**MR-Elastography, a new biomarker of the tumor vascularization in a colon cancer mice model**


1CRB3 / UMR 773, CLICHY, Ile de France, France, Metropolitan, 2UMR 8151, Unité de pharmacologie chimique et génétique et d’Imagerie. -UPCGi/Chimie-Paristech, Paris, France, Metropolitan, 3Institut Langevin, ESPCI, Paris, France, Metropolitan

**Introduction**

Assessment and follow-up of neo-angiogenesis are major challenges to characterize the malignancy of tumors and to test the efficacy of novel treatments. Here, Magnetic Resonance Elastography (MRE) has a vast potential to provide new biomarkers characterizing tumors in animal models (1). In our work, we aim at studying the alterations during the spontaneous growth of the tumor and after a treatment with an antivascular agent (combretastatin A4 phosphate CA4P)(2,3). Our working hypothesis is that alteration of the vasculature will induce significant changes in the viscoelastic properties of tissue.

**Material & Methods**

Balb-C mice were used with a colorectal cancer model (CT26) implanted either subcutaneously into the flank (ectopic model) or on the cecum (orthotopic model). First, the spontaneous growth of the tumor was followed at day 5 (primitive stage), day 11 (angiogenic stage), day 14 and 18 (late stage). Secondly, mice were treated at day 10 with 100mg/Kg of CA4P and MRI/MRE was performed 24h after injection. Studies were performed in vivo in a horizontal 7T scanner (Bruker, Pharmascan). We recorded for each animal high resolution T2-weighted images (RARE sequence, 125µm x 125µm in plane resolution), 3D steady-state MR-Elastography images with a vibration frequency of 1000 Hz (250µm isotropic image resolution) and Diffusion MR images (b-values: 250, 500, 750, 1000 and 2000 s/mm²). After MRI, the tumors were excised and the endothelial cells were marked with CD31 as well as the proliferative cells with Ki67 for detailed histological analysis.

**Results**

Histology (Fig.1) showed that the blood vessel density (BVD) (full lines) increased significantly (P<0.01) between the primitive stage at day 5 and the angiogenic stage at day 11 for the two implantations. After antivascular treatment, a significant decrease (P<0.05) of the BVD in the viable rim was measured in the ectopic model (see blue arrow in Fig.1) and not in the orthotopic model (red arrow).

Regarding the cellularity (Fig. 1, dotted lines), only the ectopic model and not the orthotopic model showed a significant increase (P<0.01) between primitive and angiogenic stage. The alterations in cellularity for the two tumor models were properly reflected by changes in ADC: the ADC dropped significantly for the ectopic model between primitive and angiogenic stage (0.66+/-.06 10⁻³ mm²/s versus 0.45 +/-0.04 10⁻³ mm²/s, P<0.05) and correlated well to cellularity (r=0.85, p=0.02) whereas no significant changes ADC were observed for the orthotopic model (0.60 +/-0.08 10⁻³ mm²/s versus 0.56 +/-0.04 10⁻³ mm²/s). After injection of CA4P, the ADC increased significantly (0.65+/-.015 10⁻³ mm²/s in ectopic model and 0.78+/-.12 10⁻³ mm²/s in orthotopic model) which could be attributed to cell death and to a decrease of cellularity.

**Discussion & Conclusion**

Our results show that it was possible to follow the evolution of a tumor and the efficacy of an antivascular agent using MRE and that MRE performed better than Diffusion MRI in this regard. It was established that the switch between primitive stage and angiogenic stage for both models could be followed by MRE. Although several alterations of the structure (vascularization, cellularity and extracellular components) could induce alterations of the mechanical properties, there was a close correlation between the vascularization and the mechanical properties. Finally, the viscosity and the elasticity are potentially new biomarkers to trace alterations of the vascularization induced by antivascular treatments.

**References**