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"The Role of Mitophagy in Diabetic Cardiomyopathy"

by
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ABSTRACT

Macroautophagy is characterized by the presence of double-membrane vesicles, called autophagosomes, which contain cytosolic proteins and organelles and are degraded by lysosomal enzymes. When macroautophagy selectively degrades mitochondria, it is termed mitophagy. Increasing lines of evidence suggest that mitophagy plays an important role in degrading damaged or unnecessary mitochondria in CMs at baseline and in response to stress. Together with mitochondrial fission and fusion and mitochondrial biogenesis, mitophagy is one of the most important steps necessary to maintain the quality of mitochondria. Diabetic cardiomyopathy is commonly accompanied by the presence of mitochondrial dysfunction. In fact, previous studies have shown that autophagy, which non-selectively degrades mitochondria, and mitophagy are either downregulated or upregulated in the heart with metabolic syndrome. Importantly, the occurrence of mitophagy in the heart during the development of diabetic cardiomyopathy and its underlying mechanism are not unequivocally documented. Furthermore, how stimulation or inhibition of mitophagy affects the development of diabetic cardiomyopathy has been poorly addressed. We believe that a better understanding of how mitophagy is regulated during diabetic cardiomyopathy is essential in order to develop a specific strategy to alleviate cardiac dysfunction in type II diabetic patients. In this study, we reported that HFD induces Atg7-dependent mitophagy in the early phase but that this form of mitophagy declines after peaking at around 6 weeks of HFD consumption. Interestingly, HFD consumption continuously increases mitophagy after 6 weeks, which is mediated by an alternative mechanism, namely an Ulk1-Rab9-dependent but Atg7-independenrt mechanism. Alternative mitophagy is transcriptionally regulated by TFE3 during the chronic phase of HFD consumption. Mitophagy observed during the chronic phase of HFD consumption serves as an essential mitochondrial quality control mechanism in the heart. The impairment of mitophagy in the chronic phase of HFD consumption induces mitochondrial dysfunction, resulting in the exacerbation of diabetic cardiomyopathy. Thus, activation of alternative mitophagy during the chronic phase of HFD consumption is adaptive and protects the heart against stress caused by HFD consumption.