OBJECTIVES/SPECIFIC AIMS: Treatment of acute myeloid leukemia (AML) is challenging, as apoptosis-resistant AML cells often persist within the bone marrow microenvironment despite chemotherapy. The overall goal of our laboratory is to identify and ultimately target the bone marrow factors that protect AML cells.

RESULTS/STUDY POPULATION: Using cell cultures, we previously reported that SDF-1 (CXCL12), an abundant bone marrow chemokine, induces apoptosis of isolated CXCRA+ AML cells, including freshly isolated bone marrow-derived AML cells from approximately one-third of AML patients. However, co-culture of AML cells with differentiating osteoblasts protected AML cells from apoptosis. RESULTS/ANTICIPATED RESULTS: Histone deacetylase inhibitors (HDACi) abrogated the ability of osteoblasts to protect AML cells and altered expression of matrix mineralization genes including tissue nonspecific alkaline phosphatase (TNAP). A different drug, cyclosporine A (CSA), similarly inhibited osteoblast-mediated protection of AML cells and reduced TNAP expression. Specifically targeting osteoblast TNAP via siRNA was sufficient to prevent osteoblasts from protecting AML cells in co-cultures. In addition, we are targeting TNAP enzymatically.

DISCUSSION/SIGNIFICANCE OF IMPACT: Our results indicate that cells in co-cultures. In addition, we are targeting TNAP enzymatically. TNAP via siRNA was sufficient to prevent osteoblasts from protecting AML cells and altered expression of matrix mineralization genes including tissue nonspecific alkaline phosphatase (TNAP). A different drug, cyclosporine A (CSA), similarly inhibited osteoblast-mediated protection of AML cells and reduced TNAP expression. Specifically targeting osteoblast TNAP via siRNA was sufficient to prevent osteoblasts from protecting AML cells in co-cultures. In addition, we are targeting TNAP enzymatically.

OBJECTIVES/SPECIFIC AIMS: Pre-clinical and clinical observations have noted that increased aortic dilatation is associated with male sex. Using an experimental model of severe, syndromic thoracic aortic aneurysms, we quantify aortic dilatation and dilatation stability in male versus female mice.

METHODS/STUDY POPULATION: Ascending aortas from male and female FBN1mgR/mgR mice and their wild type littermates were assessed every 4 weeks from 6 to 18 weeks of age by ultrasound. Measurements were taken luminal edge to luminal edge in diastole. At termination, aortas were harvested for RT-PCR analysis of extracellular matrix genes. Aortas were serially sectioned and elastic fragmentation was imaged by auto-fluorescence.

RESULTS/ANTICIPATED RESULTS: At 12 weeks of age, differences of aortic diameters between male and female FBN1mgR/mgR mice were significantly different (2.46±0.43 vs. 1.57±0.22 mm; p=0.002), while there were no significant differences between sexes of wild type littermates (1.29±0.13 vs. 1.23±0.08 mm; p=0.71). Male sex was associated with increased elastin but not fibrillin-1 mRNA expression. Ascending aortas from male and female FBN1mgR/mgR mice significantly differed in the degree of elastin fragmentation (2.76 vs. 1.85 breaks/100 μm aorta; p=0.03).

DISCUSSION/SIGNIFICANCE OF IMPACT: Sexual dimorphism of thoracic aortic dilation observed in human TAA patients was recapitulated in the fibrillin-1 hypomorphic mouse model of syndromic thoracic aortic aneurysms. Differences in this mouse model could be explained by the differential expression of extracellular matrix genes.

OBJECTIVES/SPECIFIC AIMS: The goals of our study are: (1) To test the hypothesis that the presence of any autoimmune cytopenia (ITP, AHA, or ES) at time of cSLE diagnosis is associated with decreased risk of developing LN. (2b) To test the hypothesis that there is a lower risk of LN in patients with cSLE who develop an autoimmune cytopenia at time of cSLE diagnosis. DISCUSSION/SIGNIFICANCE OF IMPACT: Our study will be conducted on one of the largest single-center cohorts of cSLE patients. We will determine whether pediatric patients with SLLE and autoimmune cytopenias have a distinct clinical or serological phenotype and less severe disease. Our results will be significant in developing hypothesis for further retrospective or prospective multi-center or large database and immunological studies to understand the relationship of each individual autoimmune cytopenia to cSLE. It will provide the necessary background for further clinical and immunological studies to identify predictive biomarkers of cSLE severity.

Sodium-glucose transporter 2 is a novel diagnostic and therapeutic target for early-stage lung adenocarcinoma

Claudio Scagfoglio, Gihad Abdeldaby, Jie Liu, Jane Yanagawa, Dean Wallace, Jorio Barrio, Steven Dubinett and David Shackelford

OBJECTIVES/SPECIFIC AIMS: Lung cancer claims 160,000 lives in the United States every year, and lung adenocarcinoma (LADC) is the most frequent type. Early diagnosis is crucial. Computed tomography (CT) is very sensitive in identifying early-stage lung nodules, but has low specificity. Increased glucose uptake is a hallmark of cancer measurable in vivo by fluorodeoxyglucose (FDG) positron-emission tomography (PET). FDG PET is widely used for cancer staging but has low sensitivity in the diagnosis of solitary lung nodules. We have previously identified an alternative glucose transporter, SGLT2, expressed in different types of cancer but not detected by FDG PET. SGLT2 activity can be measured in vivo with 3-O-methyl-D-glucose (3OMG) PET. The objective of this study was to test the hypothesis that SGLT2 is a novel diagnostic and therapeutic target in FDG-negative, early stage LADC.

METHODS/STUDY POPULATION: To study glucose transporter expression in LADC, we performed immunohistochemistry with SGLT2- and GLUT1-specific antibodies in human lung pre-malignant lesions and LADC samples. To verify the possibility of detecting SGLT2 activity in vivo, we performed microPET imaging with the SGLT-specific tracer Me4FDG in a Kras-driven, p53-null genetically engineered mouse model and in patient-derived xenografts.

Sexual dimorphism in a mouse model of syndromic thoracic aortic aneurysm

Zheying Chen, Alan Daugherty and Mary Sheppard

OBJECTIVES/SPECIFIC AIMS: Treatment of acute myeloid leukemia (AML) is challenging, as apoptosis-resistant AML cells often persist within the bone marrow microenvironment despite chemotherapy. The overall goal of our laboratory is to identify and ultimately target the bone marrow factors that protect AML cells.