Journal of Cardiovascular Magnetic Resonance

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Meeting abstract

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2089 Detecting inflammation in atherosclerosis using protein cage nanoparticles as cellular imaging agents

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from 11th Annual SCMR Scientific Sessions
Los Angeles, CA, USA. 1–3 February 2008

Published: 22 October 2008

Journal of Cardiovascular Magnetic Resonance 2008, **10**(Suppl 1):A358 doi:10.1186/1532-429X-10-S1-A358

This abstract is available from: http://jcmr-online.com/content/10/S1/A358

Introduction

Macrophages are important imaging targets for identifying and monitoring high-risk atherosclerotic plaque. Human heavy chain ferritin (HFn) is a promising nanoscale protein cage platform for cellular and molecular imaging, demonstrating substantial in vitro uptake by macrophages.

Purpose

To evaluate the in vivo uptake and distribution of MRI and fluorescent HFn nanoparticles in mouse atherosclerosis.

Methods

A macrophage-rich carotid lesion in FVB mice (n = 12) was induced as follows: high fat diet for 4 weeks then diabetes induction by 5 daily intraperitoneal injections of streptozotocin. Two weeks later, we performed carotid ligation of the left common carotid artery. In the first group of mice (n = 5), an MRI form of HFn containing iron oxide (HFn-3000Fe) was injected via tail vein (25 mgFe/kg) 2 weeks after carotid ligation. Mice were sacrificed 48 hours after injection and HFn-Fe uptake was assessed histologically by Perl's iron staining. In the second group of mice (4 diseased and 3 sham), HFn was labeled with the near-infrared (NIR) fluorophore Cy5.5 (HFn-Cy5.5: 4.6 Cy5.5 dye/cage) and injected via tail vein (8 nmol of Cy5.5) 2 weeks after carotid ligation. Mice were imaged serially by in vivo NIR imaging up to 48 hours. At 48 hours, both carotid arteries were exposed for in situ NIR imaging, and then removed for ex vivo NIR imaging. All mice were imaged under 2% isoflurane anesthesia using the MaestroTM in-vivo imaging system (CRI, Woburn, MA). After the NIR imaging, both carotid arteries were removed and cut into 2 mm sections for confocal fluorescence microscopy to detect HFn-Cy5.5 colocalized with macrophages.

Results

HFn iron oxide nanoparticles (HFn-Fe) were taken up by macrophages in the ligated left carotid artery at 48 hours, as demonstrated by histology (Fig 1A). No HFn-Fe uptake was seen in the control right carotid arteries. In vivo fluorescence imaging detected HFn-Cy5.5 at 10 min after intravenous injection, with the predominant signal in the liver, bladder, and neck lymph nodes. In situ (Fig 2A), the average fluorescence signal was significantly higher in the ligated left carotid arteries at 48 hours (Left: 0.27 ± 0.05, Right: 0.13 ± 0.04, p = 0.04). No significant signal was seen in sham-operated mice (Left: 0.16 ± 0.06, Right: 0.12 ± 0.01, p = 0.3). The enhanced signal in the ligated left carotid arteries was further confirmed by ex vivo fluorescence imaging (Left: 429 ± 23, Right: 10 ± 10, p = 0.0001), with minimum signal detected in the sham-operated mice (Left: 12 ± 12, Right: 0 ± 0, p = 0.4) (Fig 2B). On confocal fluorescence microscopy, HFn-Cy5.5 nanoparticles colocalized with macrophages in the neointima of the ligated carotid artery (Figure 1B).

