quiring high resolution metabolic maps similar to anatomical MRI is challenging due to low metabolite concentrations, and alternative approaches that increase resolution by post-acquisition image processing can mitigate this limitation. We developed deep learning super-resolution MR spectroscopic imaging (MRSI) to map tumor metabolism in patients with mutant IDH glioma. We used a generative adversarial network (GAN) architecture comprised of a UNet neural network as the generator network and a discriminator network for adversarial training. For training we simulated a large data set of 9600 images with realistic quality for acquired MRSI to effectively train the deep learning model to upsample by a factor of four. Two types of training were performed: 1) using only the MRSI data, and 2) using MRSI and prior information from anatomical MRI to further enhance structural details. The performance of super-resolution methods was evaluated by peak SNR (PSNR), structure similarity index (SSIM), and feature similarity index (FSIM). After training on simulations, GAN was evaluated on measured MRSI metabolic maps acquired with resolution 5.2×5.2 mm^2 and upsampled to 1.3×1.3 mm^2. The GAN trained only on MRSI achieved PSNR = 27.94, SSIM = 0.88, FSIM = 0.89. Using prior anatomical MRI improved GAN performance to PSNR = 30.75, SSIM = 0.90, FSIM = 0.92. In the patient measured data, GAN super-resolution metabolic images provided clearer tumor margins and made apparent the tumor metabolic heterogeneity. Compared to conventional image interpolation such as bicubic or total variation, deep learning methods provided sharper edges and less blurring of structural details. Our results indicate that the proposed deep learning method is effective in enhancing the spatial resolution of metabolite maps which may better guide treatment in mutant IDH glioma patients.

BIMG-23. SINGLE-VOXEL VERSUS MULTI-SLICE MRSI IN PATIENTS WITH GLIOMA ON A KETOGENIC DIET INTERVENTION

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BACKGROUND: Ketogenic diet therapies (KDTs) may be beneficial by exploiting glioma metabolic vulnerabilities. The GLioma modified Atkins-based Diet study (GLAD; NCT02286167) evaluated systemic and cerebral (MR spectroscopy) biomarkers to determine the feasibility and biological effects of a KDT in glioma patients. While we observed metabolic changes in tumor and normal brain after KDT using single-voxel MRS (SV-MRS), optimal voxel placement was not always achieved. AIMS: We performed an exploratory analysis comparing cerebral metabolite changes using multi-slice MRSI (MS-MRSI) versus SV-MRS acquisition. **METHODS:** We evaluated four patients from the GLAD study (mean age 39years; 2 female, 3 AA IDH-mutant, 1 GBM IDH-wildtype) who underwent MRS at baseline and following eight weeks of KDT. SV-MRS (sLASER, TR/TE 2.2s/34ms) was acquired from a 2x2x2cm voxel placed in the residual tumor and the contralateral homologous brain. MS-MRSI was acquired with a multi-slice spin echo sequence (TR/TE 3.6/144ms, 4 slices, nominal resolution 13x7x7mm, SENSE factor 3) and maps of total choline (tCho), total N-acetyl-aspartate (tNAA), and lactate (Lac) were reconstructed and normalized relative to creatine. Metabolite levels were measured on the MS-MRSI maps using a region of interest placed in the same areas studied with the SV-MRS. **RESULTS:** Lesional tCho and tNAA levels showed strong correlation between SV-MRS and MS-MRSI both at baseline (Pearson's r=0.92 and 0.97, respectively) and after 8 weeks of KDT (r=0.96 and 0.84, respectively). tCho and tNAA correlated less robustly between SV-MRS and MS-MRSI in the contralesional region (r=0.56–0.96). Lesional Lac was significantly lower after KDT (1.01±0.48 versus 0.59±0.24, paired t-test p=0.02). **CONCLUSIONS:** While SV and MS-MRSI provided generally concordant lesional results, MS-MRSI offers added potential to map regional variations not captured by SV-MRS and thus may better define the control regions. MS-MRSI detected a decrease in tumoral lactate levels following study intervention, suggesting KDT-related changes in tumoral energy metabolism.

