Functional and Molecular Imaging of Liver and Kidney Fibrosis

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Fibrosis refers to the excessive deposition of extracellular matrix (ECM) proteins as a reactive process to chronic injuries and results in a pathological obliteration of organ architecture and function. Two of the most commonly affected organs are the liver and the kidney, affecting millions of people worldwide. Remarkably, however, hardly any diagnostic probes and protocols are available for the non-invasive diagnosis and staging of liver and kidney fibrosis. The aim of our efforts is to establish novel contrast agents and imaging techniques for the visualization and quantification of liver and kidney fibrosis, using two-photon microscopy as a stepping stone between preclinical and clinical non-invasive imaging modalities.

As collagen accumulation is one of the key events during both liver and kidney fibrosis, it presents a suitable target for investigation. CNA-35 is a collagen-specific peptide that has been mostly used for cardiovascular imaging, because atherosclerotic plaques contain extended amounts of collagen (Type I, III, IV). However its application for liver and kidney fibrosis has not been evaluated. For this purpose, four different mouse models were used, two for liver (carbon tetrachloride (CCl4) and bile duct ligation (BDL)) and two for kidney (unilateral ureteral obstruction (UUO) and Alport mice) fibrosis. Functional imaging of blood vessels in fibrotic livers and kidneys was performed by contrast-enhanced micro-CT, providing information on the relative blood volume (rBV) and disease progression. Fluorescently labeled CNA-35 was injected in vivo and its binding and extravasation was evaluated using two-photon microscopy at time point starting at 30 min post injection up to 24h. We showed that CNA-35 accumulates specifically and with much higher efficacy in the diseased kidney and liver. As a proof of concept for noninvasive imaging, we conjugated a NIR-dye (Cy7) to CNA-35 and performed whole-body imaging using CT/FMT in UUO-mice. Our noninvasive imaging data are in agreement with the two-photon findings, showing preferred accumulation in the diseased kidney.

Our findings contribute to a better understanding of fibrosis, and to the establishment of novel and clinically relevant imaging protocols for facilitating the diagnosis and treatment of liver and kidney fibrosis.