all-cause mortality. Selection of Subjects: We will include all patients admitted to the JPNATC Trauma and Neurosurgical ICUs intubated and mechanically ventilated and meeting the definition of Berlin definition of ARDS8. We will collect data for a total of 12 months. RESULTS/ANTICIPATED RESULTS: Due to gaps in reporting, the incidence, mortality, and practice-based management algorithms applied in trauma patients suffering from ARDS in India is unknown. We hypothesize that the overall incidence of trauma-related ARDS is higher, and the fraction of patients managed with evidence-based therapies is lower than global reported averages. DISCUSSION/SIGNIFICANCE OF IMPACT: Although the true incidence of ARDS in trauma subjects in India is currently unknown, we suspect that it is much higher than reported. Such data are important in identification of resource allocation including ICU bed and mechanical ventilator availability, particularly in a resource-limited environment. This proposal will aid in the development of research infrastructure at JPNATC, contribute to capacity building, and the establishment of a Clinical Research unit at the Apex Institute. Finally, a provision to develop a consortium and trauma quality improvement program among the existing trauma centers in New Delhi to disseminate important research findings and guidance to the rest of India is a future benefit of the study.

2261

Tumor suppressor RARRES1 regulates cell survival by modulating mitochondrial energetics

Sara Maimouni[1], Mi-Hye Lee[2], You-Me Sung[2], Chokri Ouaari[3] and Stephen Byers[2]

[1] Georgetown University – Howard Universities; [2] Lombardi Comprehensive Cancer Center; [3] University of the District of Columbia

OBJECTIVES/SPECIFIC AIMS: One of the driving mechanisms of cancer progression is the reprogramming of metabolic pathways in intermediary metabolism. Cancers increase their energy expenditure by increasing ATP production for utilization in anabolic pathways to increase production of proteins, nucleic acids and lipids. The Warburg effect, where cancer cells predominantly use aerobic glycolysis rather than oxidative phosphorylation to produce ATP, was long thought to be the main initiating pathway in increasing tumor burden. However, compelling new evidence shows that there exists metabolic heterogeneity among and within tumors. Mitochondrial respiration often plays a major role in tumor progression, as many different cancers contain a subpopulation of slow-cycling tumor-initiating cells that are multidrug-resistant and dependent on oxidative phosphorylation. These cells represent a target for cancer therapy. In this study, we identification a novel endogenous regulator of mitochondrial respiration, retinoic acid receptor responder 1 (RARRES1). METHODS/STUDY POPULATION: We assessed the metabolic phenotype of RARRES1-depleted normal epithelial cells through metabolomics, a flux analyzer and blotting for phosphorylation of AMP kinase, a major regulator of energy homeostasis. We further examined mitochondrial energetics by staining the mitochondria with TMRM and Mito-Tracker. We then analyzed the apoptotic phenotype of epithelial cells with depletion of RARRES1 with fluorescence-activated cell sorting analysis of annexin V-staining. RESULTS/ANTICIPATED RESULTS: Remarkably, fluorescence-activated cell sorting analysis of annexin V-stained epithelial cells with depletion of RARRES1 were resistant to all studied modes of cell death, implying an effect on a fundamental cell process. By using proteomics, metabolomics, cellular and molecular analyses, our data show that RARRES1 regulates mitochondrial membrane potential and subsequently alters 1-carbon metabolism by modulating the function of the mitochondrial voltage-dependent anion channel. We believe this is the first example of a tumor suppressor protein that functions to directly regulate mitochondrial energetics. Using an extracellular flux analyzer, our data also show that depletion of RARRES1 causes an increase in mitochondrial respiration and ATP production, thus enhancing biosynthetic pathways that drive the pathogenicity and survival of cancer. The metabolic and anti-apoptotic phenotype of RARRES1-depleted cells was reversed by treatment of metformin, a mitochondrial inhibitor. DISCUSSION/SIGNIFICANCE OF IMPACT: These data lay the foundation for metabo-therapy of the many tumor types that exhibit RARRES1 depletion and may have the added benefit of targeting drug-resistant tumor-initiating cells.

2213

Tumor suppressors p53 and ARF control oncogenic potential of triple-negative breast cancer cells by regulating RNA editing enzyme ADAR1

Che-Pei Kung[1], Emily A. Bross[2], Catherine E. Kuzmicki[2], Michael Benjamin[2], Leonard B. Maggi Jr[2] and Jason D. Weber[2]

[1] Washington University in St. Louis; [2] Institute of Clinical and Translational Sciences, Washington University in St. Louis

