7194
Topic Category: 4017-ASIP Signaling in cardiac disease

First Author: Traci Parry
University of North Carolina
MBRB 2336 Chapel Hill, NC 27599
United States
Phone:
traci_parry@med.unc.edu

First Author is a: Postdoctoral Fellow
First Author is a member of: American Society for Investigative Pathology, The American Physiological Society
First Author Degree: PhD, DSc, or equivalent

Presentation Preference: Oral

Sponsor: Traci Parry
Sponsor Phone: 9705206962
traci_parry@med.unc.edu
Sponsor's Society: Pathology - American Society for Investigative Pathology (ASIP) - Host Society
Keywords: 1. autophagy 2. inflammation
Awards: ASIP Trainee Travel Award, ASIP Trainee Travel Award for Excellence in Cardiovascular Research

The muscle-specific ubiquitin ligase MuRF1 regulates autophagy via FOXO1/3 ubiquitination to inhibit NF-κB signaling and protect against cardiac inflammation *in vivo*

Traci L. Parry, Jonathan C. Schisler, Jean Marie Mwiza, Joel K. Durand, Albert S. Baldwin, Monte S. Willis. University of North Carolina, Chapel Hill, NC

The muscle-specific ubiquitin ligase MuRF1 (muscle ring finger-1) has recently been shown to regulate signal transduction by modulating transcription factor activity through ubiquitin-mediated post-translational modification. Therefore, we investigated the ability of MuRF1 to regulate autophagy. MuRF1-/- hearts exhibited decreased autophagic flux (decrease in LC3II and VPS34 protein levels), while MuRF1Tg+ hearts exhibited increased autophagic flux (increase in last phase autophagosomes and VPS34 protein levels). Interestingly, the FOXO1/3a transcription factors, known supporters of autophagy, correlated with MuRF1 expression. MuRF1-/- hearts expressed significantly less of the FOXO-regulated P62, while MuRF1Tg+ expressed significantly more P62 by immunoblot analysis. Since P62 supports NF-κB signaling by IKKβ phosphorylation, MuRF1-/- and MuRF1Tg+ mice were challenged with LPS to determine resistance to endotoxin-induced cardiac dysfunction to identify the role of MuRF1-P62 in inhibiting cardiac NF-κB signaling. MuRF1-/- mice were significantly protected against LPS-induced systolic dysfunction, while MuRF1 Tg+ mice were more susceptible to LPS-induced heart failure. NF-κB activity was significantly inhibited in MuRF1-/- mice at the level of the IKK complex, consistent with decreased FOXO-regulated P62 to reduce downstream NF-κB signaling. These studies identify the first ubiquitin ligase to regulate autophagy in the heart and describe novel therapeutic targets that could be used to block myocyte-specific inflammation