MR Imaging and Spectroscopy for evaluation of brain tumor metabolic profiles in primary glioblastoma multiforme xenografts

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Introduction: Malignant brain tumors generally develop rapidly to a fatal stage with a median survival of 12 months. More effective treatments are urgently needed. To evaluate the effects of drug candidates for brain tumors, a clinically faithful animal model is essential. Cell line xenografts, utilizing cell lines such as U87-MG, generally do not recapitulate clinical characteristics such as infiltrative growth. In contrast, direct inoculation of surgical resection material, so called primary xenograft tumor models, often more closely replicating clinical disease. We used multimodality imaging to characterize an orthotopic (intracranial) glioblastoma multiforme (GBM) primary xenograft model. Bioluminescence imaging (BLI) was used to monitor tumor growth. MRI and MR spectroscopy (MRS) were used to evaluate the tumor metabolic properties.

Methods: A primary human GBM line, BT145, was lentivirally transduced with a Luc-mCherry-puro virus to generate BT145-mCLP cells. BT145-mCLP cells (180,000 in 1 μl) were stereotactically injected in the right striatum of nude mice. BLI was performed using an IVIS Spectrum system (Caliper Life Sciences) to monitor tumor growth. Peak total tumor BLI signal through standardized regions of interest (ROI) were calculated using the Living Images software package (version 4.0, Caliper Life Sciences), with data presented as total flux in photons per second per ROI.

Results: In this study, we demonstrate that in this primary GBM xenograft model, tumor tissue had higher T1, T2 and diffusion values by MRI and MRS. 10% error was added to all values. Table 1 shows the T1, T2 and ADC values in tumor were significantly higher than those in contralateral brain tissue. The 5 tumor spectra and 5 contralateral spectra were summed respectively to yield one spectrum in each case as shown in Fig. 3. Major metabolites were identified with corresponding peaks; the ratios of detected metabolites to Cr were calculated and plotted for both groups in Fig 4. Major metabolites that were shown to change are also shown in Fig. 4. The ratios of NAA, GABA, Cho, Trp/Glc/myo-inositol (myo-ino) were significantly different compared to those in contralateral brain tissue. These metabolic peaks were indicated with black arrows in Fig. 3. The Cho/NAA statistical index (CNI) was significantly higher in tumor (CNI=4.3) than in control tissue (CNI=1.4).

Discussion and Conclusions: In this study, we demonstrate that in this primary GBM xenograft model, tumor tissue had higher T1, T2 and diffusion values by comparison to the contralateral region in the brain, consistent with GBM in human patients (2). MRS assessment of the metabolic profile of the primary GBM xenografts revealed a reduction of NAA and GABA, and elevation of Lipid, Cho, Myo, Glx in tumors, which is likewise in agreement with prior human MRS GBM studies (3). Moreover, histologic analysis revealed an infiltrative pattern of growth, similar to disease in humans. Together, these results demonstrate that this primary xenograft model of GBM closely recapitulates the histological, radiologic and metabolic profile of human GBM.

Fig.1. Tumor growth curve by BLI.

Fig.2. Comparison of MRI and histologic findings

Table 1. T1, T2 and ADC values

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<tr>
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<th>T1 (ms)</th>
<th>T2 (ms)</th>
<th>ADC (×10−3 mm2·s−1)</th>
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<tbody>
<tr>
<td>Tumor</td>
<td>1901±164</td>
<td>63±1</td>
<td>0.70±0.008</td>
</tr>
<tr>
<td>Contralateral</td>
<td>1612±47</td>
<td>46±2</td>
<td>0.53±0.097</td>
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P-value: 0.005 1.65E-05 0.01

Fig.3. Comparison of average spectra from tumor and contralateral sides of mouse brain. Five spectra were summed up in each case.

Fig.4. Comparison of metabolite integral ratio to Cr of major metabolites in tumor and contralateral sides identified by MRS. 10% error was added to all values.