METABOLIC DRUG TARGETS, RESISTANCE

DDRE-01. METABOLIC PLASTICITY AND HETEROGENEITY IN IDH1MUT CELL LINES PRODUCES RESISTANCE TO GLUTAMINASE INHIBITION BY CB839

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BACKGROUND: Mutant IDH1 ($IDH1^{mut}$) gliomas have characteristic genetic and metabolic profiles and exhibit phenotype that is distinct from their wild-type counterparts. The glutamine/glutamate pathway has been hypothesized as a selective therapeutic target in $IDH1^{mut}$ gliomas. However, little information exists on the contribution of this pathway to the formation of D-2-hydroxyglutarate (D-2HG), a hallmark of IDH^{mut} cells, and the metabolic consequences of inhibiting this pathway. **METHODS:** We employed an untargeted metabolic profiling approach in order to detect metabolic changes arising from glutaminase (GLS) inhibition treatment. Subsequently, ^{13}C metabolic tracing analysis through a combined Nuclear Magnetic Resonance and Liquid Chromatography-Mass Spectrometry approach, we explored the fate of glutamine and glucose under treatment with CB839 a glutaminase-GLS-inhibitor and their respective contributions to D-2HG formation. **RESULTS AND CONCLUSIONS:** The effects of CB839 on cellular proliferation differed among the cell lines tested, leading to designations of GLS-inhibition *super-sensitive*, *-sensitive* or *-resistant*. Our data indicates a decrease in the production of downstream metabolites of glutamate, including those involved in the TCA cycle, when treating the sensitive cells with CB839 (glutaminase -GLS- inhibitor). Notably, CB839-*sensitive* $IDH1^{mut}$cells respond to GLS inhibition by upregulating glycolysis and lactate production. In contrast, CB839-*resistant*$IDH1^{mut}$ cell lines do not rely only on glutamine for the sustenance of TCA cycle. In these cells, glucose contribution to TCA is enough to compensate the downregulation of glutamine-derived TCA metabolites. This investigation reveals that the glutamine/glutamate pathway contributes differentially to D-2HG in a cell-line dependent fashion on a panel of IDH^{mut} cell lines. Further, these results demonstrate that there is a heterogeneous landscape of $IDH1^{mut}$ metabolic phenotypes. This underscores the importance of detailed metabolic profiling of $IDH1^{mut}$ patients prior to the decision to target glutamine/glutamate pathway clinically.

DDRE-02. SMOOTHENED-ACTIVATING LIPIDS DRIVE RESISTANCE TO CDK4/6 INHIBITION IN HEDGEHOG-ASSOCIATED MEDULLOBLASTOMA

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BACKGROUND: Medulloblastoma is an aggressive pediatric brain tumor that is associated with misactivation of the Hedgehog (HH) pathway. Our lab has shown that *CDK6*, a critical activator of the cell cycle, is a direct transcriptional target of oncogenic HH signaling, and that inhibiting CDK6 blocks the growth of HH-associated medulloblastoma in mice. A clinical trial exploring the efficacy of CDK6 inhibition in medulloblastoma patients is underway, but prior attempts to target the HH pathway in medulloblastoma have been encumbered by resistance to molecular monotherapy. Thus, we sought to identify mechanisms of resistance to CDK6 inhibition in HH-associated medulloblastoma. **METHODS:** We performed orthogonal CRISPR and CRISPR interference screens in HH-associated medulloblastoma cells treated with pharmacologic inhibitors of CDK6 *in vitro*, and RNA-sequencing of HH-associated medulloblastomas with genetic deletion of CDK6 *in vivo*. Mechanistic and functional validation of resistance pathways was performed using CRISPR interference, immunoblotting, immunofluorescence, genetics, and pharmacology. Lipid quantification was carried out by ultra-high performance liquid chromatography-tandem mass spectrometry. **RESULTS:** Our results reveal that decreased ribosomal protein expression underlies resistance to CDK6 inhibition in HH-associated medulloblastoma, leading to endoplasmic reticular (ER) stress and activation of the unfolded protein response (UPR). We show that ER stress and the UPR increase the activity of enzymes producing Smoothened-activating sterol lipids that sustain oncogenic HH signaling in medulloblastoma despite CDK6 inhibition. These discoveries suggest that combination molecular therapy against CDK6 and HSD11ß2, an enzyme producing Smoothened-activating lipids, may be an effective treatment for HH-associated medulloblastoma. In support of this hypothesis, we demonstrate that concurrent genetic deletion or pharmacological inhibition of CDK6 and HSD11ß2 additively blocks the growth of multiple models of HH-associated medulloblastoma in mice. **CONCLUSIONS:** Smoothened-activating lipid biosynthesis underlies resistance to CDK6 inhibition in HH-associated medulloblastoma, revealing a novel combination therapy to treat the most common malignant brain tumor in children.

DDRE-03. IDH1-MUTANT GBM CELLS ARE HIGHLY SENSITIVE TO COMBINATION OF KDM6A/B AND HDAC INHIBITORS

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