Lactate as tumor biomarker

Increased lactate (Lac) level in brain tumors is in vivo detectable by Proton magnetic resonance spectroscopic imaging (MRS) but is frequently overlapped by strong lipid signals, which either leads to a weak quality of the Lac signal or even inhibit its detection.

Bisdas et al. sought to optimize the separation of Lac from lipid signals in intermediate-echo time MRS acquisitions thus allowing its applicability as clinical biomarker in glioblastomas.

Data of 27 patients with glioblastoma multiforme (GBM) were analysed using standard post-processing software as well as in-house modified technique based on the same commercially available software. The patients' Lac concentration values provided by the MRS post-processing technique were converted to realistic concentrations by using an appropriately calibrated phantom. The Cramér-Rao lower bound (%CR) was the principal criterion for estimating the quality of the MRS post-processing results.

Results: Based on the ex vivo calibration, the analysis of the in vivo MR spectroscopy measurements led to an improvement of the %CR(Lac) value from 18 % to 8 %. In a single case, the detection of Lac was achievable only by the modified technique, as Lac signal was contaminated with lipids using the standard analysis. The resulting in vivo Lac values from the modified analysis (median: 4.77 mmol/l, range: 1.5-9.2) were considered as a realistic order of magnitude for the metabolite concentrations, whereas no Lac was identified in the normal appearing white matter. This qualified also Lac mapping as a biomarker for regional heterogeneity in GBM.

Conclusions: The proposed methodology is a promising first step for more reliable analysis of Lac signal, decontaminating it from lipid peaks in MRS, and may help to establish Lac as a biomarker for brain tumours in clinical routine [1)].

Highly malignant brain tumors harbor the aberrant propensity for aerobic glycolysis, the excessive conversion of glucose to lactic acid even in the presence of ample tissue oxygen. Lactic acid is rapidly effluxed to the tumor microenvironment via a group of plasma-membrane transporters denoted monocarboxylate transporters (MCTs) to prevent “self-poisoning.” One isoform, MCT2, has the highest affinity for lactate and thus should have the ability to respond to microenvironment conditions such as hypoxia, lactate, and pH to help maintain high glycolytic flux in the tumor. Yet, MCT2 is considered to not respond to hypoxia, which is counterintuitive. Its response to tumor lactate has not been reported. In this report, we experimentally identify the transcription initiation site/s for MCT2 in astrocytes (normal) and glioma (tumor). We then use a BACmid library to isolate a 4.2-kbp MCT2 promoter-exon I region and examine promoter response to glycolysis-mediated stimuli in glioma cells. Reporter analysis of nested-promoter constructs indicated response of MCT2 to hypoxia, pH, lactate, and glucose, the major physiological “players” that facilitate a tumor's growth and proliferation. Immunoblot analysis of native MCT2 expression under altered pH and hypoxia reflected the reporter data. The pH-mediated gene-regulation studies we describe are the first to record H+-based reporter studies for any mammalian system and demonstrate the exquisite response of the MCT2 gene to minute changes in tumor pH. Identical promoter usage also provides the first evidence of astrocytes harnessing the same gene regulatory regions to facilitate astrocyte-neuron lactate shuttling, a metabolic feature of normal brain [2)].

We assess whether serum lactate is a potential biomarker for non-glial cell brain tumors. Rapidly growing tumor cells typically have glycolytic rates up to 200 times higher than those of their normal tissues of origin and produce lactate even in the presence of oxygen. This phenomenon is called the Warburg effect. We recently showed that serum lactate levels can be used as a potential non-invasive biomarker in glial cell brain tumors, which correlates with both tumor grade and the extent of malignancy. In the present study, we found that patients with metastatic brain tumors had significantly higher baseline serum lactate levels compared to patients with meningioma and pituitary tumors. There was a statistically significant association between metastatic brain tumors and elevated serum lactate. We demonstrate that lactate can be used as a non-invasive biomarker to determine malignancy for brain tumors. Further analyses of larger populations will be needed to establish the value of serum lactate in determining the response to therapy or early recurrence [3].

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Bisdas S, Schäfer R, Kolb R, Bender B, Klose U. Lactate as clinical tumour biomarker: Optimization of lactate detection and quantification in MR spectroscopic imaging of glioblastomas [published online ahead of print, 2020 Jul 9]. Eur J Radiol. 2020;130:109171. doi:10.1016/j.ejrad.2020.109171
2)
Caruso JP, Koch BJ, Benson PD, Varughese E, Monterey MD, Lee AE, Dave AM, Kiousis S, Sloan AE, Mathupala SP. pH, Lactate, and Hypoxia: Reciprocity in Regulating High-Affinity Monocarboxylate Transporter Expression in Glioblastoma. Neoplasia. 2017 Jan 13;19(2):121-134. doi: 10.1016/j.neo.2016.12.011. [Epub ahead of print] PubMed PMID: 28092823.
3)
Bharadwaj S, Venkatraghavan L, Mariappan R, et al. Serum lactate as a potential biomarker of non-glial brain tumors. J Clin Neurosci. 2015;22(10):1625-1627. doi:10.1016/j.jocn.2015.05.009