Neurochemical profile differentiation of glioma induced by cancer stem cells expressing WIF1: a ^{1}H-MRS longitudinal study at 14.1T

Marta Lai[1], Cristina Cudalbu[5], Bernard Lanz[1,2], Irene Vassallo[3], Marie-France Hamou[3], Monika Hegi[3], Rolf Gruetter[2,4]

[1]Laboratory of Functional and Metabolic Imaging (LIFMET), Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland, [2]Department of Radiology, University of Lausanne, Lausanne, Switzerland, [3]Laboratory of Brain Tumor Biology and Genetics, Department of Neurosurgery, Lausanne University Hospital, Lausanne, Switzerland, [4]Departments of Radiology, University of Lausanne and Geneva, Lausanne and Geneva, Switzerland

[5] Centre d'Imagerie Biomedicale, EPFL, Lausanne,Switzerland

Introduction: In vivo ^{1}H MRS at high fields is a powerful tool able to assess the concentration of about 20 metabolites implicated in different cellular functions(1). Longitudinal studies on cerebral diseases involving modifications in the metabolites concentrations are routinely applied given the non-invasiveness of the technique. This constitutes a valuable feature in cancer research when looking for early signs of tumor development, biomarkers or treatment response. Injection of human glioma stem cells (GSC) in immunodeficient rodent brain is a technique recently introduced to study the development of glioblastoma (GBM). Although other studies already proved the possibility to follow GBM from its early onset via ^{1}H MRS (2) an unanswered question is whether it is possible to distinguish between different genetic profiles of the GSC. The aim of the study was to investigate the metabolic profile of CSC expressing Wnt inhibitor factor-1 (WIF1), which has been recently identified as a candidate gene with tumor-suppressor features(3).

Methods: Seven immunodeficient male mice (Swiss Nude, 8 weeks old) were injected intracranially in the striatum with GSC derived from the same human GBM. Three of them were injected with the non-modified cell line (LN266_GS822) whereas a second group of four mice were injected with the same cell line modified for the expression of the WIF1 gene (LN266_GS824). Structural modifications of the brain were monitored every two weeks by collection of T2-weighted images. ^{1}H spectra were collected in the injection site using short-TE localized SPECIAL(4) sequence (TR/TE = 4000/2.8ms, VOI=2x2x2mm^3) every week after 3 months from the injection. Data were acquired in a 14.1T system (Varian/Magnex Scientific) using a home-build 12mm surface coil in quadrature configuration.

Results and Discussion: Spectra collected starting from 12 weeks after GSC injection showed significant metabolic modifications in both cell lines (Fig.2) while any morphological modifications was recorded in the images. Mice injected with LN266_GS822 showed increasing concentrations of Glc, Lac, myo-Ins and Gln. Glu and NAA decreases are probably due respectively to a "slowdown" of mitochondrial activity and possibly neuronal loss. At later time points a decreasing trend of myo-Ins, Glc and Lac was noticed which seems to correlate with brain swelling in the late stage of development (weeks 14-16 post-injection). GSC expressing WIF1 lead to a higher survival rate and a more stable trend in Gln and Lac, while a less severe variation is registered for Glu, myo-Ins and NAA.

Conclusion: We conclude that our study records for the first time significant differences in the metabolic profile of two GSC with different gene expression although derived from the same human specimen. Moreover we demonstrated that GSC expressing WIF1 leads to less significant metabolic modifications in the neurochemical profile lending support to the theory that confers to the gene tumor suppressing potentiality.

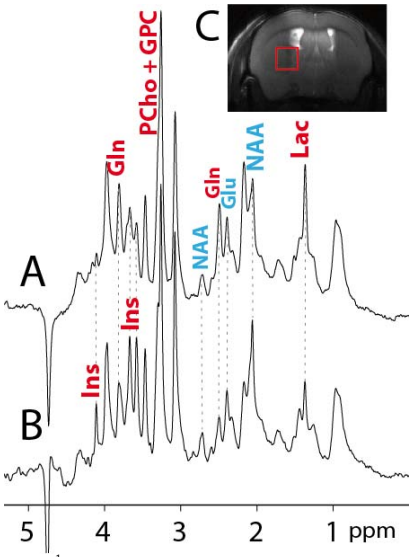

Fig.1: ^{1}H-NMR spectra of the injection site (C, 2x2x2mm^3) 16 weeks after the injection of the cell line LN266_GS822 (A) and LN266_GS824 (B) i.e. expressing WIF1. Metabolites indicated in red or blue are respectively above and below physiological level for mice of the same age and in the same brain region.

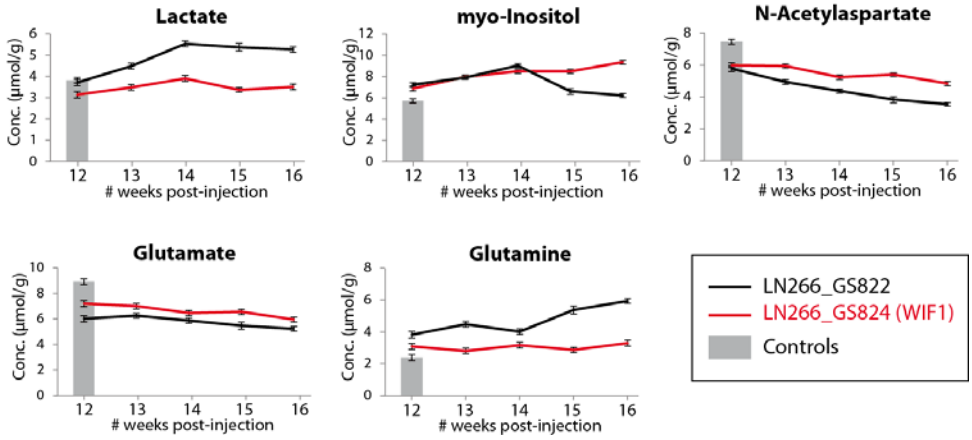

Fig.2: Evolution of the metabolite concentrations over the tumor development in the injection site between 12 and 16 weeks after the GSC injection recorded in the two groups with ^{1}H-NMR (2x2x2mm^3, Fig.1C). Metabolite concentrations in the tumors are compared with physiological concentration in a group of healthy mice (n=4) of the same age at 12 weeks post-injection (grey bar). Values represent mean ± SD.

References: (1) Duarte JMN et al., NeuroImage 2012; (2) Mlynárik V et al., NMR in Biomed 2012; (3) Lambiv WL et al., Neuro Oncol. 2011; (4) Mlynárik V et al., Magn Reson Med 2006. **Acknowledgements:** Supported by Centre d'Imagerie BioMédicale (CIBM) of the UNIL, UNIGE, HUG, CHUV, EPFL, the Leenards and Jeantet Foundations; Grant FP7-PEOPLE-2010-ITN-264780.