mouse pancreas for in vivo studies. As a second approach, recombinant wild-type or engineered CXCL12 monomer or dimer proteins were applied to cells in culture or administered intra-peritoneal to study the effects on tumor growth. RESULTS/ANTICIPATED RESULTS: Mice engrafted with CXCL12-expressing cells had a better survival rate, delayed tumor growth and smaller tumors. Tumors from these mice had significantly less proliferation, measured by Ki-67 staining. In vitro analysis of CXCL12-expressing cells showed decreased viability and growth rates. Percent of cells in the cell cycle G2 phase was also decreased, suggesting cell cycle progression blockade. Viability of human PDAC cells dose-dependently declined upon wild-type CXCL12 treatment, with the non-motile dimer-dominant dose (1000 nM) exhibiting maximal effect. Treatment in an allogeneic mouse model of PDAC with locked-dimer CXCL12, but not wild-type, reduced tumor burden. DISCUSSION/SIGNIFICANCE OF IMPACT: Our results support the notion that biased CXCL12 signaling may be therapeutically exploited to limit pancreatic cancer progression.

2070

High-intensity focused ultrasound (HIFU) can be used synergistically with tamoxifen to overcome resistance in preclinical and patient derived xenograft models

Rachel Sabol[1], Hakm Murad[2], Matthew Burow[3], Damir Khismatullin[1] and Bruce Bunnell[3]

[1] LA CaTS, Tulane University School of Medicine; [2] Tulane School of Science and Engineering; [3] Tulane School of Medicine

OBJECTIVES/SPECIFIC AIMS: The goal of this study is to evaluate a potential strategy to overcome tamoxifen (tam) resistance by using tam in combination with high-intensity focused ultrasound (HIFU). Tam is the most commonly used anti-cancer therapeutic agent in estrogen receptor positive (ER+) breast cancer (BC) which accounts for ~70% of BC cases. Tam treatment decreases a woman's risk of recurrence by 50%; however, BC that is initially responsive to tam often develops resistance. METHODS/STUDY POPULATION: HIFU deposits acoustic energy locally to a cancerous region, which induces strong vibrations of molecules inside and outside of the cells. The resulting absorption causes rapid heating and mechanical disruption. This clinically relevant, noninvasive, and nonionizing physical force modality, has been shown to synergistically enhance chemical anticancer therapies. RESULTS/ANTICIPATED RESULTS: In this study we found that treatment of MCF7 cells with HIFU and tam has additive antiproliferative effects and mediates increased cell death. Additionally, we used tam resistant (TR) MCF7 cells that had been exposed to low-dose tam over time until they acquired resistance. When MCF7 TR are treated with tam there is no change in viability; however, treatment with HIFU in combination with tam decreased viability of both MCF7 and MCF7 TR to 19% and the viability of the cell lines was indistinguishable. We next evaluated the effect on MCF7 Y537S mutant ESR1, where ER is mutated to be constitutively active. Treatment of MCF7 Y537S had no significant decrease in viability of combination therapy compared with viability after HIFU alone. Analysis of ERalpha gene expression showed that HIFU treatment increased ERalpha expression in MCF7 TR cells, thus resensitizing these cells to tam and allowing these therapies to work synergistically. Our team developed a system to evaluate the potential of this combination of therapies in a patient-derived xenografts (PDX) model. PDX have emerged as a novel translational tool for cancer research with the potential to more accurately recapitulate the molecular and behavioral aspects of cancer. The WHIM20 PDX is a tamoxifen resistant tumor where the patient developed the Y537S mutation in ESR1. Ex vivo experiments on PDX tumor pieces demonstrated that combination therapy of HIFU and tam work synergistically to increase cell death of these tumors. Further, cryogenic-scanning electron microscopy was utilized to directly demonstrate the physical disruption to both cellular and tumor microenvironment post exposure to combination treatment. DISCUSSION/SIGNIFICANCE OF IMPACT: These studies present a novel translational strategy to overcome tamoxifen resistance in ER+ BC.

