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Detection of in vivo atherosclerotic plaque progression with a fibrin-targeted MR contrast agent

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Introduction

Molecular MRI has emerged as a promising, non-invasive modality to accurately detect high-risk atherosclerotic plaques. Due to the inherently low sensitivity of MRI, contrast agents targeted at an abundant and robust component of the lesion are required. Fibrin represents a clinically relevant target and imaging of aortic, coronary, carotid and cardiac thrombi have been demonstrated both in animal models and men. It has been recognised as an important component of atherosclerotic plaques and is present throughout plaque development.

Purpose

This study aimed to investigate the feasibility of intraplaque fibrin detection throughout plaque development with EP-2104R, a fibrin targeted contrast agent, in an *in vivo* mouse model of progressive atherosclerosis.

Methods

Male C57BL/6 apolipoprotein E-knockout mice (ApoE -/-) were fed a high fat diet (HFD) for 4, 8 and 12 weeks prior to MRI of their brachiocephalic artery pre- and post i.v. administration of EP-2104R. A fourth group of mice were treated with pravastatin during the 12 week HFD period. MRI was performed on a 3 T scanner (Philips Achieva, Best, Netherlands). A cardiac-triggered inversion-recovery gradient-echo sequence was used for contrast detection. Both the CNR and T1 relaxation time within the plaques were determined and compared to the absolute gadolinium concentration measured by inductively coupled mass

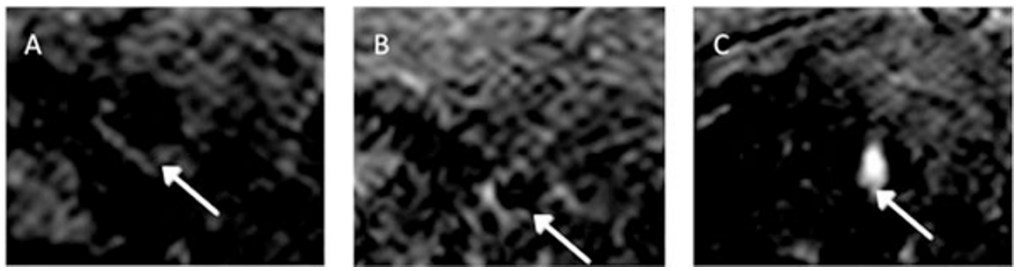

Figure 1
Representative images from (A) pre- EP-2104R in 12 week HFD ApoE -/- mice, and 1.5 - 2 hours after i.v. administration of 10 μmol/kg EP-2104R in (B) week HFD Apoe -/- mice and (C) 12 week HFD ApoE -/- mice.

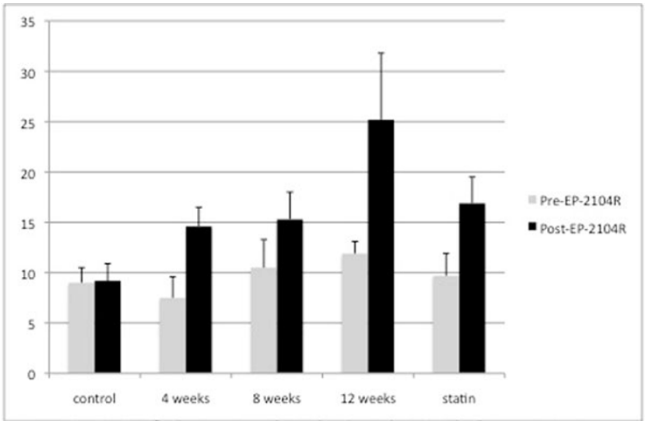

Figure 2
CNR of plaques within the brachiocephalic arteries with molecular MRI pre- (grey) and 1.5 - 2 hours post (black) i.v. administration of EP-2104R (n = 5.9). All EP-2104R treated HFD groups show significant visual enhancement of plaques compared to non-contrast enhanced images and the control.

spectroscopy (ICP-MS). Histological sections were stained with MSB for fibrin visualization and compared to MRI.

Results

MRI with EP-2104R significantly enhanced the plaques (Figure 1) in the brachiocephalic arteries of 4, 8 and 12 week HFD mice compared to their respective non-contrast enhanced images ($P < 0.05$), and wild-type control mice ($P < 0.05$). Furthermore, plaque CNR and T1 increased during the HFD and were in good agreement with ICP-MS. Plaques from the 12 week HFD ApoE -/- mice displayed a sudden increase in both CNR and gadolinium concentration, which is in agreement with spontaneous plaque rupture as previously reported in this model ($P < 0.05$). The statin-treated mice had a reduction of CNR as compared to the 12-week untreated group (Figure 2). Histological sections correlated well with the MRI results.

Conclusion

These results demonstrate the feasibility of intraplaque fibrin detection using EP-2104R. Direct fibrin imaging could be potentially useful for the detection of vulnerable coronary atherosclerotic lesions during the development of disease *in vivo*, which could aid earlier diagnosis and intervention.