Non-invasive quantification of hepatic fibrosis in mouse models by magnetic resonance relaxometry (MRR)

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Background: To date studies in mouse models of hepatic fibrogenesis have been hampered by the need for tissue specimens to quantify liver fibrosis. Hence, the development of non-invasive methods of quantifying hepatic scarring is crucial to monitor potential antifibrotic therapies. Our aim was to develop non-invasive magnetic resonance-based quantification of liver fibrosis in mice with different aetiologies of fibrosis.

Methods: We analysed 13 BALB/cJ inbreed mice after toxic induced liver fibrosis (1.4 mg CCl₄/kg/wk i.p. for 6 wks), 27 Abcb4 knockout (Abcb4⁻/⁻) mice with biliary fibrosis, and 26 controls. To assess hepatic fibrosis, we ascertained fibrosis stages (F-scores) after Sirius red staining and hepatic collagen (hydroxyproline) contents. Magnetic resonance imaging (MRI) and relaxometry (MRR) were performed on a horizontal bore 9.4 T animal scanner (Bruker Biospec) with a circular polarized receive/transmit coil. Relaxation times T₁, T₂ and T₂* were acquired with turbo spin and multiple gradient echo sequences. Four MRI experiments were performed, varying the spoiled gradient echo sequence from T₁ to T₂* weighting with signal intensity (Si) measurements.

Results: Compared to wild-type controls, animals treated with CCl₄ and Abcb4⁻/⁻ mice display significantly (p<0.01) enhanced hepatic collagen contents (Fig. 1) and F-scores (not shown). As illustrated in Fig. 2, MRI experiments demonstrate differences in tissue morphology between Abcb4⁻/⁻, CCl₄ treated animals, and controls. While Si (Fig. 3A) is significantly reduced, Si deviation (Fig. 3B) is enhanced much larger in animals treated with CCl₄ as compared to healthy controls. T₁ relaxation times (Fig. 4A) differ between healthy controls and Abcb4⁻/⁻ mice as well as CCl₄-treated animals. However, Abcb4⁻/⁻ mice display significantly increased T₂ relaxation times (Fig. 4B) in comparison to healthy animals.

Conclusion: Our study demonstrates the feasibility of MRR as a non-invasive method to discriminate between fibrotic and non-fibrotic liver tissue in mice independent of the aetiology of hepatic injury. Additional studies are currently being performed to develop algorithms allowing the refined differentiation of fibrosis stages and the assessment of fibrosis resolution to provide a tool for the monitoring of antifibrotic therapies in vivo.

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