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Hippocampal network disruption in early amyloid pathology

Adam Caccavano and Stefano Vicini

Georgetown – Howard Universities

OBJECTIVES/SPECIFIC AIMS: We aim to show that amyloid accumulation in an animal model of Alzheimer's disease leads to a preferential disruption of inhibitory parvalbumin-expressing interneurons, and the peri-neuronal nets that surround them, resulting in downstream network alterations to potentially explain early mechanisms of memory impairment in the disease. METHODS/STUDY POPULATION: We employ the 5xFAD mouse model of familial Alzheimer's disease crossed with transgenic mouse lines which fluoresce red or green in specific neuronal populations. We conducted immunostaining and immunoblotting in amyloid accumulating animals compared with healthy littermate control. Future experiments will be performed in human post-mortem tissue to translate these results from mouse model to the human population. Electrophysiological recordings from acute mouse brain slices were conducted as a functional assay. RESULTS/ANTICIPATED RESULTS: Preliminary results indicate that PNNs are disrupted and that activity-associated levels of PV are reduced. Both inhibitory PV and excitatory pyramidal cell populations exhibit altered spiking and synaptic activity during sharp wave ripple events. DISCUSSION/SIGNIFICANCE OF IMPACT: By elucidating the specific neuronal sub-type that is responsible for hippocampal network disruption, future studies could attempt a targeted optogenetic or pharmacological intervention to restore network activity important for memory consolidation.

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Identifying the genetic determinants of human brown adipose tissue

Tobias Becher[1], Paul Cohen[2], Andreas Wibmer[2] and Daniel J. Kramer[3]

[1] The Rockefeller University; [2] Department of Radiology, Memorial Sloan Kettering Cancer Center; [3] Laboratory of Molecular Metabolism, The Rockefeller University

OBJECTIVES/SPECIFIC AIMS: Brown adipose tissue (BAT) increases energy expenditure by dissipating chemical energy as heat. The combustion of glucose and lipids produces beneficial metabolic effects and renders BAT an attractive target to battle obesity and associated diseases. The majority of adults do not display active BAT on positron emission tomography (PET) without prior cold exposure. Interestingly, a fraction of individuals with BAT positive PET scans exhibits excessive BAT (eBAT) activity, indicating a possible underlying genetic contributor. We aim to identify genetic determinants of BAT activity by studying individuals with eBAT activity using next-generation sequencing. A cellular model will be used to validate variants and perform in-depth pathway analysis. METHODS/STUDY POPULATION: We performed a retrospective review of PET scans over a period of 12 months in patients presenting with suspected or diagnosed cancer (n = 20,348). The distribution of BAT positive individuals (n = 1251) was used to implement a threshold to define eBAT activity. Samples from prospectively recruited individuals with BAT activity above the threshold will undergo whole exome sequencing. Variants associated with eBAT activity will be engineered into an immortalized BAT cell line using CRISPR to validate results and perform in-depth pathway analysis. RESULTS/ANTICIPATED RESULTS: We expect to identify genetic variants associated with eBAT. Studying the effects of these variants on thermogenesis followed by in-depth pathway analysis in genetically engineered cellular and mouse models may enable us to find new regulators of BAT activity. These findings may eventually contribute to the development of new drugs targeting obesity and its sequelae. DISCUSSION/SIGNIFICANCE OF IMPACT: The contribution of genetic factors to individual BAT activity is currently unknown. Identifying individuals with eBAT on PET scans and studying the underlying genetic determinants may provide the foundation for the discovery of new pathways for BAT activation.

2050

Identifying the role and immunobiological mechanisms of Fli-1 mediated pathogenicity in graft Versus host disease

Steven Schutt, Yongxia Wu, Anusara Daenthanasanmak, David Bastian, Carole Wilson, Lynn Schnapp, Xian Zhang, Xue-Zhong Yu, Hung Nguyen[1], Mohammed Hanief Sofi[1] and Supinya Iamsuwat[1]

[1] Medical University of South Carolina

OBJECTIVES/SPECIFIC AIMS: Allogeneic hematopoietic stem cell transplantation (allo-HCT) is a curative procedure for hematological malignancies. Chronic graft Versus host disease (cGVHD) is a lethal complication that often develops after allo-HCT. Fli-1 is an aberrantly expressed protein in cancers including erythroleukemia and melanoma, while being implicated in pathogenesis of systemic lupus in mice and humans, a disease with marked similarity to cGVHD. METHODS/STUDY POPULATION: cGVHD was induced using hematopoietic cells from conditional knock-out mice deficient for the fli-1 gene specifically on T cells and progression of cGVHD in murine allo-HCT recipients was

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