Magnetic resonance molecular imaging of atherosclerotic plaque in an atherosclerosis mouse model

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Introduction:
Magnetic resonance imaging (MRI) is a powerful imaging modality for detection and diagnosis of life-threatening diseases such as cancer and atherosclerosis. However, current clinically used contrast enhanced MRI is not suitable for molecular imaging because of the low sensitivity of MRI and non-specificity of the contrast agents. There is a clinical need of safe and effective targeted MRI contrast agents for accurate detection and diagnosis of plaques with MR molecular imaging. The CLT1 peptide showed specific binding to fibrin-fibronectin complexes (FFC) formed by clotting of plasma proteins in atherosclerotic plaque tissues and little binding in normal tissues [1,2]. We have developed a safe and effective FFC targeted MRI contrast agent (CPLDG) for detection of atherosclerotic plaques.

Materials and Methods:
CPLDG was synthesized by conjugating four Gd-DOTA chelates to a small peptide CLT1 that binds FFC in atherosclerotic plaques. Scrambled CPLDG (SCPLDG) was synthesized by replacing the targeting CLT1 with a scrambled control peptide, which does not bind to plaques. Atherosclerotic apolipoprotein E–deficient mice were used to evaluate the efficacy of CPLDG. The animals were fed with high fat diet (HFD) for 10 and 20 weeks, and randomly assigned to two groups, the CPLDG group and SCPLDG group. The agents were injected at a dose of 0.1 mmol-Gd/kg into the mice via a tail-vein catheter. MR images were acquired on a 9.4 Tesla Bruker Biospec small animal MRI scanner using a T1-weighted black blood spin echo sequence. Signal enhancement of arch aorta was measured before and after contrast agent injection. The targeting efficacy of CPLDG was verified with fluorescence imaging using a fluorescently labeled peptide.

Results:
Figure 1 shows axial MR images acquired in atherosclerotic ApoE-deficient mice 10 and 20 weeks after the onset of HFD (n=6~9). After injection of CPLDG, strong enhancement of the aortic wall in ApoE-deficient mouse was observed for both 10-week and 20-week HFD time points, and the enhancement lasted for the whole experimental period up to 35 minutes. In comparison, SCPLDG showed much lower enhancement which only limited to early time points. Figure 2 shows the Contrast-to-Noise Ratio (CNR) of atherosclerotic aortic wall in ApoE-deficient mice injected with targeted agent CPLDG and control SCPLDG at 10-week and 20-week HFD mice. Compared to mice on a 10-week HFD, stronger enhancement was observed in 20-week HFD mice after injection of the targeted CPLDG. Fluorescence imaging studies also confirmed that targeted CPLDG could specifically bind to plaques in atherosclerotic aortic wall.

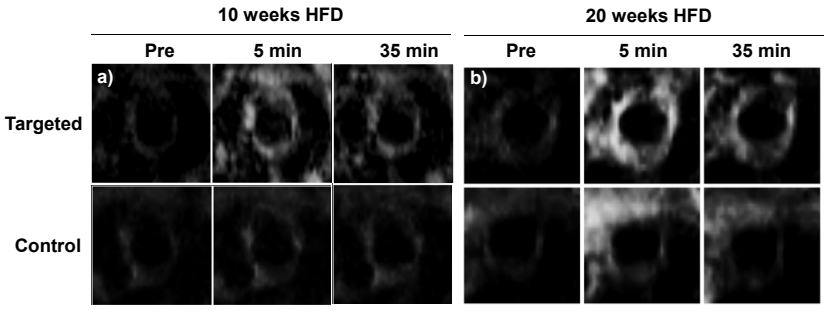

Figure 1. In vivo MR images acquired in atherosclerotic ApoE-deficient mice 10 and 20 weeks after the onset of HFD (n=6~9 per group). At baseline (before injection) and up 35 min after injection of targeted CPLDG and control SCPLDG to mice (a) with 10 weeks HFD; (b) with 20 weeks HFD. MRI CAs administered at 0.1 mmol Gd/kg.

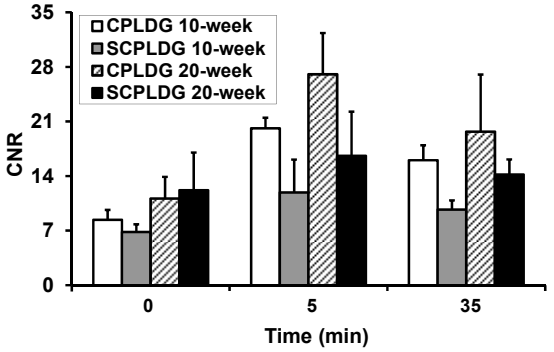

Figure 2. In vivo MR image SI of aortic wall at different times measured with Contrast-to-Noise Ratio (CNR) in ApoE-deficient mice injected targeted CPLDG and control SCPLDG on 10-week and 20-week FHD mice.

Conclusions:
We have designed and synthesized a peptide-based low molecular weight MRI contrast agent specifically binds to fibrin-fibronectin complexes formed in atherosclerotic plaques. Our preliminary results showed the targeted agent was able to deliver a sufficient amount of Gd-DOTA chelates to its molecular target. The newly developed targeted MRI contrast agent is promising for noninvasive assessment of plaque progression in an atherosclerotic mouse model.

References:
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