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(HER2+) breast cancer, and the unique brain microenvironment contributes to this therapy resistance. Nutrient availability can vary across tissues, therefore metabolic adaptations required for breast cancer growth in the brain microenvironment may also introduce liabilities that can be exploited for therapy. Here, we assessed how metabolism differs between breast tumors growing in the brain versus extracranial sites and found that fatty acid synthesis is elevated in breast tumors growing in the brain. We determine that these metabolic adaptations to decrease lipid availability in the brain relative to other tissues, which results in a site-specific dependency on fatty acid synthesis for breast tumors growing at this site. Genetic or pharmacological inhibition of fatty acid synthase (FASN) reduces HER2+ breast tumor growth in the brain, demonstrating that differences in nutrient availability across metastatic sites can result in targetable metabolic dependencies.

DDRE-08. NRF2/GLUTATHIONE METABOLISM AS A NOVEL THERAPEUTIC TARGET FOR IDH1-MUTATED GliOMA

Yu, Moustafa1, Amanda

For generating GMP over AMP which is exacerbated when purinosome assembly is disrupted. This is likely due to the dual-role of the DNPS enzyme ADSL which is required for AMP production.

DDRE-10. METABOLIC TARGETING OF HUMAN GLOBLASTOMA USING 5-AMINOLEVULINIC ACID (ALA)-MEDIATED SONODYNAMIC THERAPY: A FIRST-IN-HUMAN STUDY

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Heme biosynthesis is altered in glioblastoma (GBM). Systemic dosing with ALA, the first committed molecule in the heme pathway, results in accumulation of the fluorescent intermediate protoporphyrin IX (PPyIX) only within the tumor site (Gleason label, 2019). PPyIX is a photosensitizer that is effective in photodynamic therapy (PDT); in recurrent GBM patients, the safety and feasibility of ALA PDT has been demonstrated (Johansson A, et al. Lasers Surg Med 2013:45:223), although the practicality of this strategy in clinical care remains uncertain. Importantly, preclinical models of GBM show that PPyIX is also a sonosensitizer and, in combination with transcranial MRI-guided focused ultrasound (MRgFUS), leads to non-ablative cytotoxic effects in vivo (Jeong EJ et al. Ultrasound in Medicine and Biology 2013:38:2143, Suehiro S et al. J Neurosurg 2018: 1377, Wu et al Nature Science Reports 2019: 9:10465). The Ivy Brain Tumor Center is conducting a first-in-human study of 5-ALA sonodynamic therapy (SDT) for recurrent GBM (NCT 04959685). In this Phase I/II clinical trial, nontherapeutic, single-treatment SDT is administered prior to planned tumor resection. A Dose-Escalation Arm varies the power/energy of the MRgFUS while using a fixed time-interval from exposure to surgery. A subsequent Time-Escalation Arm varies the time interval between MRgFUS and surgery, but fixes the power/energy of the delivered ultrasound. In both arms, patient tumor size is assessed for sonodynamic and pharmacodynamic effects. In each patient, half of the tumor volume is not targeted with SDT and serves as an internal control. This first-in-human study will demonstrate the safety and feasibility of ALA sonodynamic therapy in GBM and may provide the first-ever biological evidence of sonosensitization in a brain tumor patient. If successful, this Phase 0 trial will introduce a new, metabolically-driven, GBM treatment modality that may be applicable to any brain tumor that selectively accumulates PPyIX after ALA administration.

DDRE-11. TARGETING FATTY ACID BIOSYNTHESIS IN GLOBLASTOMA

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We recently provided evidence that endoplasmic reticulum (ER) stress promotes fatty acid (FA) biosynthesis in glioblastoma (GBM) cancer stem cells (GSCs). We determined that Stearoyl CoA Desaturase 1 (SCD), a key FA desaturase, is essential for regulating ER homeostasis in GSCs, and showed that these cells are highly susceptible to pharmacological perturbation of SCD activity. An impaired SCD activity leads to the toxic accumulation of saturated FA and activates cell death signaling mediated by the ER sensor Insoluble-requiring enzyme 1 (IRE1). This in turn promotes an IRE1-mediated mRNA decay of key DNA damage repair genes and impairs the ability of GSCs to repair DNA damage caused by radiation or chemotherapy. Consequently, combining SCD inhibition with temozolomide (TMZ) leads to major cytotoxicity both in TMZ-sensitive, and TMZ-resistant patient-derived GBC cells. Pharmacological inhibition of SCD delivered through the nasal route in mice, had a remarkable therapeutic benefit in patient-derived orthotopic GSCs mouse models, yet the modest brain permeability of SCD inhibitors limits the clinical translation. To overcome this challenge, we have recently acquired a first-in-class, clinically relevant SCD inhibitor. This compound has undergone extensive pharmacokinetic and pharmacodynamic studies which confirmed brain permeability, efficacy, and safety in small animals and non-human primates. We show that the combination of this SCD inhibitor with TMZ is effective both in cultured GSCs, and in preclinical GSCs orthotopic mouse models. Our results support the clinical investigation of this new class of SCD inhibitors, in combination with TMZ, in patients diagnosed with GBM.

