^{19}F MRI of Colitis-Associated Colon Cancer (CACC) in a Murine Model of Inflammatory Bowel Disease

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Target Audience: This study is for MRI researchers interested in tracking inflammatory processes that precede the development of cancer.

Purpose: Inflammatory bowel diseases (IBD) significantly increases the risk of colitis-associated colon cancer (CACC), and previous studies have shown that longevity and severity of inflammation are directly correlated with the risk of CACC[1,2]. However, these studies were based on colonoscopy and mucosal biopsy, invasive diagnostic methods that cause patient discomfort and sampling errors. The aim of this study is to non-invasively image inflammatory sites and the subsequent formation of premalignant lesions. To this end, perfluorocarbon (PFC) emulsions and ^{19}F MRI were used to longitudinally follow the inflammatory sites and visualize the onset of CACC development in the colon of an IBD mouse model.

Methods: IBD-driven CACC model: The protocol developed by Neufert et al. was followed[3]. Five female A/J mice (8 wk, 18-20g) were treated with an intraperitoneal injection of azoxymethane (AOM, 10mg/kg) on day 0 and fed with 2.5% (w/v) dextran sodium sulfate (DSS) solution every 3 weeks until week 7 (**Fig. 1**). PFC injection: 200µl of perfluoro-15-crown-5-ether emulsion (Celsense Inc., VS-580H) was injected through the tail vein 48 hours before the first MRI. *In vivo & ex vivo* imaging: *In vivo* MR imaging was performed periodically from day 50 to day 120 using 11.7T Bruker Scanner and a double tuned 20 mm ^{19}F/^{1}H transceiver coil (Bruker Biospin). ^{1}H images were acquired using a fast spin echo sequence (RARE, TR/TE=1200/30 ms, Matrix size=256x256, FOV=3.2cm x 2cm, Rare Factor=8, Slice Thickness=2mm). ^{19}F MR images were acquired using the same FOV and slice thickness using a fast spin echo sequence (RARE, TR/TE=1000/14ms, Matrix size=64x32, rare factor=8). After *in vivo* imaging, the colons were excised and fixed in 4% paraformaldehyde. *Ex vivo* images were acquired with a 750 MHz microimaging system and a 25mm ^{19}F-^{1}H/^{17}O double channel volume coil (Bruker Biospin). Colon tissues were cut longitudinally after MR imaging for histological evaluation of CACC development.

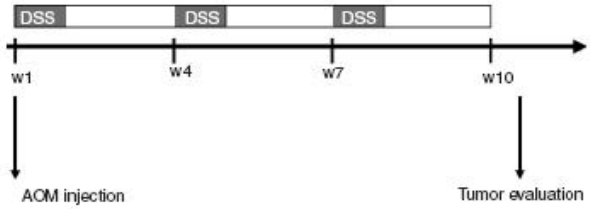

Figure 1. Protocol for inducing IBD-driven CACC in mice. Neufert et al.[3]

Results and Discussion: ^{19}F signals could be detected in the colon wall after the onset of IBD (**Fig.2**). Since PFC emulsions label macrophages with high specificity[4,5], these signals are derived from macrophages that have infiltrated the colon wall as a result of inflammation driven by DSS. The ^{19}F signal in the colon wall steadily decreased over time. CACC tumor outgrowths were observed from d80 on at the inflammatory sites. *In vivo* data were validated by *ex vivo* imaging of excised colon tissues that enabled us to exactly co-localize the inflammatory sites and tumor mass (**Fig.3**). As the colon tissues were examined longitudinally, several tumors could be observed, specifically arising from the regions with ^{19}F signals.

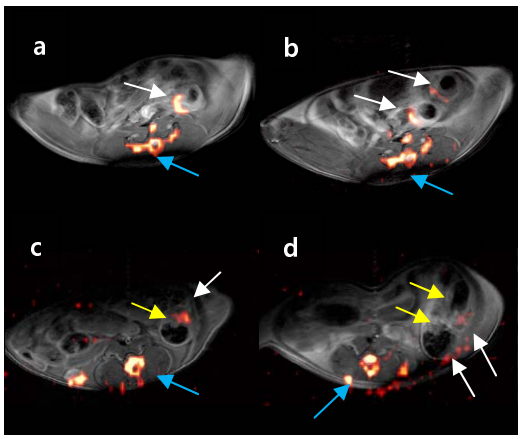

Figure 2. Representative *in vivo* MR images of mice with IBD (n=5).^{1}H (grey) and ^{19}F images (color) are superimposed. (a) d50, (b) d65, (c) d80, (d) d90. White arrows indicate the ^{19}F signals from colon wall. Blue arrows indicate spinal cords for anatomical reference. Yellow arrows indicate tumor outgrowth.

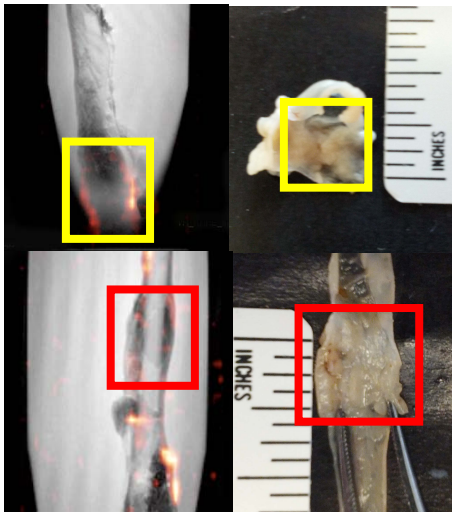

Figure 3.*Ex vivo* ^{19}F MR images of colon inflammation (left) and corresponding tumor formation (right).

Conclusion: We demonstrated the feasibility of ^{19}F MR imaging to non-invasively visualize inflammatory lesions leading to the formation of CACC tumor growths. Both *in vivo* and *ex vivo* images show the inflammatory sites on the colon wall, and the CACCs were detected growing from within those inflammatory sites. Future studies will tell if the ^{19}F signal intensity can be used as a surrogate marker for premalignant lesion formation.

References

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