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# The Molecular Mechanisms of Mitochondrial Degradation in the Stressed Heart

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The degradation of damaged mitochondria by mitophagy, a mitochondria-specific form of autophagy, is essential for the maintenance of healthy mitochondrial function. Mitophagy is often downregulated during chronic cardiac stress, whereas rescue of mitophagy delays the development of cardiac dysfunction. However, the molecular mechanisms through which mitophagy is activated during stress remains poorly understood in the heart. Using electron microscopy and mitochondria-targeted-Keima, a fluorescent dye that indicates the pH environment in which it is located, it has been observed that glucose deprivation (GD) and hypoxia (HO), stresses known to impose energy stress, induce mitophagy in cardiomyocytes (CMs). Although downregulation of Atg7, an intervention that abrogates a non-selective form of autophagy (hereafter conventional autophagy), does not affect GD- or HO-induced mitophagy, downregulation of Ulk1, one of the two mammalian orthologs of Atg1, markedly attenuates mitophagy in CMs. Autophagosomes observed in this form of mitophagy are associated with Rab9 but not LC3. Thus, mitophagy in CMs during energy stress is likely to be mediated by a mechanism distinct from conventional autophagy. In response to energy stress, Ulk1 and Rab9 form a complex, recruit Rip1, a Drp1 kinase, and induce Ser616 phosphorylation of Drp1 and mitochondrial fission. Through this mechanism, damaged portions of mitochondria in CMs are segregated and sequestered in Rab9-positive autophagosomes. In summary, mitophagy during energy stress is mediated by a molecular mechanism distinct from conventional autophagy in CMs and Ulk1 mediates mitochondrial fission and mitophagy through the coordinated actions of Rab9, Rip1, and Drp1, thereby playing a central role in degrading damaged mitochondria during energy stress. In the lecture, I will also discuss the functional significance of mitophagy mediated through the Ulk1-Rab9-Rip1-Drp1-dependent mechanism during pressure overload and myocardial ischemia.