University of Utah
UNDERGRADUATE RESEARCH JOURNAL

THE ROLE OF P62 IN THE REGULATION OF HYPOXIA INDUCIBLE FACTOR1-ALPHA (HIF1α) IN THE MOUSE HEART

Isaac Duy Cao, Ellenor Chi, Rajeshwary Ghosh and, Sihme Boudina
Department of Nutrition and Integrative Physiology

Ischemic heart disease (IHD) is a major cause of death worldwide. IHD is characterized by cardiac tissue hypoxia (low oxygen levels), dysregulated metabolism, and cell death. A major component of the hypoxia pathway is the hypoxia-inducible factor 1a (HIF1α) whose stabilization is required to regulate several metabolic and angiogenic genes during hypoxia. In this study, we hypothesize that a protein called Sequestosome 1 (p62) is necessary for the regulation of HIF1α in the heart. p62 is a multifunctional protein with established functions in the regulation of several cellular pathways including autophagy function and redox homeostasis. However, its role in the heart during hypoxia is not known. To test our hypothesis, H9c2 cardiac myoblasts were cultured and exposed to physiological hypoxia (1% O_2) or normoxia (21% O_2) for 24h or chemically-induced hypoxia (treatment with 100 or 200 μM $CoCl_2$) for 24h. p62 knockdown in the H9c2 cardiac myoblasts was downregulated and did not alter HIF1α protein levels or its target gene (*Hmox, Egln1, Vegfa, Bnip3*) expression in either physiologically or chemically-induced hypoxia. Additionally, mice with tamoxifen-inducible cardiomyocyte specific p62 deletion (cip62KO mice) were generated and exposed to 7% O_2 for 6h to verify the effect of p62 deletion *in vivo*. Cip62KO mice did not show any changes in HIF1α target genes and were comparable to the control animals. Our study reveals that p62 may negatively regulate HIF1α and transcriptional activation. Further experiments are required to validate the role of p62 in the stabilization of HIF1α and hypoxia tolerance in the heart.