OBJECTIVES/SPECIFIC AIMS: Triple-negative breast cancer (TNBC) accounts for one-fifth of the breast cancer patient population. The heterogeneous nature of TNBC and lack of options for targeted therapy make its treatment a constant adventure. The deficiency of tumor suppressors p53 and ARF is one of the known genetic signatures enriched in TNBC. Crucial questions remain about how TNBC is regulated by these genetic alterations. METHODS/STUDY POPULATION: In order to address this issue, we established p53/ARF-defective murine embryonic fibroblast and mammary epithelial cell to study the molecular and phenotypic consequences. Moreover, transgenic mice were generated to investigate the effect of p53/ARF deficiency on mammary tumor development in vivo. RESULTS/ANTICIPATED RESULTS: Increased proliferation and transformation capability were observed in p53/ARF-defective cells, and an aggressive form of mammary tumor was also seen in $p53^{-/-}ARF^{-/-}$ mice. Gene expression profiling and knock-down experiments using shRNAs were conducted to identify inflammatory marker ISG15 and RNA-editing enzyme ADAR1 as potential culprits for the elevated oncogenic potential. Interestingly, we found that the overexpression of ISG15 and ADAR1 is also prevalent in human TNBC cell lines. Reducing ADAR1 expression abrogated the oncogenic potential of human TNBC cell lines, while non-TNBC cells are less susceptible. DISCUSSION/SIGNIFICANCE OF IMPACT: These results indicate critical roles played by the tumor suppressors p53 and ARF in the pathogenesis of TNBC, likely through regulating ADAR1-mediated RNA modifications. Further understanding of this pathway promises to shed light on genetics-driven vulnerabilities of TNBC and inform development of more effective therapeutic strategies.

2516

Ultra-low Na18F tracer dosing for preclinical skeletal imaging enables new concepts in digital PET/CT

Maria I. Menendez, Richard Moore, Katherine Binzel, Michael Friel, Jun Zhang, Rebecca Jackson and Michael Knopp

The Ohio State University

OBJECTIVES/SPECIFIC AIMS: The aim of this study was to assess the ultra-dose Na18F dPET protocol feasibility for skeleton imaging in a canine model with reduced radiation dose and preserved quantitative characteristics. We hypothesized that administering an ultra-low Na18F dose would provide suitable image quality while reducing subject's exposure to radiation. METHODS/STUDY POPULATION: In total, 13 adult male beagles [weight (kg) mean ± SD; 14.3 ± 2.2] were scanned. The dogs were administered 3 different Na18F doses: 3 (standard dose/SD), 1 (low dose/LD), and 0.05 (ultra-low dose/ULD) mCi. Imaging started ≃45 minutes post injection for ≃ 33 minute total acquisition time. Covering the whole body, 11 bed positions, acquiring 120 (3 mCi) and 180 (1, 0.05 mCi) seconds per bed position. All imaging was performed on a digital photon counting system (Philips Vereos, pre-commercial release). PET list mode data were reconstructed using Time-of-flight with 4, 2, and 1 mm^3 voxel volumes. Point spread function, and Gaussian filtering were applied. Two experienced blinded readers evaluated image sets overall quality, tissue characterization, and quality of background in the whole body skeleton. Three-dimensional (3D) regions of interest (ROI) were traced over the distal femur, first lumbar vertebra, and a portion of the liver, recording standard uptake values (SUVmax and SUVmean). RESULTS/ANTICIPATED RESULTS: All the scans and reconstructions were successfully completed in all subjects. Decreasing Na18F dose from the standard dose (3 mCi) to the ultra-low dose/ULDO (0.05 mCi), demonstrated acceptable image quality and quantification. Ultra-low dose Na18F SUVmean values for the 3D ROIs reported (mean ± SD) 2.6 ± 0.7, 2.5 ± 1.1, 9 ± 1.6, and 0.6 ± 0.3 from the right and left distal femur, first lumbar vertebra, and a portion of the liver, respectively. When compared the SD with the LD and ULD, dPET demonstrated acceptable image quality and definition for qualitative overall assessment. This was also found for the overall quantitative ROI assessment of the healthy canine skeletons. DISCUSSION/SIGNIFICANCE OF IMPACT: Ultra-low dose Na18F at a level of 50 μCi for a 14 kg canine appears to be diagnostically feasible and a robust option to reduce (60-fold) radiotracer doses in a translational animal model using a dPET system. Furthermore, it allows us to move preclinical nuclear medicine imaging forward with substantial reduced exposure levels while preserving image quality. Both visual and quantitative results indicate that the standard-dose bone Na18F dPET can be decreased with a satisfactory diagnostic image quality. Ultra-low Na18F dose is indeed important for younger populations, control patients, and nononcological diseases/conditions. Favorable pharmacokinetics of Na18F (such as high bone uptake, minimal binding to serum proteins, rapid single-pass extraction, and fast clearance from the soft tissues) in addition to the technological capabilities of dPET/CT demonstrated feasibility enabling dose reduction strategies. Ultra-low dose has diagnostic reproducibility and lower radiation burden compared with higher fixed dose techniques in current available guidelines [Society of Nuclear Medicine and Molecular Imaging; SNMMI (5–10 mCi)]. Na18F dPET/CT provides higher sensitivity and diagnostic accuracy,

https://doi.org/10.1017/cts.2018.143 Published online by Cambridge University Press