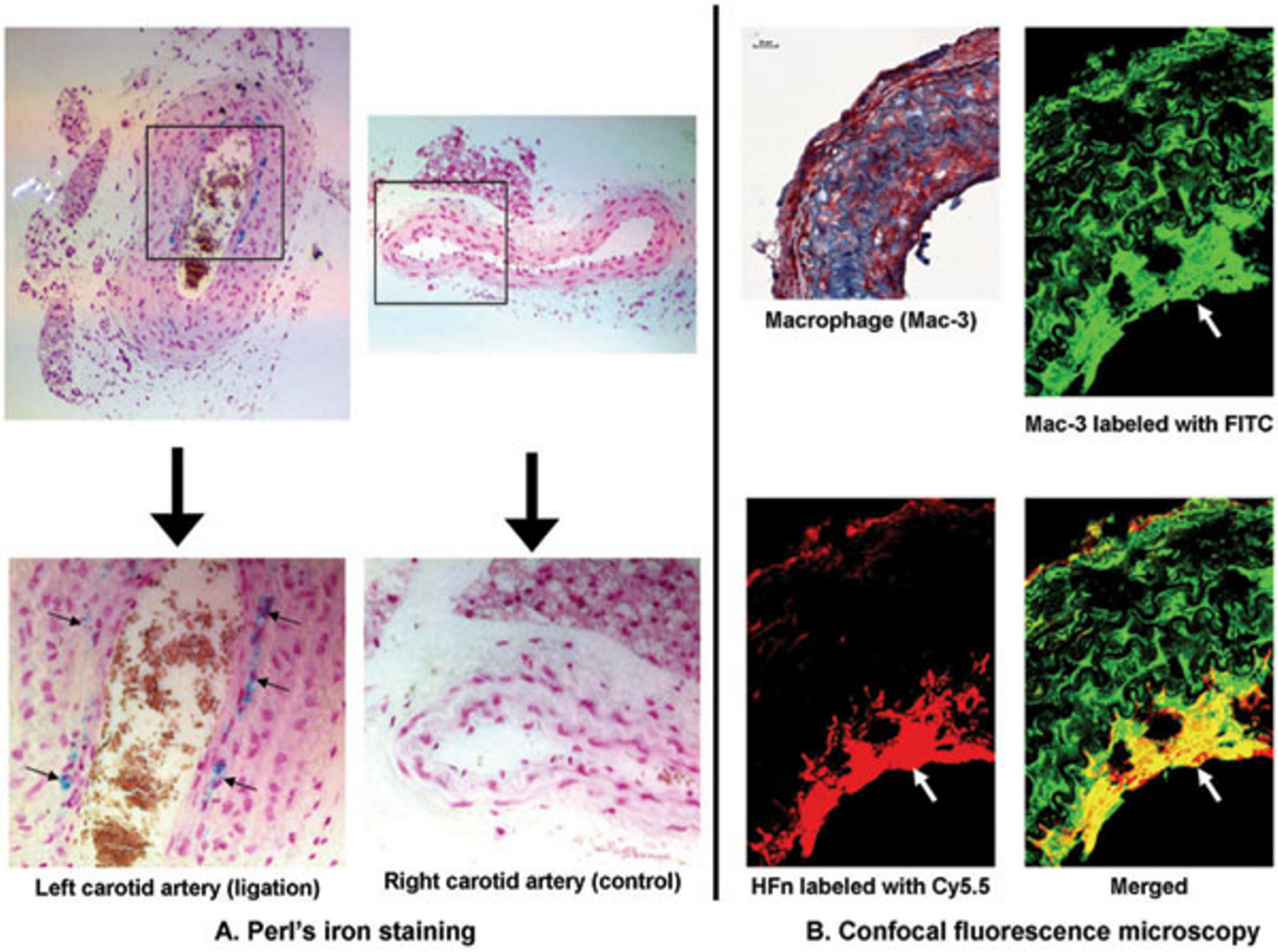

Figure 1

Conclusion

Human ferritin protein cages labeled with iron oxide or fluorophore localize to macrophages in the atherosclerotic lesions in vivo. These initial results encourage further investigation into the use of protein cage architectures as a novel platform for MR or NIR contrast agents for detecting macrophage infiltration within atherosclerotic plaques.

