Title: Comparison of Tumour pH Environment and Glycolysis Measurements in a C6 Rat Model of Glioma

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Structured Abstract:

Introduction: Glioblastoma multiforme (GBM) is one of the most aggressive brain tumours and patients diagnosed with glioma have a median survival time of 12-15 months. One of the hallmarks of GBM is the reliance on glycolytic metabolism, even without adequate oxygen supply, leading to a more acidic tumour environment. There is an intrinsic relationship between tumour glycolysis and its pH environment. The tumour pH environment can be evaluated with chemical exchange saturation transfer (CEST) MRI. Glucose metabolism can be evaluated with 18F-FDG PET and also by MRSI, using an injection of hyperpolarized [1-13C]pyruvate. In this study, we compared tumour pH measurements from CEST to FDG-PET and lactate to pyruvate (Lac:Pyr) ratio from MRSI to explore the relationship between tumour pH environment and glycolytic metabolism.

Methods: 1 million C6 glioma cells were implanted in the brains of Wistar rats (n=11) using stereotactic surgery. Tumours were monitored actively using CT starting from Day 7 post-surgery. Glucose metabolism was measured in the tumour using SUV derived from PET images acquired 60 minutes after a bolus of FDG (30 ± 2 MBq) 11 to 13 days post-surgery. CEST measurements were acquired the following day. CEST spectra were acquired on a 9.4 T MRI. One set of CEST spectra was acquired pre-glucose infusion followed by two sets of CEST spectra acquired during a bolus + constant infusion of glucose solution. The effect of glucose infusion on intracellular pH (pHi) was evaluated using AACID. Rats were transported to a 3T MRI and injected with 3 ml of 80 mM hyperpolarized pyruvate. The correlations were evaluated using Pearson's correlation.

Results: Significant correlations between tumour glycolysis measurements of Lac:Pyr and ΔAACID within the tumour (r = 0.83, P = 0.01) and peri-tumoural region (r = 0.76, P = 0.028) was observed. No significant correlations were found between tumour SUV and ΔAACID within the tumour (r = -0.45, P = 0.17) and peri-tumour regions (r = -0.6, P = 0.051).

Discussion: An inversely proportional relationship was found between tumour glycolytic metabolism with changes of tumoural AACID and peri-tumoural AACID. A higher rate of tumour glycolysis correlates with more basic pH changes at the tumour and peri-tumoural region after glucose infusion. The pHi tends to be more alkaline regardless of high glycolytic metabolism. This might suggest that tumour and peri-tumoural cells tried to maintain cell pH homeostasis in order to avoid cell death from acidosis. The blood glucose conditions were different prior to the two glycolysis measurements: the averaged blood glucose level was 7.62 ± 1.78 mmol/L before FDG-PET acquisition, whereas it was above 33 mmol/L prior to MRSI experiment. This may have contributed to an opposite trend in the correlation of peri-tumour AACID with tumour Lac: Pyr.