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# Drp1-Dependent Mitochondrial Autophagy Plays a Protective Role Against Pressure Overload-Induced Mitochondrial Dysfunction and Heart Failure

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We thank Drs. Papalia and Okonko for their interest in our work[1]. Autophagy is an essential mechanism by which cells maintain the quality of proteins and organelles. Although pressure overload (PO) sequentially activates non-selective autophagy (hereafter autophagy) and mitochondria-selective autophagy (hereafter mitophagy), these autophagic activities do not last long and mitochondrial dysfunction develops thereafter. Understanding the molecular mechanism by which autophagy and mitophagy are transiently activated but then inactivated during PO should provide a key to sustaining the level of autophagy and delaying the development of heart failure.

Drs. Papalia and Okonko propose that iron-dependent mechanisms may explain the transient nature of autophagy and the consequent development of mitochondrial dysfunction. The hypothesis that suppression of nutrient-deprivation autophagy factor (NAF)-1, a protein that facilitates interaction between Beclin 1 and its endogenous inhibitors, by reactive oxygen species (ROS) induces activation of endogenous Beclin 1 may well explain the activation of

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autophagy in the early phase of PO. PO is accompanied by increases in ROS, which in turn inactivate Fe-S containing proteins, including NAF-1, and activate PERK[2], an endoplasmic reticulum kinase, both of which can stimulate autophagy. Thus, we believe that ROS are an important trigger of autophagy and mitophagy in the early phase of PO. Since TAT-Beclin1[3], which prevents the development of heart failure, also activates autophagy and mitophagy by mobilizing endogenous Beclin 1 from intracellular anchorage sites, it is of great interest to further test whether the availability of free Beclin 1 is the key event in the regulation of autophagy and mitophagy in the context of PO.

Drs. Papalia and Okonko also propose that sustained PO induces chronic iron deficiency, causing upregulation of N-myc downstream-regulated gene 1 (NDRG1), an endogenous inhibitor of autophagy, and downregulation of iron-containing molecules, including heme and other Fe-S proteins in mitochondria, thereby exacerbating mitochondrial dysfunction. This hypothesis may provide additional support for the use of iron replenishment therapy for heart failure[4]. However, although the total iron content in the body may decrease in heart failure patients with cachexia, whether or not the iron content is also decreased in the heart remains unclear. The level of heme, an iron-containing protein, is increased in human failing hearts[5], and accumulation of iron in cardiac mitochondria exacerbates ROS production, mitochondrial dysfunction and cell death[6]. In addition, cardiomyopathy patients with Friedreich Ataxia, a hereditary disease caused by reduced levels of frataxin, a mitochondrial protein involved in Fe-S cluster biosynthesis, show iron accumulation, rather than depletion, in their hearts. Thus, further investigation is needed to clarify how PO and heart failure affect the iron content in the heart. In addition, since autophagy and mitophagy are activated and inactivated with distinct time courses during PO, it may be that they are regulated in part by non-overlapping mechanisms. Whether NDRG1, a regulator of autophagy, also similarly affects mitophagy remains to be clarified. Finally, we propose that activation of Mst1, a serine/threonine kinase known to inhibit autophagy by inactivating Beclin1, may explain the inactivation of both autophagy and mitophagy during heart failure. Thus, it would be interesting to test how the activity of Mst1 is regulated by iron in cardiomyocytes.

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