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NEURO-ONCOLOGY ADVANCES

ABSTRACTS

ABSTRACTS FROM THE 2021 SNO-NCI JOINT SYMPOSIUM: TARGETING CNS TUMOR METABOLISM

Submission Categories and Abbreviations:
BIMG - Metabolic Biomarkers and Imaging
DDRE - Metabolic Drug Targets, Resistance
ETMM - Epigenome, Transcriptome, Metabolome and Modeling
FSMP - Metabolic Fluxes and Signaling of Metabolic Pathways
TBMT - Technologies for Studying Brain Metabolism

METABOLIC BIOMARKERS AND IMAGING

BIMG-02. IMAGING IMMORTALITY: TERT EXPRESSION ALTERS GLUCOSE METABOLISM IN LOW-GRADE GLIOMAS IN A MANNER THAT CAN BE LEVERAGED FOR NONINVASIVE METABOLIC IMAGING

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Telomerase reverse transcriptase (TERT) is essential for tumor immortality and uncontrolled proliferation, including in low-grade oligodendrogliomas (LGOGs). Since it is silenced in somatic cells, TERT is also a therapeutic target. Non-invasive imaging of TERT can differentiate tumor from normal brain or lesions such as gliosis and allow assessment of response to therapy. The goal of this study was to identify magnetic resonance spectroscopy (MRS)-detectable metabolic alterations associated with TERT that can be leveraged for noninvasive imaging in LGOGs. We examined patient-derived BT54 neurospheres in which TERT expression was silenced by RNA interference. ^{1}H-MRS showed that steady-state levels of NAD(P)/H, glutathione, aspartate and AXP were elevated in $BT54_{TERT+}$ neurospheres relative to $BT54_{TERT-}$. Glucose flux through the pentose phosphate pathway (PPP) is essential for generating NADPH, which maintains glutathione homeostasis. ^{13}C-MRS confirmed that [2-^{13}C]-glucose flux through the PPP was elevated in $BT54_{TERT+}$ neurospheres relative to $BT54_{TERT-}$, an effect associated with higher activity of the PPP enzyme glucose-6-phosphate dehydrogenase (G6PDH). Hyperpolarized ^{13}C-MRS is a method of increasing the signal to noise ratio of ^{13}C-MRS such that it can monitor metabolic fluxes noninvasively in cells, animals and patients. Consistent with elevated PPP flux and G6PDH activity, hyperpolarized [U-^{13}C]-glucose metabolism via the PPP to 6-phosphogluconate (6-PG) was elevated in $BT54_{TERT+}$ neurospheres relative to $BT54_{TERT-}$. Importantly, examination of an additional patient-derived LGOG model, the SF10417 model which readily forms orthotopic tumor xenografts in rats, showed that 6-PG production from hyperpolarized [U-^{13}C]-glucose demarcated tumor from normal brain. Furthermore, LGOG patient biopsies had elevated NAD(P)/H, glutathione, aspartate, AXP and G6PDH activity relative to gliosis biopsies, confirming the clinical validity of our observations. Collectively, we have identified a metabolic signature of TERT expression that can be leveraged via hyperpolarized [U-^{13}C]-glucose to improve diagnosis and treatment response monitoring for LGOG patients.

