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Muscle-specific regulation of right ventricular transcriptional responses to chronic hypoxia induced heart failure by the Muscle Ring Finger-1 (MuRF1) ubiquitin ligase *in vivo*

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Background. We recently identified a role for the muscle-specific ubiquitin ligase MuRF1 (Muscle Ring Finger-1) in right-sided heart failure secondary to pulmonary hypertension induced by chronic hypoxia (CH). MuRF1-/- challenged to chronic hypoxia for three weeks were resistant to CH induced changes in right ventricle (RV) weight, ejection fraction, and volume (systolic and diastolic) and provided significantly increased perfusion to skeletal muscle. In contrast, MuRF1 Tg+ mice exhibited significant decreases in RV weight and ejection fraction indicative of a maladaptive dilated phenotype (heart failure), consistent with the significant decreases in skeletal muscle perfusion observed. The present study was undertaken to understand the underlying transcriptional alterations in the right ventricle of MuRF1-/- and MuRF1 Tg+ mice using microarray analysis.

Results. After three weeks of chronic hypoxia (15% O_2) exposure, right ventricular total RNA was isolated, labeled, and hybridized to microarray chips. Microarray analysis of the MuRF1-/- right ventricle identified 37,095 defined genes with signals, with 590 found to be significantly different ($p<0.01$) from WT controls. Analysis of the 70 top differentially expressed genes (>2 fold or <-2 fold) revealed their function in 1) transcriptional regulation; and 2) oxidoreductase function. Analysis of these differentially expressed genes for common transcription factor promoter regions identified homeobox (HOX) D12 and HOXC13 transcription factors, along with RREB-1. Microarray analysis of the MuRF1 Tg+ right ventricle identified 37,095 defined genes with signals, with 150 found to be significantly different ($p<0.01$) from WT controls. Analysis of the 46 top differentially expressed genes (>3 fold or <-3 fold) revealed their function in 1) oxidoreductase-metabolic regulation, 2) glycoprotein-transmembrane integral protein structure, and 3) alternative splicing / splice variants.

Conclusions. The differentially expressed genes in MuRF1-/- and MuRF1 Tg+ RV after CH exposure have common functional annotations related to oxidoreductase (including antioxidant) and transmembrane component functions. Moreover, the functionally-enhanced MuRF1-/- hearts regulate genes related to transcription, homeobox proteins, and kinases/phosphorylation. These studies also reveal potential indirect effects MuRF1 may have with known substrates such as SFR and PPARalpha by regulating RREB-1 and reveal for the first time mechanisms by which MuRF1 may transcriptionally regulate anti-oxidant systems in the face of right heart failure.