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Identification of the Apelin-mediated Transcriptome in Right Ventricular Failure using Single Cell RNA-Seq

INTRODUCTION AND BACKGROUND:

RV function is the primary prognostic factor for both morbidity and mortality in PH, but despite this importance, no RV-directed therapies exist. Furthermore, patients with more common cardiopulmonary diseases such as chronic obstructive pulmonary disease, pulmonary fibrosis, sleep disordered breathing and left heart disease are at major risk for developing PH and/or RV failure. Intriguingly, despite increased susceptibility to PH, women have better RV function and survive longer with PH than men. Therefore, there is an unmet, scientific need to identify the sex- and cell-specific pathways driving RV failure, and to target those pathways to prevent, delay or reverse RV failure. We hypothesize that apelin-mediated signaling will promote a prolonged adaptive remodeling response in the pressure-overloaded RV. The goal of this proposal is to identify the hitherto unknown molecular, sex and cell-specific targets of apelin during the progression of RV failure and how it may be used to prevent or delay RV failure, which would allow for the development of novel, RV-targeted therapies (an area that has been identified as a critical need in PH therapy).

Apelin is a secreted peptide that plays a critical role in cardiac development, angiogenesis, pro-survival signaling, inflammation, and pro-contractile signaling. Our hypothesis is based on preliminary data demonstrating that decreased RV apelin expression in rats with RV failure and in PH patients is a hallmark of maladaptive (decompensated), but not adaptive (compensated) RV remodeling. Furthermore, we found that apelin enhances pro-survival signaling in RV-specific endothelial cells (ECs) and cardiomyocytes (CMs).

Upon completion of this project, we will have leveraged the power of single cell RNA-Seq to identify the cell-specific changes to the male and female transcriptome and provided the first molecular characterization and cellular targets of apelin signaling during the progression of RV failure. This work will lay the foundation for the development of personalized RV-directed therapies for male and female patients with PH.

HYPOTHESIS:

Our compelling data led us to hypothesize that apelin-mediated signaling will promote a prolonged adaptive remodeling response in the pressure-overloaded RV. This proposal will decipher apelin's role in the progression of RV failure and, by using a single cell RNASeq approach, identify novel cell-specific targets of apelin-mediated signaling.

SPECIFIC AIM 1:

To investigate whether apelin treatment preserves vascular density, contractile function and abrogates the progression of RV failure. We hypothesize that long-term apelin treatment will delay the development of RV failure by stimulating pro-angiogenic and pro-contractile signaling.

SPECIFIC AIM 2:

To identify the apelin-mediated transcriptional profile during RV failure development using single cell RNA-Seq.We hypothesize that apelin mediates cell-specific, sex-specific and time-dependent protective responses that delay progression of RV failure.