Multiparametric MRI studies in murine tumor models

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Tumor microenvironment properties as vascularization, hypoxia, metabolism and acidosis play a fundamental role in the tumor progression and metastasis formation process. These features can be non-invasively investigated as alternative tumor biomarkers by functional imaging approaches. The aim of this PhD project involves the implementation of multimodal protocols to characterize tumor microenvironment and evaluate early response to pharmacological treatments in several tumor murine models. The dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) technique was used to quantify the tumor vascularization properties by exploiting a dedicated preclinical gadolinium-blood pool contrast agent. It was developed to accurately assess tumor vessels perfusion and permeability, owing to its specific extravasation only in presence of tumor leaky vasculature, in comparison to clinical small molecular contrast agents. In addition, the diffusion weighted imaging (DWI) technique was investigated to obtain information about tissue cellularity changes. Moreover, a quantitative clustering approach was developed to assess tumor heterogeneity and changes in the evaluation of the response to pharmacological treatments. A remarkable point relies on the combination of these techniques with low magnetic field scanner, facilitating the translation of these approaches in the clinical settings. An additional MRI approach was developed to detect contrast enhancement properties generated by several iodinated contrast agents that are clinically approved for computed tomography (CT). Their capability to quantify tumor perfusion and vascularization properties with the proposed chemical exchange saturation transfer (CEST) MRI approach were compared to the information obtained by CT. In addition, the potential of iodinated as perfusion agents for MRI applications were compared to contrast enhancement and perfusion estimates provided by conventional gadolinium ones. Furthermore, iodinated contrast agents are indicated as responsive of extracellular pH in tissue, which is reported to be particularly acidic in tumor as a consequence of its altered glycolytic pathways. This relation between acidosis and abnormal glucose consumption in tumor was investigated by comparing extracellular pH measurement by the MRI-CEST approach with 18F-FDG uptake measured by positron emission tomography (PET) in a murine tumor model. Moreover, changes in tumor acidosis were investigated to monitor the tumor progression and the response to pharmacological treatment.

The combination of these functional MRI techniques were in particular implemented for the characterization and treatment monitoring of gastrointestinal stromal tumor (GIST) xenografts sensitive and resistant to the first line treatment imatinib. For this purpose, imatinib sensitive and resistant GIST xenograft mouse models were generated and characterized by DCE-MRI, DWI and MRI MRI-pH CEST modalities. Secondly, the multiparametric MRI approach was combined with PET technique to evaluate early therapeutic response to imatinib treatment.