1.5T micro-MRI of macrophages in obesity-associated inflammation: feasibility study

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Rational and objectives

Obesity-associated inflammation plays a critical role in the development of non-alcoholic fatty liver disease. Increased adipose inflammation is associated with the recruitment of pro-inflammatory macrophages[1]. Our aim was to determine if macrophage imaging using Magnetic Resonance microscopy following systemic injection of a new kind of iron-oxide nanoparticles (P904 developed by Guerbet Research) could enable in vivo detection of adipose inflammation in a murine model of obesity.

Materials and Methods

Three C57BL6JRj Ob/Ob obese leptin-deficient mice and one C57BL6J Ob+ control mouse underwent the retro-orbitary injection of 1000µl/kg of P904 contrast agent, while 2 Ob/Ob and 1 Ob+ mice served as non-injected controls. All animals were examined 11 days after P904 or vehicle injection, using a 1.5 T Philips Achieva (CIERM Kremlin Bicêtre) MR scanner equipped with a high temperature superconducting coil[2] cooled at 80 K. Micro-MRI with isotropic encoding of $(80\mu m)^3$ was performed with 40 min 3D scans based on a standard 3D gradient-echo RF-spoiled sequence (TR/TE = 61/12 ms, bandwidth = 167 Hz/pixel), encompassing both epididymal (EPI) and sub-cutaneous (SC) fat along the flank of the animals. SPIO within the tissue were identified as hypo-intense spots on magnitude acquisitions. Their presence was quantified by measuring the signal variance normalized to the mean signal (SV) in regions of interest picked in SC and EPI fat. All animals were sacrificed immediately following MRI procedures: fat tissue samples were collected for histological examinations including Hematoxylin Eosin and Perls staining and F4/80 immuno-histochemical assay. Additionally, iron compounds within fat tissue samples were quantified using Electron Spin Resonance and ICP measurements.

Results All Ob/Ob mice injected with P904 showed accumulation of nanoparticles within epididymal and or subcutaneous fat, which was clearly depicted in both case with a mean signal-to-noise ratio of 15 (Figure 1). On the other images of non-injected Ob/Ob mice and all Ob+ mice were void of any detectable hyposignal. These results are in good agreement with the SV values which varied significantly ($p<0.03$) on Ob/Ob mice injected compared to the other mice (Figure 2). The hypointense foci detected on MRI were consistent with the presence of Perl's stained macrophages with increased F4/80 expression, detectable only in injected Ob/Ob mice.

Conclusion

We have demonstrated the efficiency of very-high-resolution 1.5T MRI, combining superconducting RF detection and an improved USPIO, for micrometric evaluation of the fat tissue in obese mice, allowing detection of macrophages related to fat inflammation injection. This approach is of great potential for the follow-up of animals involved in therapeutic trials aimed at limiting fat inflammation.

[1] Weisberg 2003, [1] Poirier-Quinot, M et al. Magn Reson Med 60, 917, 2008

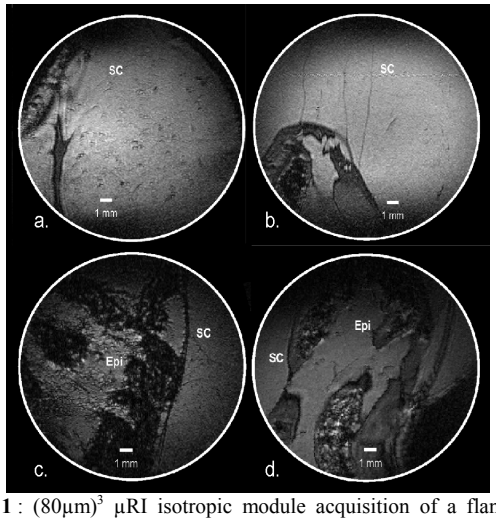

Figure 1 : $(80\mu m)^3$ µRI isotropic module acquisition of a flank of the mice, a. Ob/Ob injected, b. Ob/Ob mouse control, c. lean mouse injected, d. lean mouse control. Both epididymal (EPI) and subcutaneous (SC) fat are well delineated. Accumulations of nanoparticles (hypo intense signal) are observed on the Ob/Ob injected mouse.

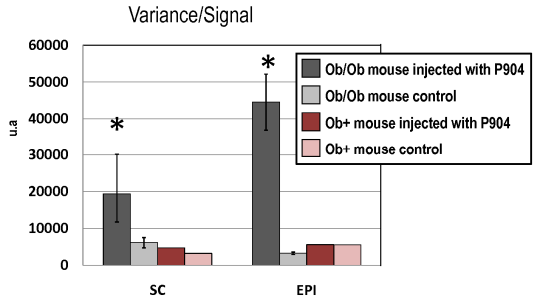

Figure 2 : variance of the signal normalized by the signal mean measured in region of interest picked in both subcutaneous and epididymal fat. $p<0.03$