SP4 Cancer metabolites monitoring: Wendy Bautista, MD PhD, National Cancer Institute/NIH
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Significance: Dr. Bautista is a research scientist at Neuro-Oncology Branch NCI NIH. She has over seven years of experience in neuroscience and electrophysiology, four years of experience in cellular and molecular biology in addition to stem cell research and also a strong background in the brain tumor stem cells and liver tumor metabolism fields [1-10]. She is also pursuing to establish a complete panel of oncometabolites on IDH1 (isocitrate dehydrogenase) mutant tumors exposed to TMZ (temozolomide) to identify the genes involved in this developmental changes since most of this tumors occur during development.

Glioblastoma is a deadly brain tumor for which there are limited therapies and chemo-radioresistance remains a serious problem to solve. Heavy metal exposure in the general population has been observed in industrialized areas in the US and other countries. Environmental lead exposure has been studied in the children population especially the ones with lower income who are exposed to industrial habitats and the fact that leaded gasoline is of frequent use in these areas. Low levels and chronic exposure of this metal has also been associated with a higher risk of cardiac disease and cancer as has been studied in the US according to USA NHANES (National Health and Nutrition Examination Survey). Lead and heavy metals have been also being present in the West Coast since these sites have been the principal industrial sites in the US for over 50 years. Interestingly, the highest incidence of pediatric brain tumors is localized in the West Coast [11,12]. Epigenetic alterations are the hallmark of cellular damage produced by environmental metals, hyper-methylation occurs when methyl groups are added to cytosine bases at DNA CpG promoter islands resulting in gene silencing. Recent studies have suggested that heavy metal deposition in malignant cell lines increase their potential to develop drug resistance mechanisms[13-15]. Furthermore, recent studies have demonstrated that cadmium induces methylation of VEGF and other angiogenic signals[16,17]. Global methylation changes are of particular importance in this study since it is now recognized that transgenerational epigenetic inheritance could potentially be occurring [18-20], for many DNA changes related to the presence of heavy metals, thus implying the importance of monitoring these changes in the population to avoid exposure, genetic alterations in tumor samples.
Approach: Altered glucose metabolism in glioblastoma has been extensively investigated in vitro[21,22] and, more recently, in vivo in patients [21] and in human orthotopic glioblastoma models [22-24]. These studies established that glucose is oxidized in the citric acid cycle in addition to confirming that there is a significant fraction of glucose that is shunted to lactate generation. Recent studies have described that high grade gliomas are further subtyped into different molecular subclasses the first two main subdivisions involve MGMT methylation status and IDH1 132 H mutation. This subclasses have been found in the 70% of the low grade astrocytomas and oligodendrogliomas containing 1p/19q deletion [25,26]. IDH mutant low grade gliomas are frequently found in patients <50 % [26] and although their progression is slow compared to IDH wildtype tumors these tumors have the highest morbidity due to their infiltrative nature in frontal locations, the majority of these patients have high incidence of seizures. It has been demonstrated that the glycolytic metabolism in malignancies highly correlates with radioresistance [25-29]. It is a potential strategy to overcome radioresistance by modulating tumor glucose metabolism and the cellular redox status [26]. Tumor heterogeneity, neuronal microenvironment and vascularization pattern within the tumor are some of the important features that tailor glioma response to therapy [25]. To date no attempt has been made to discern glioma tumor temozolomide response in relation to intrinsic metabolic and extrinsic tumor microenvironment features including location and vascularization.

We hypothesize that heavy metal exposure and intrinsic and extrinsic tumor microenvironment induces chemo and radioresistance. NIR Raman spectroscopy from in vivo and ex vivo tumor patient samples can be used as a diagnostic tool to assess the nuances between the response difference and the major mechanisms among the different molecular subtypes of gliomas. It can be further developed to work as a minimally-invasive diagnostic method that can be used in combination with hyperpolarized MRI for quantifying glioblastoma glucose metabolism. As a LBRC service project, we will (1) analyze in vitro mechanisms of radio and chemoresistance of cells exposed to TMZ and radiation IDH1 wt and IDH1mt cell lines by metabolic profile detection of 2HG, 2KG Glutamate, GABA, 5HT and long chain fatty acids using NIR Raman microscopy. Heavy metal exposure on these cell lines and samples will be evaluated and quantified with ICP-MS spectrometry, (2) analyze and quantify metabolomic and drug-induced changes of TMZ treated glioma patient derived xenografts using tumor sections FFPE, frozen samples and dissociated tumor. Cells will be isolated from the tumor and submitted for Raman measurements.
Center Offering: LBRC will provide Raman microscope and clinical Raman instrumentation for this project. We will further provide chemometric algorithm and assistance in characterizing brain tissue and in quantifying glucose concentration. Since Dr. Bautista does not have previous photonic expertise, we will assist Dr. Bautista in experiment design and will providing training in basic biophotonics and Raman equipment usage.

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