# BAG3 protein plays critical role in protecting heart from reperfusion injury, research shows

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The inability of cells to eliminate damaged proteins and organelles following the blockage of a coronary artery and its subsequent re-opening with angioplasty or medications - a sequence known as ischemia/reperfusion - often results in irreparable damage to the heart muscle. To date, attempts to prevent this damage in humans have been unsuccessful. According to a new study by scientists at the Lewis Katz School of Medicine at Temple University (LKSOM), however, it may be possible to substantially limit reperfusion injury by increasing the expression of a protein known as Bcl-2-associated athanogene 3 (BAG3).

"We found that BAG3 plays a pivotal role in protecting the heart from damage caused by reperfusion injury," explained the study's lead author, Feifei Su, MD, PhD, a postdoctoral fellow in the laboratory of Arthur M. Feldman, MD, PhD, Professor of Medicine at LKSOM.

Ischemia impairs the function of cellular organelles including mitochondria, the cell's energy-producers, resulting in harmful effects that set the stage for a sudden burst in the generation of toxic oxidizing substances when oxygenated blood reenters the heart. The toxins lead to fundamental changes in the biology of the heart. Notably, they activate cell death pathways and decrease autophagy - the process by which cells remove malfunctioning proteins and organelles. Autophagy plays a critical role in removing damaged myocardial cells (the muscular tissue

of the heart) and misfolded heart muscle fibers.

The new work shows that BAG3 expression both inactivates cell death pathways, helping prevent the loss of heart cells triggered by ischemia, and activates autophagy, thereby enabling cells to clear out impaired components of the heart cell before they inflict extensive damage. The findings, published online November 17 in the journal *JCI Insight*, open the door to the investigation of BAG3 as a therapeutic target during reperfusion in heart attack patients.

In initial work, the research group found that BAG3 promotes autophagy and inhibits programmed cell death (apoptosis) in cultured cardiac myocytes. Subsequently, they found that when heart cells were exposed to the stress of hypoxia/reoxygenation or when living mice were stressed with ischemia/reperfusion, they suffered dramatic reductions in BAG3 expression.

Those paradoxical changes in BAG3 levels turned out to be directly associated with increases in biomarkers of autophagy and with decreases in biomarkers of apoptosis. By artificially knocking down BAG3 in mouse heart cells, the researchers were able to produce an apoptosis-autophagy biomarker phenotype nearly identical to that produced by hypoxia/reoxygenation. By contrast, BAG3 overexpression normalized apoptosis and autophagy.

In a key experiment, the Temple team further showed that tissue damage sustained following ischemia/reperfusion could be substantially reduced by treating mice with BAG3 prior to vessel re-opening. BAG3 overexpression before the onset of ischemia/reperfusion also resulted in normalization in apoptosis and autophagy biomarkers.

According to Dr. Feldman, the senior investigator on the project, his team's interest in the role of BAG3 in the heart has grown in recent

years, owing to their discovery of a unique BAG3 mutation in a family with familial dilated cardiomyopathy, a genetic condition characterized by the development of heart failure between early and late adulthood.

"After finding that a mutation in BAG3 caused heart failure in a Philadelphia family, we have been trying to figure out what the protein does in the heart," Dr. Feldman said. "Now that we have a better understanding of its role and what happens when its levels are increased, we can investigate the possibility of targeting BAG3 in human patients using gene therapy or a small molecule."

Provided by Temple University

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