Next, we expressed either WT zebrafish or human TP53 in tp53-/- animals along with kRASG12D and both genes suppressed tumor initiation and growth. We co-expressed TP53C176F (found in two ERMS patients) and TP53P153del (identified in a patient with osteosarcoma in our clinic) in zebrafish ERMS, and find that the TP53C176F allele significantly suppressed tumor initiation with effects predominantly on enhanced apoptosis. However, the TP53P153del allele initiated tumors at similar frequency compared to tp53-/- animals but increased the initiation of tumors in the head musculature. DISCUSSION/SIGNIFICANCE OF FINDINGS: Different TP53 alleles identified in patient tumors have very different effects on tumorigenesis in vivo and can respond differently to potentially therapeutic compounds. Thus, the type of precision modeling demonstrated here promises to help further define patient-specific TP53 biology and improve clinical strategies in the future.

92418

Molecular imaging of the tumor microenvironment to predict response to combination treatment with immunotherapy in triple negative breast cancer

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ABSTRACT IMPACT: Insights from this project will provide clinical guidance in treatment of immunotherapy in triple negative breast cancer and identify early imaging biomarkers of treatment response. OBJECTIVES/GOALS: Significant research that addresses monitoring and predicting patient response of triple negative breast cancer (TNBC) to immunotherapy is needed. Using positron emission tomography (PET) imaging to probe the tumor microenvironment (hypoxia, T-cell activation), we aim to predict early response to immunotherapy for in mouse models of TNBC tumors. METHODS/STUDY POPULATION: Female Balb/c mice with 4T1-luciferase mammary carcinoma cell tumors were administered paclitaxel (PTX; 10 mg/kg), anti-PD1 (200 μg), both, or vehicle (saline) intraperitoneally. Treatment was given on days 0, 2, and 5 for cohort 1 (n=16) who underwent granzyme B specific (GZP) PET imaging (T-cell activation) and days 0, 2, 5, and 8 for cohort 2 (n=12) who underwent [18F]-fluoromisonidazole (FMISO)-PET imaging (hypoxia). Bioluminescence (BLI) imaging and caliper measurements were performed to track tumor size changes at multiple timepoints and tumors were collected for histological validation on day 20. Mean standard uptake value (SUVmean) was calculated as percent of day 0, and statistical analyses were performed with unpaired t-tests and Wilcoxon-rank sum tests. RESULTS/ANTICIPATED RESULTS: Non-responders to treatment had a significantly higher tumor volume compared to responders starting on day 6 ($p<0.05$). Although no significant differences in BLI between control and single-agent therapies were found, BLI data revealed that treatment with combination PTX and anti-PD1 significantly decreased viability signal between days 3 and 6 ($p=0.04$). SUVmean from GZP-PET was over 250% higher in responders compared to non-responders by day 6 ($p=0.03$). SUVmean from FMISO-PET was 80% less in responders compared to nonresponders, indicating less tumor hypoxia ($p=0.04$). DISCUSSION/SIGNIFICANCE OF FINDINGS: Non-invasive PET imaging of the tumor microenvironment can provide data on T cell activation and hypoxic response predicting response to combination immunotherapy and chemotherapy. Utilizing advanced imaging to understand biologically distinct features of the TNBC tumor microenvironment can aid in personalizing anti-cancer therapies.

Team Science

84357

A TL1 Team Approach to Integrating Mathematical and Biological Models to Target Myeloid-Derived Immune Cells in Glioblastoma

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ABSTRACT IMPACT: Predicting therapeutic responses in GBM. OBJECTIVES/GOALS: The goal of this team approach is to integrate mathematical models of glioblastoma (GBM) infiltrating myeloid cells that contribute to the immunosuppressive phenotype in glioma with experimental data to predict therapeutic responses to combined chemokine receptor and immune checkpoint blockade. METHODS/STUDY POPULATION: Orthotopic murine KR158-luc gliomas were established in fluorescent reporter CCR2WT/RFP CX3CR1WT/GFP mice. Subsequently, an anti-CD31 injection was administered to label the vasculature. Fluorescent imaging and quantification of anti-CD3 stained sections were performed on a range of tumor sizes to acquire vasculature, tumor, T cell, and myeloid cell densities. In parallel, a system of ordinary differential equations was formulated based on biological assumptions to evaluate the change over time of tumor cells, T cells, and infiltrating myeloid cells. The model was then refined and validated by experimental results. RESULTS/ANTICIPATED RESULTS: Fluorescent imaging and quantification revealed a correlation between tumor size and abundance of (CX3CR1+, CCR2-) and (CX3CR1+, CCR2+) myeloid cell populations in the tumor microenvironment. The density of these cell populations and vasculature remained constant as the tumors increased in size. Computer simulations of the mathematical model will predict tumor, myeloid, and T cell dynamics. These simulations will be particularly useful to uncover information regarding myeloid cell dynamics, such as cell entry time into the tumor microenvironment. Parameter sensitivity analysis of the model will inform us of the biological processes driving these tumor-immune cell dynamics. DISCUSSION/SIGNIFICANCE OF FINDINGS: GBM is a challenge as current intervention are ineffective. This study improves the understanding of glioma infiltrating myeloid cells and their impact on tumor progression. The data will serve as a basis for quantitatively predicting therapeutic responses of a novel combination treatment.

Translational Science, Policy, & Health Outcomes Science

11791

Gray matter volume differences in bilingual compared to monolingual children

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ABSTRACT IMPACT: This study examines gray matter volume differences resulting from the bilingual experience in children and

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