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MARYAM SHARIFI-SANJANI, PHD

University of Pittsburgh
Pittsburgh Heart, Lung and Blood Vascular Medicine Institute
Division of Cardiology
Pittsburgh, PA

Insight into Right Ventricular Defenses to Pulmonary Arterial Hypertension: Potential Role of TRF2, A Telomeric Protein

INTRODUCTION:

Right ventricular (RV) failure due to pressure overload is the leading cause of morbidity and mortality in pulmonary arterial hypertension (PAH). However, the underlying causes continue to be poorly understood, and identifying effective RV targeted therapy remains unresolved.

BACKGROUND:

Preliminary data support the mitigated expression of telomeric repeat-binding factor 2 (TRF2), an essential telomere length-protecting protein, in RVs of PAH mouse models of hypoxia and pressure-overload model of pulmonary arterial banding (PAB), while its expression does not change in the lungs or cardiac fibroblasts. These data suggest that TRF2 is a cardiomyocyte (CM)-specific signal affected by PAH models. Therefore, the principal investigator (PI) generated a unique mouse with constitutive CM-specific deletion of TRF2 (cTRF2+/-). Preliminary data show premature RV dysfunction and early death in cTRF2+/- mice similar to late stages of PAH without concurrent CM telomere attrition, supportive of a telomere length maintenance-independent role for TRF2 in CMs. Interestingly, cTRF2+/- CMs present relocalized H3K9me3 (a marker of heterochromatin) away from the nuclear periphery, a hallmark of gene transcription activation, coupled with aberrant RV dysfunction-associated gene expression.

HYPOTHESIS AND OBJECTIVES:

The PI hypothesizes that TRF2 governs RV cardiomyocyte gene transcription changes associated with RV dysfunction in PAH via regulating nuclear chromatin localization.

SPECIFIC AIMS:

To test this hypothesis, we will characterize RV function and morphology in tamoxifen-induced conditional CM-specific TRF2-deficient (conTRF2+/-) mice following hypoxia and PAB. To identify whether CM-TRF2 deficiency alters the expression of RV dysfunction-associated genes via chromatin relocalization, we will assess H3K9me3-DNA interaction at genomic binding sites of candidate genes by chromatin immunoprecipitation (ChIP)-qPCR. Further, nuclear relocalization (distance from nuclear periphery) of core histones and the above-identified activated genes will be evaluated via state-of-the-art high-resolution 2D FISH (fluorescence in situ hybridization) immunostaining. To determine whether TRF2 overexpression has translational therapeutic potential in humans, we will adenovirally overexpress TRF2 in human-induced pluripotent stem cell (hiPSC)-derived CMs with and without hypoxia or TNF-α (PAH-related stimuli) in the presence and absence of heterochromatin protein1 (known to induce chromatin compaction via H3K9me3) siRNA and outcome on the expression of PAH-associated RV dysfunction genes and nuclear localization evaluated.