MRS of orthotopic mouse brain tumors growing from directly implanted human tumor tissue

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Introduction: For the effective development and testing of novel therapies animal models of brain tumors are essential. However, frequently therapies that have shown to be effective in animal models do not show the anticipated benefit in clinical trials. One reason for this is that until recently these animal brain tumor models were typically heterotopic models where brain tumor cells were injected subcutaneously. Tumor growth could then be easily followed with caliper-based methods, and effects of treatment regimes could be assessed with little difficulty. More recently, the tumor microenvironment has been shown to play a significant role in tumor growth and response to therapy. With that realization has come the development of orthotopic models of brain tumor in animals. It remains to be established, however, how well these new models reflect the patterns of these tumors in humans. The goal of this study was to determine whether mouse brain tumors growing from human brain tumor cells implanted immediately after surgery show metabolic profiles comparable with that of the original tumor.

Methods: PRESS spectra (TE=20ms, TR 2.5s, 512-1024 averages, Bruker 7T) were acquired from mice with atypical teratoid/rhabdoid tumor (AT/RT) and choroid plexus carcinoma (CPC). Results were compared with spectra obtained from the tumors prior to surgery in the patients (PRESS, TE 30ms, TR 1.5s, GE, 1.5T). As controls and to test the variability of the metabolic profiles of tumors grown from a single cell line, 7 mice with a medulloblastoma (D283MED) and 3 mice with glioblastoma (UW87MG) were studied as well. LCModel software (S. Provencher Inc.) was used for automated processing and quantitation of animal and human spectra.

Results: AT/RT in mouse exhibited choline (Cho), creatine (Cr), and myo-inositol (mI) levels comparable with those observed in vivo in the patient (**Fig.1**). As in the patient study, Cho was the most prominent peak in experimental CPC (**Fig.2**). Tumors grown from a single cell line were highly comparable across animals and in animals studied repeatedly reflected by small standard deviations (**Fig. 3, Tab.1**).

Tab. 1: *Cr/Cho ratios in different tumors*

	AT/RT	CPC	MBL (D283MED)	GBM (UW87MG)
#mice(#studies)	2(3)	2(2)	7(13)	3(3)
Cr/Cho	2.3±0.2	0.5±0.2	0.7±01	0.9±0.2

Discussion: The metabolic pattern of tumors growing from directly implanted cells largely reflected characteristics observed in MRS of brain tumors in patients. There were two noticeable differences, however- lower lipid levels in the implanted AT/RT tumor than in patient spectra and apparent taurine (Tau) observed in all animal spectra. Despite this, the similarities of the spectra as a whole supports the hypothesis that the brains of mice supply a comparable tumor microenvironment to the human brain for tumor growth, providing further evidence that these models are indeed reflective of the clinical conditions they are meant to represent.

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References: 1. Moreno-Torres, A., et al. Neurosurgery, 2004. 55: p. 824-9. 2. Kovanlikaya, A., et al.. Radiology, 2005. 236(3): p. 1020-5.

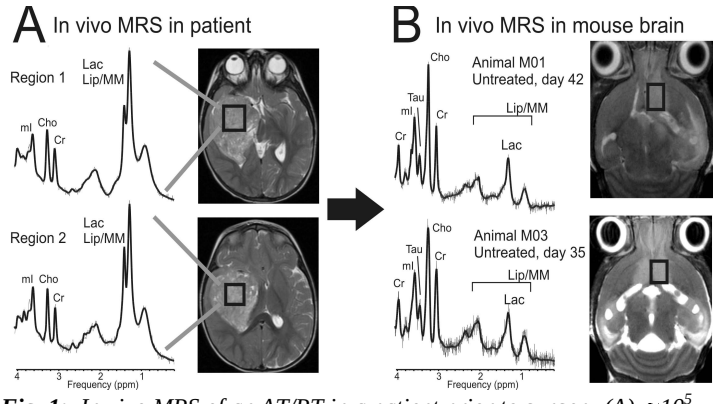

Fig. 1: *In vivo MRS of an AT/RT in a patient prior to surgery (A). ≈10^5 tumor cells were implanted immediately after surgery into NOD/SCID mice. In vivo MRS of two tumors in mice exhibited lower lipid levels whereas metabolite levels were comparable (B).*

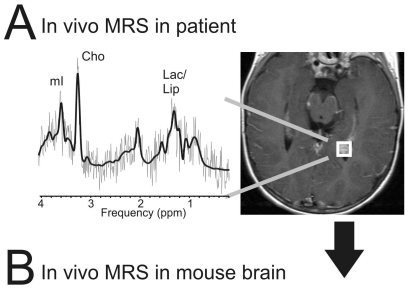

Fig. 2: *MRS of a CPC prior to surgery (A). Tumors that developed in mice showed a similar metabolic pattern with a prominent choline peak (B).*

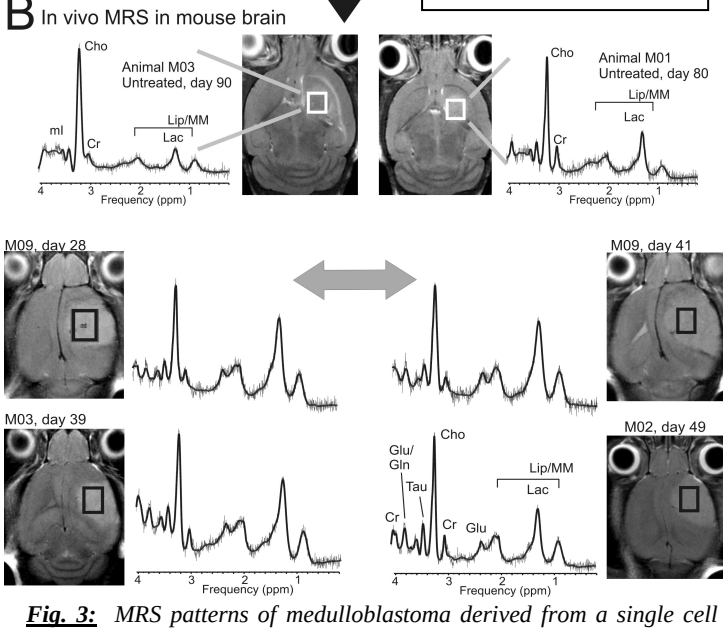

Fig. 3: *MRS patterns of medulloblastoma derived from a single cell line (D283MED) exhibited similar metabolic features. Note, top left, top right shows data from the same animal.*