BIMG-03. MOLECULAR IMAGING OF GLUCOSE METABOLISM FOR INTRAOPERATIVE FLUORESCENCE GUIDANCE DURING GLIOMA SURGERY

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PURPOSE: This study evaluated the utility of using molecular imaging of fluorescent glucose analog 2-(*N*-(7-Nitrobenz-2-oxa-1,3-diazol-4-yl)Amino)-2-Deoxyglucose (2-NBDG) as a discriminatory marker for intraoperative tumor border identification in a mouse glioma model. **PROCEDURES:** 2-NBDG and were assessed in GL261 and U251 orthotopic tumor bearing mice. Intraoperative fluorescence of 2-NBDG administered topical and intravenous in normal and tumor regions was assessed with operating microscope, handheld confocal laser scanning endomicroscope (CLE) and benchtop confocal laser scanning microscope (LSM). Additionally, 2-NBDG fluorescence in tumors was compared to 5-aminolevulinic acid-induced protoporphyrin IX fluorescence. **RESULTS:** Intravenously administered 2-NBDG was detectable in brain tumor and absent in contralateral normal brain parenchyma on wide field operating microscopy imaging. Intraoperative and benchtop CLE showed preferential 2-NBDG accumulation in the cytoplasm of glioma cells (tumor-background ratio of 2.76±0.43). Topically administered 2-NBDG did not create a sufficient tumor-background contrast for white field operating microscopy imaging, or under benchtop LSM (tumor-background ratio 1.42 ± 0.72). However, topical 2-NBDG did create sufficient contrast to evaluate cellular tissue architecture and differentiate tumor cells from normal brain parenchyma. PpIX imaging resulted in a more specific delineation of gross tumor margins than IV or topical 2-NBDG, and a significantly higher tumor-normal brain fluorescence intensity ratio. **CONCLUSION:** After intravenous administration, 2-NBDG selectively accumulated in the experimental brain tumors and provided bright contrast under wide field fluorescence imaging with a clinical grade operating microscope. Topical 2-NBDG was able to create a sufficient contrast to differentiate tumor from normal brain cells based on visualization of cellular architecture with CLE. 5-ALA demonstrated superior specificity in outlining tumor margins and significantly higher tumor-background contrast. Given its non-toxicity, using 2-NBDG as a topical molecular marker for noninvasive in vivo intraoperative microscopy is encouraging, and warrants further clinical evaluation.

BIMG-04. MAPPING HETEROGENEITY OF HIGH-GRADE GLIOMA METABOLISM USING HIGH RESOLUTION 7T MRSI

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OBJECTIVES: Neurosurgical resection in gliomas depends on the precise preoperative definition of the tumor and its margins to realize a safe maximum resection that translates into a better patient outcome. New metabolic imaging techniques could improve this delineation as well as designate targets for biopsies. We validated the performance of our fast high-resolution whole-brain 3D-magnetic resonance spectroscopic imaging (MRSI) method at 7T in high-grade gliomas (HGGs) as first step to this regard. **METHODS:** We measured 23 patients with HGGs at 7T with MRSI covering the whole cerebrum with 3.4mm isotropic resolution in 15 min. Quantification used a basis-set of 17 neurochemical components. They were evaluated for their reliability/quality and compared to neuroradiologically segmented tumor regions-of-interest (necrosis, contrast-enhanced, non-contrast-enhanced+edema, peritumoral) and histopathology (e.g., grade, IDH-status). **RESULTS:** We found 18/23 measurements to be usable and ten neurochemicals quantified with acceptable quality. The most common denominators were increases of glutamine, glycine, and total choline as well as decreases of N-acetyl-aspartate and total creatine over most tumor regions. Other metabolites like taurine and serine showed mixed behavior. We further found that heterogeneity in the metabolic images often continued into the peritumoral region. While 2-hydroxy-glutarate could not be satisfyingly quantified, we found a tendency for a decrease of glutamate in IDH1-mutant HGGs. **DISCUSSION:** Our findings corresponded well to clinical tumor segmentation but were more heterogeneous and often extended into the peritumoral region. Our results corresponded to previous knowledge, but with previously not feasible resolution. Apart from glycine/glutamine and their role in glioma progression, more research on the connection of glutamate and others to specific mutations is necessary. The addition of low-grade gliomas and statistical ROI analysis in a larger cohort will be the next important steps to define the benefits of our 7T MRSI approach for the definition of spatial metabolic tumor profiles.

BIMG-05. TO BE OR NOT TO BE GLYCOLYTIC: DEUTERATED GLUCOSE-BASED ASSESSMENT OF THE WARBURG EFFECT ALLOWS NON-INVASIVE IMAGING OF TUMOR BURDEN AND TREATMENT RESPONSE IN MUTANT IDH GLIOMAS *IN VIVO*

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