In Vivo MR Imaging of the Recruitment of Iron Oxide–labeled Macrophages in Renal Ischemic-Reperfusion Model in Mice

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Introduction: Immune cells participate importantly in the pathogenesis of kidney ischemic-reperfusion injury, but their spatial and temporal recruitment from circulation remains uncertain. Visualization of macrophage homing is important to assess the dynamic evaluation of the recruitment of immune cells. The purpose of this study was to evaluate the feasibility of MR imaging to depict the *in vivo* recruitment of iron-oxide–labeled macrophages in renal ischemia/reperfusion model in mice, thus allowing investigations on the cellular and molecular mechanisms of acute renal failure.

Materials and methods: Mouse macrophage cells (RAW 264.7) were cultured and labeled with iron oxide in vitro. Unilateral renal ischemia/reperfusion models in 12 mice were induced by clamping left renal pedicle for 60 minutes. The mouse kidneys were imaged with a 4.7 T MRI scanner before and 24 hours after the administration of iron oxide-labeled macrophages (2 x 10^6 cells) or iron oxide solution (60 µg Fe/mouse) on days 1 and 2. Changes in relative signal intensity and contrast enhancement pattern in MR images were analyzed and compared with histopathologic findings.

Results: Iron oxide particles were effectively uptaken by the macrophages after 24-hour incubation with SPIO in concentration of 112 µg Fe/ml. The intracellular iron content was 31.1 ± 1.9 pg Fe/cell which was measured by ICP-AES. On T2*-W gradient-echo MR images, the administration of the iron-oxide-labeled macrophages caused band-shaped lower signal intensity zone in the outer medulla of ischemic-injured left kidney in all mice (Figure 1). Histologically, 24 hours after iron-oxide-labeled macrophage injection, iron-labeled cells of characteristic phenotype were found in all area of injured kidney. The number of total labeled cells in one injured kidney was approximately 2700, which was counted from the H&E staining results. Over 50% out of the iron-labeled cells injected were localized in outer medullar area, which was well in accordance with the signal decrease observed on MR images. This band-like pattern was not detected in right intact kidneys in all operated mice 24 hours after the injection of iron-oxide-labeled macrophages and in control group after iron oxide solution injection (Figure 2).

Conclusion: These results suggest that intravenously administered iron-oxide–labeled macrophages homing to injured kidney can be monitored by MR imaging, and may provide a tool to early detection and investigation of pathogenesis in acute renal failure.

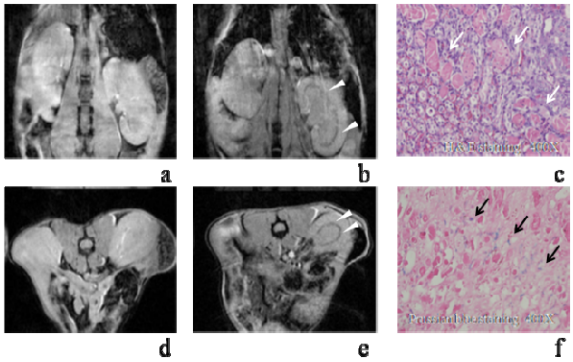

Figure 1. MR and histopathologic images of ischemic injured kidney. *In vivo* coronal and axial gradient echo MR images were obtained before (a, d), and 24 hours after the injection of iron-oxide-labeled macrophages (b, e). A sharp and black band (arrow heads) in the outer medulla is seen on the post-injection images. H&E staining of ischemia-reperfusion kidney (c) shows extensive tubular damage (white arrows) and inflammatory cell infiltration. Prussian blue staining (f) shows iron-labeled cells located in the outer medullar (black arrows).

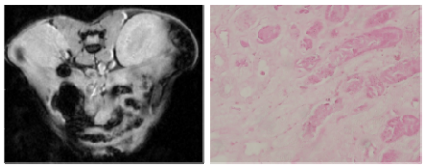

Figure 2. T2*-weighted MR image (a) and histopathology (b) results from control mice group 24 hours after the administration of iron oxide solution. Susceptibility effects due to iron oxide could not be observed. Prussian blue staining shows that iron-oxide–labeled macrophages stained blue are not present.