Nanoglobular Gd-DO3A conjugates as highly effective MRI contrast agents

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Introduction

Currently available Gd based MRI contrast agents are often used at high doses in order to generate sufficient image contrast for accurate diagnosis. Toxic side effects, e.g. NSF, have been observed in patients with renal malfunctions after they were exposed to high doses of Gd based contrast agents. Innovative design of new MRI contrast agents with effective image enhancement at substantially reduced doses can greatly reduce the dose-related toxicity of Gd based MRI contrast agents. We report here novel nanoglobular Gd-DO3A conjugates with well-defined globular structures and nanosizes as highly effective MRI contrast agents at substantially reduced doses.

Materials and Methods

Nanoglobular Gd-DO3A conjugates were synthesized by incorporating Gd-DO3A into the surface of the three-dimensional symmetric lysine dendrimers (generations 1 -3) with cubic octa(3-aminopropyl)silsesquioxane (OAS) as the core. The T_1 relaxivity of the agents was measured on a Siemens 3T MRI scanner using a spin-echo sequence. The blood pool and tumor contrast enhancement of the agents were evaluated in female nude mice bearing MDA-MB-231 human breast cancer xenografts using a 3D-FLASH and 2D spin-echo sequence before and after intravenous injection at the dose of 30 and 10 μmol-Gd/kg.

Results and Discussion

The nanoglobular MRI contrast agents have compact and well-defined molecular architectures with diameter of 2.0 – 3.3 nm for the G_1 to G_3 agents. Approximately 10 Gd-DO3A chelates were incorporated in the G_1 agent, 20 and 50 chelates in the G_2 and G_3 agents. T_1 relaxivity was 6.42, 7.18 and 10.1 $mM^{-1}s^{-1}$ per Gd(III) chelate at 3T for G_1, G_2 and G_3 agents, respectively. Figure 1 shows the representative 3D MIP and axial 2D spin-echo images of tumor tissues enhanced with the G_1, G_2 and G_3 nanoglobular contrast agents. The nanoglobular agents have shown size-dependent blood pool contrast enhancement. The G_1 and G_2 nanoglobular agents had smaller sizes and cleared more rapidly from the blood circulation via renal filtration than the G_3 agent. The G_3 agent has a larger size and longer blood circulation, resulting in strong blood enhancement for at least 30 minutes at 30 μmol-Gd/kg. The blood enhancement gradually decreases over time and, at the same time, contrast enhancement in the bladder increases gradually, indicating that the G_3 nanoglobular contrast agent gradually excretes via renal filtration and accumulates in the bladder. Significant blood contrast enhancement was also observed in the blood for the G_3 agent at a further reduced dose, 10 μmol-Gd/kg.

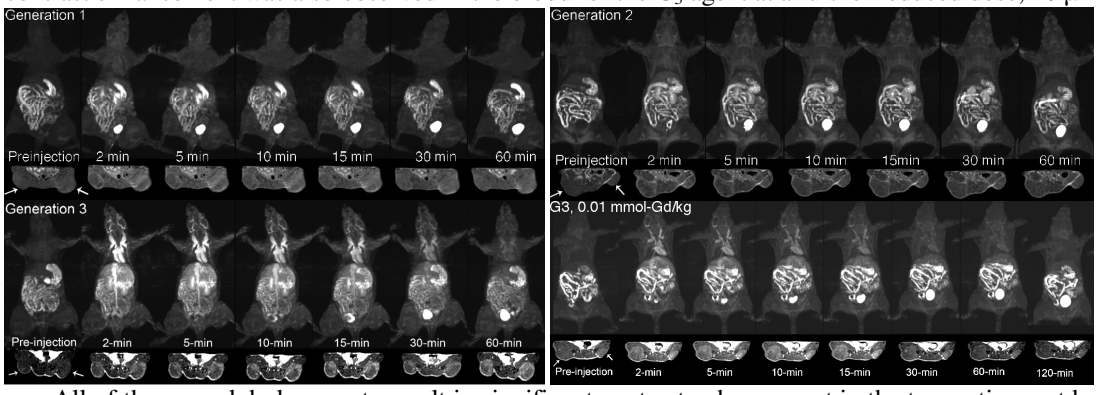

Figure 1. MR 3D MIP images (top row) and 2D axial T_1-weighted spin-echo tumor images (bottom row) of mice injected with the nanoglobular agents at a dose of 0.03 mmol-Gd/kg and the G_3 agent at 0.01 mmol-Gd/kg. Arrowheads point to tumor tissues.

All of the nanoglobular agents result in significant contrast enhancement in the tumor tissue at both flanks for at least 15 minutes. The G_3 contrast agent results in more significant tumor contrast enhancement than the G_1 and G_2 agents at 30 μmol-Gd/kg. The tumor enhancement with the G_3 agent at 30 μmol-Gd/kg increases over time and strong enhancement is still visible at 60 min post-injection. Significant tumor enhancement is also observed in the tumor with the G_3 agent at 10 μmol-Gd/kg. It might be attributed to the fact that the G_3 agent has a relatively large size and prolonged blood circulation, which limits the extravasation of the agent into normal tissue and enhances the tumor accumulation due to the hyperpermeability of tumor blood vessels. Minimal or undetectable Gd retention was determined in the major organs and tissues of mice at 10 days after the injection of the agents.

Conclusions

The nanoglobular MRI contrast agents had well-defined nanosizes and size-dependent in vivo contrast enhancement. The G_3 agent had a relatively large size and resulted in prolonged enhancement in the blood and tumor at a substantially reduced dose. The nanoglobular agents readily excreted via renal filtration with minimal long-term tissue accumulation. The nanoglobular contrast agents are promising for further development as highly effective MRI contrast agents for MRA and MR cancer imaging.