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Gd-based protein cage nanoparticles provide enhanced r1 relaxivity and detect experimental atherosclerosis

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Objective

Develop a highly sensitive T1 contrast agent based on chemically attaching a multitude of chelated Gd molecules constrained within a protein cage structure.

Background

A T1 nanoparticle contrast agent showing high r1 relaxivity is desired to provide more sensitive molecular/cellular imaging with reduced Gd dose, and may have more clinical utility than T2* (e.g., iron-based) approaches. Tethering multiple Gd-chelates to a supramolecular platform is a promising strategy to increase r1 relaxivity, as rotational correlation time of the Gd ions can become significantly larger which is highly favorable for efficient r1 relaxivity. Here we utilize a small heat shock protein cage (Hsp) with a 12nm exterior diameter and a 9nm interior cavity, as a platform to anchor Gd-DTPA.

Methods

1) Material development and evaluation

Hsp was purified from an E. coli expression system. An azide-alkyne based click reaction is cycled to produce a branched polymer network in the interior of the protein cage (Fig 1). The polymer results in a stable network containing Gd-DTPA, as the azide-containing monomer has the Gd chelate attached prior to polymer generation.

2) In vivo imaging of vascular inflammation

FVB mice underwent left carotid ligation after 4 weeks of high-fat diet and diabetes induction by streptozotocin. Two weeks later, Hsp-Gd or Magnevist (Gd-DTPA)

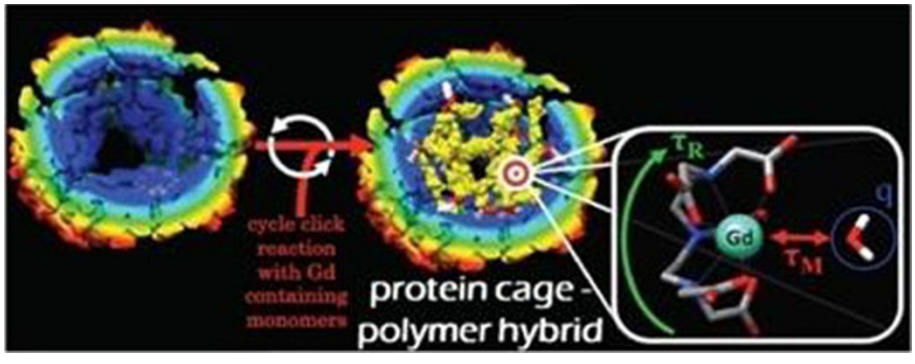

Figure 1 Illustration of Hsp-brach polymer with Gd.

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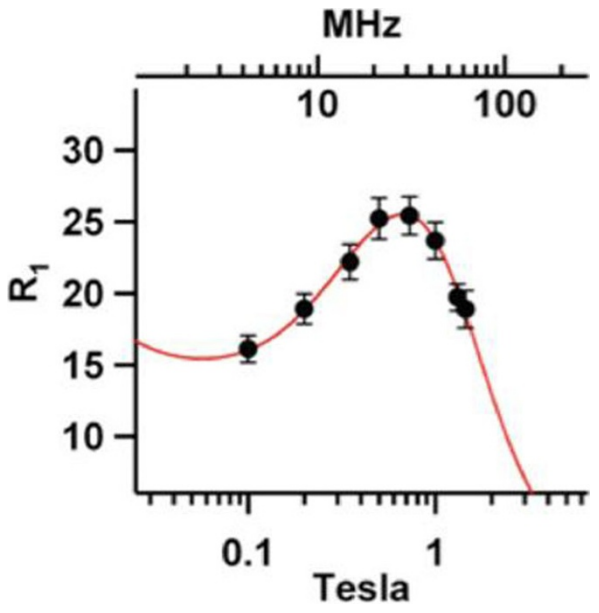

Figure 2 Graph of r1 measurement at varying field.

was intravenously injected at a dose of 20μmol Gd/kg (one-fifth the typical clinical dose). Mice were imaged on a whole-body 3T MRI scanner (Signa HDx, GE Healthcare) with a 50mT/m, 150T/m/s gradient system and a phased array mouse coil (RAPID MR International), using a T1-weighted fast spin echo sequence (TR/TE=400ms/15ms, slice thickness=1mm, FOV=3cm, matrix=256x256) before injection and 4h after injection.

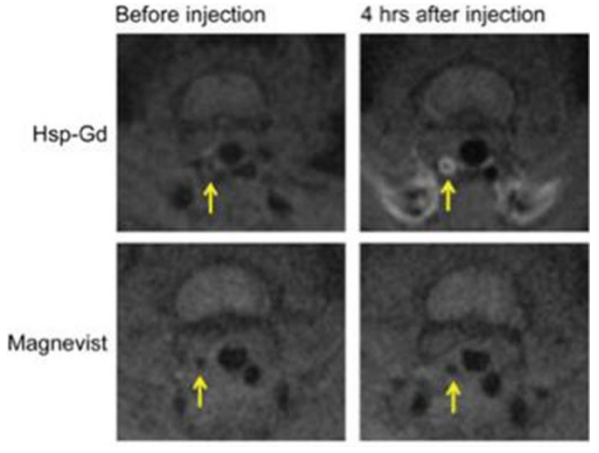

Figure 3 T1-weighted FSE MRI of ligated left carotids in mice before and after injection of Hsp-Gd (top) or Magnevist (bottom). The macrophage-rich left carotid lesion was clearly enhanced by Hsp-Gd, but not in the non-ligated right carotid artery or either carotid artery after Magnevist injection.

Results

In vitro analysis of Hsp-Gd showed about 160 Gd-DTPA molecules per cage. At 0.73T, the ionic (per Gd) r1 value is 25$mM^{-1}sec^{-1}$ and the particle r1 value is 4,200$mM^{-1}sec^{-1}$ (Fig 2). At 3T, the ionic and particle r1 values are 9.7 $mM^{-1}sec^{-1}$ and 1600 $mM^{-1}sec^{-1}$, respectively. The ionic r1 value is nearly 3 times higher than that of Magnevist. The macrophage-rich left carotid lesion, but not the non-ligated right carotid, was clearly detected on T1-weighted MR imaging 4h after injection of Hsp-Gd, whereas the same lesion was hardly detected after Magnevist injection (Fig. 3).

Conclusion

Gd can be effectively incorporated into polymer-incorporated protein cage nanoparticles providing high r1 relaxivity. Hsp-Gd allows positive contrast imaging of macrophage-rich carotid atherosclerosis with low Gd dosing. Thus, Gd-based protein cages are promising atherosclerosis imaging agents.

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