MRI of mouse experimental colitis using ultrasmall superparamagnetic iron oxide particles

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During recent years, clinical and experimental studies have shown that ultrasmall superparamagnetic iron particles (USPIO) can be taken up by macrophages and tracked *in vivo* by using MRI (Trivedi et al., 2004; Dardzinski BJ et al., 2001). Animal models reflecting inflammation related diseases, such as arthritis (Dardzinski BJ et al., 2001), have been investigated. To the best of our knowledge, no studies have been published on USPIOs and experimental inflammatory bowel disease. The aim of this study was to investigate uptake of USPIOs in the colon by using MRI, a possible inflammation biomarker in an experimental mouse model of colitis.

Materials and Methods:

Contrast medium: USPIOs (Sinerem®, Guerbet Research, France), coated with dextran and with a total diameter of approximately 30 nm, were injected i.v. as a bolus dose of 500 (n= 4) or 1000 (n= 4) µmol/kg. A control group of healthy mice injected with 1000 µmol/kg (n= 5) was also included. **Animals:** A chemically induced mouse colitis model was employed (Melgar et al, 2005), where the mice were exposed to 3% dextran sulphate sodium (DSS) in the drinking water during five days, and then replaced with water only for five days. Acute colitis was developed, and a MRI pre-scan of the colon was performed. USPIOs were injected immediately after the scanning and 24 h later a post-scan was made. **MRI:** MR scanning was performed on a 4.7 T BioSpec (Bruker, Germany). Respiration was tracked by a small pressure sensitive pad on the abdomen connected to a computer controlled monitoring system (SA Instruments, USA). A 3D dataset of the mouse bowel was acquired with a fat saturated T2* sensitive gradient echo sequence with 0.2x0.2x0.2 mm^3 resolution (TR= 50 ms, TE= 4.2 ms). The data was acquired at end expiration. Buscopan® (5 mg/kg, i.p.) was administered prior acquisition of data. **Histological analysis:** The colon was cut open longitudinally from the rectum, and formalin-fixed for histological analysis. Longitudinal sections of the colon were stained with respect to iron (Perls´ blue staining) and macrophage content (BM8 antibody).

Results: The colon wall thickness was increased in DSS exposed mice compared to healthy mice. A signal reduction was observed in the proximal part of the colon in all DSS exposed mice injected with 1000 USPIOs µmol/kg (figure 1B). This circular shaped low intensity finding most probably represent the serosa of the colon wall, and it was not observed in the prescan (figure 1A). Only one mouse injected with 500 µmol/kg displayed signal decrease in the serosa proximally. Furthermore, no signal decrease was observed in the proximal part of the colon in the healthy mice. In general, histological results demonstrated little amount of USPIOs in the submucosa/mucosa, whereas USPIOs were found incorporated in BM8 positive macrophages located in the serosa of the colon. However, the serosa was not present in all histological sections due to dissection procedures.

Discussion: The present study shows that USPIOs are phagocytosed by macrophages and can be monitored *in vivo* in the serosal side by using MRI. However, it cannot be excluded that the observed signal decrease in the serosa could be due to *e.g*. presence of USPIOs in the blood, although it seems less likely since no signal decrease was observed in major blood vessels such as abdominal aorta. In conclusion, USPIO is a promising contrast agent to investigate presence of macrophages *in vivo* by means of MRI in experimental colitis. Future studies will reveal if USPIOs may serve as a biomarker in mice, and possibly also in man.

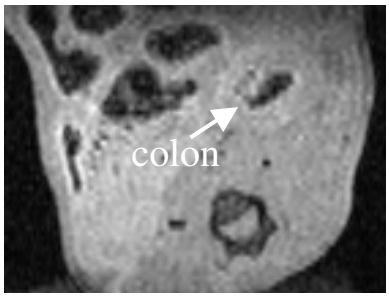

Figure 1A. Axial section of a DSS exposed mouse before administration of USPIOs.

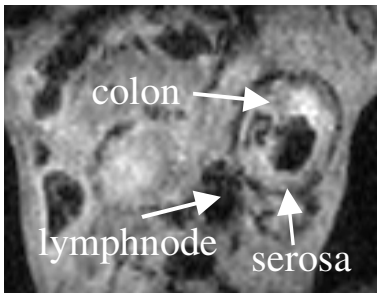

Figure 1B. Axial section of the mouse in fig 1A, 24 hours after i.v. administration of 1000 µmol/kg USPIOs.

References:

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