Using proton MRSI to predict response to Vorinostat treatment in recurrent GBM

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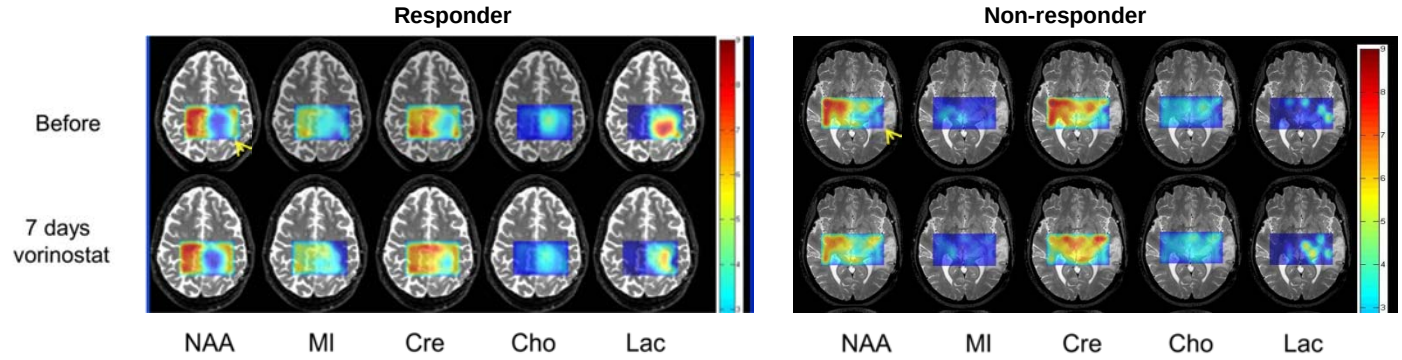
Introduction: A major impediment to the development of new therapies for glioblastoma (GBM) is a lack of biomarkers indicating response. Epigenetic modifications are now recognized as a frequent occurrence in the early phases of tumorigenesis, playing a central role in tumor development. Epigenetic alterations differ significantly from genetic modifications in that they may be reversed by ''epigenetic drugs'' such as histone deacetylase inhibitors (HDACis). As a promising new modality for cancer therapy, the first generation of HDACi is currently being tested in phase I/II clinical trials [1]. GBM alterations from therapy with HDACis, such as vorinostat (SAHA), include tumor redifferentiation/cytostasis rather than tumor size reduction limits the utility of traditional imaging methods such as MRI. Magnetic resonance spectroscopic imaging (MRSI) quantitates various metabolite levels in tumor and normal brain, allowing characterization of metabolic processes in living tissue. In this study, our main purpose is to detect the changes of metabolites in the rim of tumor before and after SAHA treatment by using chemical shift imaging and predict the response to the treatment in recurrence GBM.

Methods: Seven recurrent GBM patients were recruited by clinical oncologist for this study. The subjects received a regimen of Vorinostat 400 mg p.o./day for one week. Baseline MRS data of the patient were obtained 1-3 days before initiation of the treatment. Follow-up MRS studies were performed at day 7. The MRS data were collected on a Siemens 3T scanner with a standard quadrature head coil. T1MPRAGE images (TR = 2300 ms, TE = 3.02 ms, TI = 1100 ms, Flip Angle = 8°, voxel size = 1 × 1 × 1 mm3) and T2 weighted images (TR = 2210 ms, TE = 388 ms, voxel size = 1 × 1 × 1 mm3) were acquired for localization of the tumor. 2D Chemical shift imaging based on STEAM (TR=1590 ms, TE= 30 ms, matrix= 16x16, FOV of total acquisition time of 10 min) was performed to derive metabolite maps. All CSI data were analyzed by LC model, using an 18 metabolites basis and the intracellular water signal as the internal reference. The changes of metabolite level (ΔMet) were calculated in ratio by ($Met_{after\ treatment}/Met_{before\ treatment}$ -1). SRI (spectroscopic restoration index was calculated by (ΔNAA+ΔCre+ΔmI-ΔCho-Δ(lac/lipids)) and used in the differentiation of responders from non-responders.



Metabolic Responders				Metabolic non-Responders			
PT#	SRI	IDS-SR	Δ(Cho/NAA)	PT#	SRI	IDS-SR	Δ(Cho/NAA)
002	1.14	Better	-0.09	004	-0.02	Worse	0.022
007	1.40	Better	-0.32	009	-0.01	Worse	0.94
008	1.25	Better	-0.041	010	-0.24	Worse	0.18
				011	0.05	Worse	0.38

The figure above shows the maps of metabolites derived from STEAM-based 2D-CSI in a patient before, after 7 days of treatment with SAHA. In the responder, increased NAA, CR (creatine), and MI (myo-inositol), and decreased Lac (lactate) suggest restoration of normal brain tissue-like metabolism in SAHA treated tumor (yellow arrow). In contrast, no significant changes were seen in the non-responder.

The table summarizes the SRI and corresponding IDS-SR evaluation (self-reporting questionnaire for depression score) for the patients in two groups. SRI in the responder group is much higher than that in non-responder group. (P<0.05 tested by two sample t-test.)

Results: In our preclinical animal model, MRS detected metabolic response to SAHA after only 3 days of treatment: reduced alanine and lactate and elevated myo-inositol, N-acetyl aspartate and creatine; all moving toward normal brain levels [2]. This led to our clinical study of MRSI to evaluate the metabolic response of recurrent GBMs to SAHA. After only 7 days of SAHA treatment, MRSI can distinguish responders (SRI=1.263±0.131) (normalization/restoration of tumor metabolites towards normal brain-like metabolism) from non-responders (SRI=-0.055±0.127) (no significant change in tumor metabolites). Our initial cohort (n=7) consists of 3 responders and 4 non-responders with highly significant differences in their change in metabolite levels ($p < 0.001$). The spectroscopic result is highly consistent with IDS-SR evaluation in which all responders reported much better feelings.

Conclusions and discussion: Our results provide exciting insights into the mechanisms by which HDACi exerts its effect on GBMs. Tumor cells have increased biosynthetic needs requiring reprogramming of cellular metabolism. This creates increased energy demands, making tumor cells even more vulnerable to interventions targeting their metabolism. HDACi may induce redifferentiation in tumors by targeting tumor metabolism. Furthermore, increase of mI induced by SAHA treatment in responders indicates another benefit of SAHA for GBM patient by reducing the depression symptoms (IDS_SR result). Thus, MRSI provides a novel and robust modality to predict response to HDACi-containing combination therapy in GBM.

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References: 1. Minucci S et al., Nat Rev Cancer. 2006 Jan;6(1):38-51. 2. Wei L et al., NMR Biomed. 2012 25(9):1104-11.