOTA micelles and Gd-DOTA as a function of Gd concentration (mM) at 1.5 T; b) T_1-weighted MRI images (1.5 T, spin echo sequence: TE = 5 ms, TR = 30 ms) of the multivalent Gd-DOTA micelles.

Conclusions: Conjugation of Gd-DOTA complexes onto polymeric nanoparticles via rigid triazole ring of click chemistry led to the formation of multivalent Gd-DOTA nanoparticles with higher T_1 relaxivity and better sensitivity than that of free Gd-DOTA.

References: 1. Weissleder and R, Pittet MJ. *Nature*. 2008;**452**:580-589. 2. Xie J, Liu G, Ai H, Chen X. et al. *Acc Chem Res*. 2011;**44**:883-892. 3. Ai H. *Adv Drug Deliv Rev*. 2011;**63**:772-788; 4. Su HY, Ai H, et al. *Biomaterials* 2012;**34**:1193-1203.