**Title:** Induction of DEPP1 by HIF Mediates Multiple Hallmarks of Ischemic Cardiomyopathy

**Authors:**
Gregory A. Wyant[1,5], Qinqin Jiang[1], Clara Levrero[1], Bradley A Maron[2], William G. Kaelin, Jr[1,3,4,6]
[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02215, USA
[2]Department of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02215, USA
[3]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02215, USA
[4]Howard Hughes Medical Institute, Chevy Chase, MD 20815, USA
[5]Present Address: Massachusetts General Hospital, Cardiovascular Research Center, Division of Cardiology, Department of Medicine, Harvard Medical School, Charlestown, MA, USA.
[6]Corresponding author. Email: William_kaelin@dfci.harvard.edu

**Abstract**

HIF regulates many aspects of cardiac function. Chronic HIF activation in the heart in mouse models phenocopies multiple features of ischemic cardiomyopathy in man, including mitochondrial loss, lipid accumulation, and systolic cardiac dysfunction. In some settings HIF also causes the loss of peroxisomes. Both mitochondria and peroxisomes are key metabolic organelles that play critical roles in cardiac metabolism. Here, we identify a previously unknown pathway by which cardiac HIF activation promotes the loss of mitochondria and peroxisomes. We found that DEPP1 is induced under hypoxia in a HIF-dependent manner and localizes inside mitochondria. DEPP1 is both necessary and sufficient for hypoxia-induced mitochondrial and peroxisomal autophagy and lipid accumulation in cardiomyocytes ex vivo. DEPP1 loss increases cardiomyocyte survival in the setting of chronic HIF activation ex vivo and decreases cardiac dysfunction in hearts with chronic HIF activation caused by *VHL* loss in vivo. Our findings identify a key component in the cardiac remodeling that occurs with chronic ischemia and suggest that inhibiting autophagy would be useful in this setting.