DDRE-12. HETEROGENEOUS RESPONSE OF IDH-MUTANT AND IDH-WT GLIOMA TO NAPRT INHIBITION

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BACKGROUND: NAPRT+ is required for cell metabolism and DNA repair. It is generated from nicotinamide acid (NA) by NAPRT and from Nicotinamide
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C-C3-1 C-tracing experiments involving different probes such as U-Glutamine and the expression levels of key enzymes in 1

The inhibition of ciliary protein ADP-ribosylation factor-like protein 13B (ALR13B) is employed chromatin immunoprecipitation followed by sequencing and gene expression analysis. This identified a molecular circuit in which the expression of citrulline protein ADP-ribosylation factor-like protein 13B (ALR13B) is epigenetically regulated to promote adaptation to chemotherapy. Immuno-

Combination with Liquid Chromatography-Mass Spectrometry binding partner analysis revealed that ARL13B interacts with the purine biosynthetic enzyme inosine-5-monophosphate dehydrogenase 2 (IMPDH2). Further, radiolabeled tracing revealed that this interaction was essential for purine salvage. Inhibition of ARL-13B-IMPDH2 interaction enhances temozolomide-induced DNA damage by forcing glioblastoma cells to rely on the purine salvage pathway. Targeting the AR13B-IMPDH2 circuit can be achieved using a Food and Drug Administration-approved drug, Mycophenolate Mofetil, that can block the IMPDH2 activity and enhance the therapeutic efficacy of TMZ. Our results suggest and support clinical evaluation of MMF in combination with TMZ treatment in glioma patients.

DDRE-15. THE EVOLUTIONARY ENIGMA OF FATTY ACID DESATURATION IN GLIOBLASTOMA
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Fatty acid desaturation is an enzymatic reaction in which a double bond is introduced into an acyl chain. Of the four functionally distinct desaturase subclasses, the First Desaturase Family enzyme of IDH-WT and IDH mutant lines introduce the first double bond into a saturated fatty acid, resulting in the synthesis of monounsaturated fatty acids (MUFA). MUFA are essential components of membrane and storage lipids and exert a profound influence on the fluidity of biological membranes. Ablation of mammalian CA IX in glioblastoma (GBM) disrupts fatty acid ratio alters cell growth, differentiation and response to external stimuli, and thus affects a range of pathologies including cancer. The most abundant and key First Desaturase Family enzyme in the delta 9 desaturase catalyzes the conversion of oleoyl-CoA to stearoyl-CoA (SCD and SCD-3 in mice). SCD desaturates Stearoyl-CoA (C18) and palmitoyl-CoA (C16) to oleyl-CoA (C18:1) and palmitoyl-CoA (C16:1), respectively. Besides SCD, the only known First Desaturase in mammals with dual function is FADS2 which desaturates palmitate to Sapienate (C16:1, a positional isomer of palmitate) in skin cells. A recent study showed that some cancer cells can use FADS2 to bypass the SCD reaction. SCD and SCD-3 are by far the most abundant desaturases expressed in the human brain. We made an unexpected discovery that SCD undergoes monoallelic codeletion with PTEN on chromosome 10, and is also highly methylated in glioblastoma (GBM). More surprisingly, all GBM cell lines with SCD codeletion/methylation (that expressed very little SCD protein) are completely resistant to SCD/SCD-3 inhibition, yet their phospholipids contained abundant oleic acid. It is unknown if GBMs bypassed SCD, but retained the delta 9 desaturase reaction through a novel enzymatic activity. Our targeted and untargeted metabolomics studies revealed unexpected findings that cannot be explained by conventional wisdom, and may lead to identification of novel lipogenic targets in GBM.

DDRE-16. CYSTEINE IS AN ESSENTIAL AMINO ACID IN GLIOMAS
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BACKGROUND: Cysteine is a non-essential amino acid, since it can be synthesized from methionine through the transsulfuration pathway; moreover, cysteine is also uptake from the diet as cystine. We have investigated the metabolism of cysteine in glioma cell lines, and how cysteine/cystine-deprivation alters their antioxidant response in addition to the effect of this nutrient restriction to viability and proliferation in vitro and in vivo. METHODS: Cysteine metabolism was investigated through LCMS-based 13C-tracing experiments involving different probes such as 13C-methyl-Methionine, 13C-C3-Cysteine, 13C-C3-C3'-Cysteine, 13C-C3'-Serine and 13C-Glutamine and the expression levels of key enzymes in the transsulfuration pathway were also explored. Finally, a mouse model of ID11 mutant glioma was subjected to a cysteine/cystine-free diet and tumor metabolism was tracked by LCMS. RESULTS: We demonstrate that exogenous cysteine/cystine are crucial for glutathione synthesis, and impact growth and viability. We also found that methionine cycle is disconnected from the transsulfuration pathway based on 13C-Tracing data and protein expression levels of cystathionine synthase and cystathionase. Accordingly, cysteine-related metabolites such as GSH, involved in REDOX hemostasis, are downregulated, revealing a hypersensitive phenotype to ROS. Animal models upon a cysteine/cystine-free diet experienced an increase in survival and elevated levels of oxidative stress in tumor tissue. CONCLUSION: This result presented herein reveal an alternative therapeutic approach combining cysteine/cystine-deprivation diets and treatments involving ROS production by limiting the ability of glioma cells to quench oxidative stress through dietary interventions.