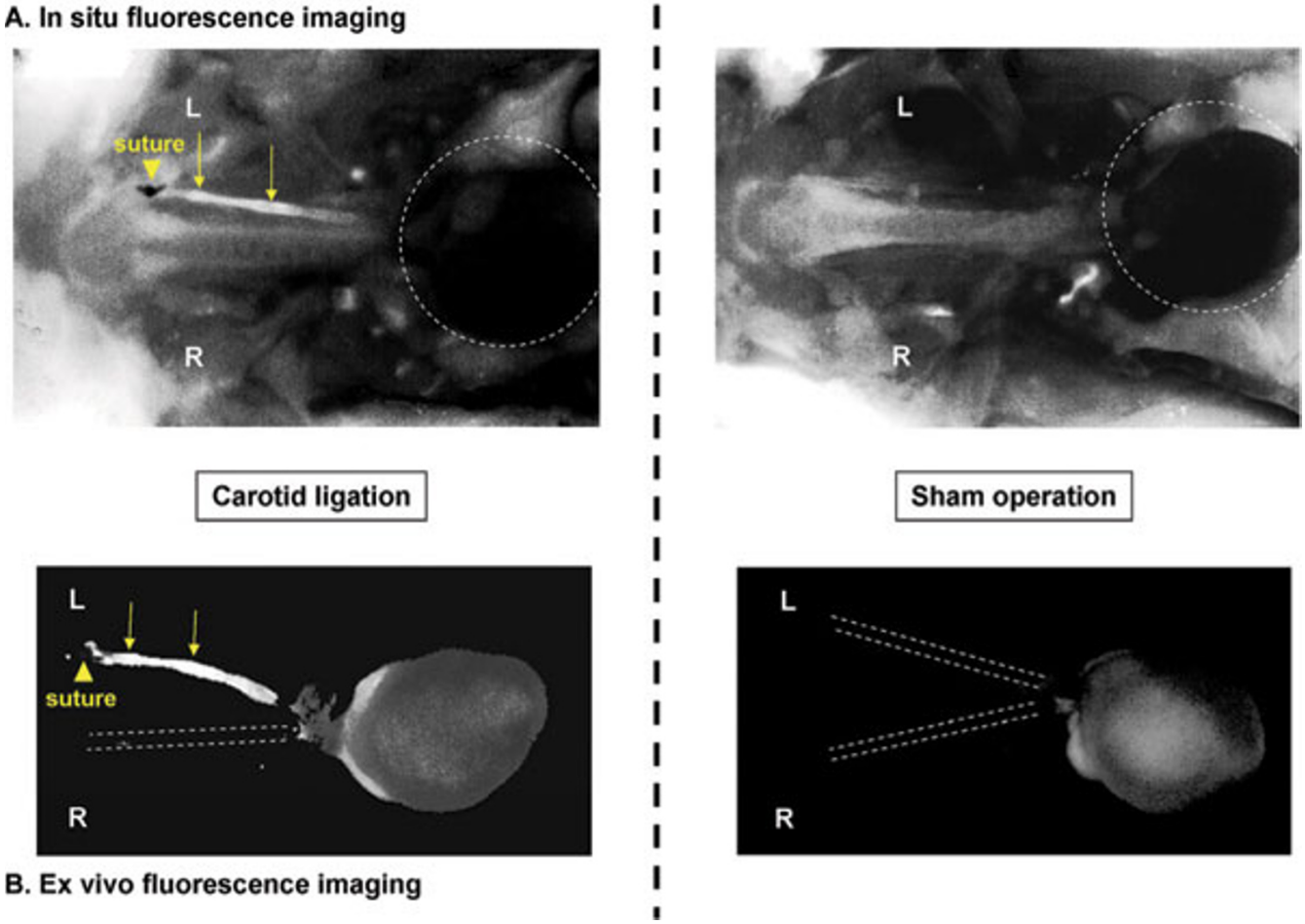

Figure 2