MRI Tracking of Migration of Bone Marrow Cells to the Sites of Injured Arteries

B. Qiu[1], F. Gao[1], S. Kar[2], J. Zhang[1], P. Walczak[1,3], M. Larabi[1], R. Xue[1], E. Frost[1], Z. Qian[4], J. W. Bulte[1,3], X. Yang[1]

[1]Radiology, Johns Hopkins Univ School of Medicine, Baltimore, MD, United States, [2]Biomedical Engineering, Johns Hopkins Univ School of Medicine, Baltimore, MD, United States, [3]Institute for Cell Engineering, Johns Hopkins Univ School of Medicine, Baltimore, MD, United States, [4]Pathology, Johns Hopkins Univ School of Medicine, Baltimore, MD, United States

Introduction:

Hematopoietic progenitor cells play an important role in the formation of atherosclerosis (1,2). For both basic science and clinical practice, it is essential to develop a non-invasive imaging method to monitor the trafficking of bone marrow (BM)-derived progenitor cells to the targets. We attempted to develop an MRI-based method to track the migration of BM cells to the sites of injured arteries.

Materials and Methods:

BM-derived cells from LacZ-transgenic mice were labeled with a superparamagnetic MR contrast agent, Feridex, and then transplanted into recipient Balb/c nude mice with cuff-induced injuries in the left femoral arteries. Migrated Feridex/LacZ-BM cells were monitored *in vivo* on a 4.7T MR scanner using a fast spin echo (FSE) sequence. To further confirm the accuracy of MRI tracking of Feridex/LacZ-BM cells at the targets, we performed *ex vivo* 3D, high-resolution MR imaging of the bilateral groin area of the mice on a 9.4T or 11.7T MR scanner with a 30 mm birdcage coil and an FSE sequence. Both the control and injured artery segments were then harvested for histological examination. Histochemistry included staining for Feridex-positive cells using Prussian blue and/or LacZ-positive cells using X-gal. On the *ex vivo* 3D high resolution images, we measured and statistically compared the volumetric sizes of hypointense areas at the targeted femoral arteries among the different animal groups with various treatments, including (a) the arteries with both Feridex-labeled BM cell transplantation and cuff placement (n=8); (b) the arteries with Feridex-labeled BM cell transplantation only (n=8); (c) the arteries with cuff placement only (n=4); and (d) the uninjured arteries without Feridex-labeled BM cell transplantation (n=4).

Resutls:

Both *in vivo* and *ex vivo* MR imaging showed significantly larger regions of hypointensity because of the migration of the Feridex-labeled to the sites of the injured arteries (1.71±0.57 mm^3, $p<0.01$, ANOVA) compared to control arteries (0.25±0.19 mm^3; 0.73±0.20 mm^3 and 0.51±0.34 mm^3)(Fig. 1). Histochemistry demonstrated Feridex- and/or LacZ-positive cells in the thickened adventitia of the injured arteries and in the tissues immediately surrounding the cuffs (Fig. 2).

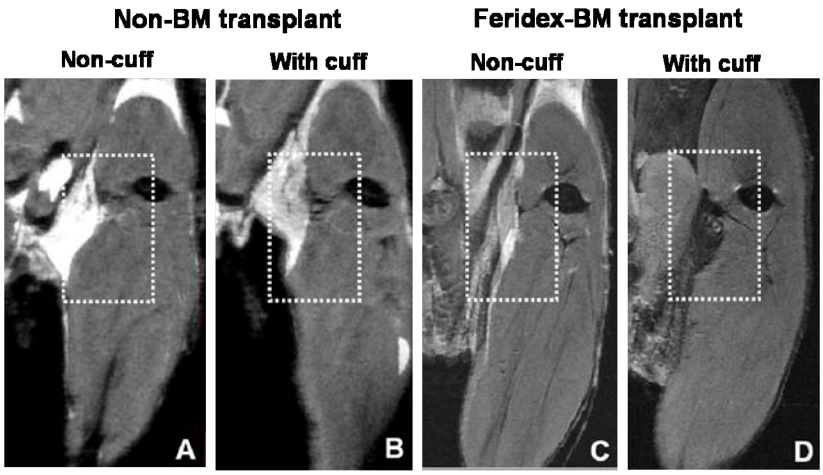

Fig. 1. Near-coronal view of representative *ex vivo* 9.4T MR images of the different animals with various treatments. Insets outline the femoral artery areas, showing a remarkably large hypointense area at the site of the injured femoral artery in animal D with both BM transplantation and cuff placement, which is not visualized at the sites of the uninjured femoral arteries in animals A and C. In animal B, the cuff itself with accumulated blood creates a small hypointense area.

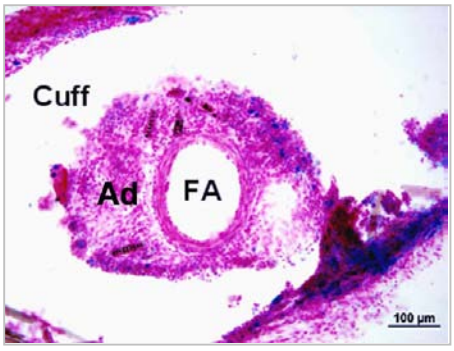

Fig. 2. X-gal histochemical staining, showing LacZ-positive cells (blue color) distributed and accumulated in the inflammation-thickened adventitia (Ad) of the cuff-induced femoral artery (FA) and in the tissues around the cuff.

Conclusion:

This study provides the first evidence to support the potential use of MRI to track the migration of magnetically labeled bone marrow cells to the sites of injured arteries.

Reference: 1) Krause D, et al. Cell 2001;105:369. 2) Sata M, et al. Nat Med 2002:8:403.