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Research uncovers new steps on pathway to enlarged heart

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Researchers have new insight into the mechanisms that underlie a pathological increase in the size of the heart. The research, published by Cell Press in the October 24th issue of the journal *Molecular Cell*, may lead to the development of new strategies for managing this extremely common cardiac ailment that often leads to heart failure.

High blood pressure, heart valve disease and heart attacks can lead to a abnormal thickening of the heart muscle, called myocardial hypertrophy. At the molecular level, signals driving myocardial hypertrophy, such as elevated levels of catecholamine hormones (i.e. adrenaline), activate the Myocyte Enhancer Factor (MEF) proteins. This alters gene expression in heart muscle cells and induces an adverse developmental paradigm known to cardiologists as the "fetal gene response".

"Previous research has shown that the signaling pathways leading to MEF2 are altered during pathological cardiac hypertrophy," says senior study author Dr. John D. Scott, a Howard Hughes Medical Institute Investigator from the Department of Pharmacology at the University of Washington. "Although we know that enzymes called histone deacetylases (HDACs) control MEF2 activity, it was not clear that HDACs and MEF2 were integrated into a larger signaling unit."

To further identify the molecular mechanisms associated with cardiac hypertrophy, Dr. Scott and colleagues studied cardiac A-Kinase Anchoring Proteins (AKAPs), which are known to play a critical role in organizing signaling complexes in response to catecholamine hormones

and transmitted signals within cells.

The researchers found that AKAP-Lbc functions as a scaffolding protein that selectively directs catecholamine signals to the transcriptional machinery to potentiate the hypertrophic response. "Our study supports a model where AKAP-Lbc facilitates activation of protein kinase D, which in turn phosphorylates the histone deacetylase HDAC5 to promote its export from the nucleus. The reduction in nuclear HDAC5 favored MEF2 transcription and the onset of cardiac hypertrophy."

These studies reveal a role for AKAP-Lbc in which increased expression of the anchoring protein selectively amplifies a signaling pathway that drives cardiac muscle cells to a pathophysiological outcome. "It will be important to explore the role of the AKAP-Lbc/PKD/HDAC5 signaling pathway in whole animal models to establish whether AKAP-Lbc is a valid biomarker for hypertrophic cardiomyopathy and to determine which genes are initiated upon up-regulation of the anchoring protein," offers Dr. Scott.

Source: Cell Press