Cardiac Autophagy in Diabetic Cardiomyopathy

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Autophagy is a process for bulk degradation and recycling of cytoplasmic components in lysosomes [1]. A low level of constitutive autophagy is cytoprotective by maintaining the quality of proteins and organelles. It allows recycling of amino acids and removal of damaged organelles to eliminate oxidative stress and promote remodeling for survival. In the heart, autophagy plays an important role in cytopalsmic quality control and cardiac homeostasis under physiological and pathological conditions [2]. Down-regulation of autophagy would cause abnormal proteins and organelles to accumulate, leading to apoptosis and cardiac dysfunction, the pathologies seen in diseases such as myocardial hypertrophy, cardiomyopathy, and ischemic heart disease. However, excessive induction of autophagy may destroy the cytosol and organelles and release apoptosis related factors, triggering cardiomyocyte death and impairing cardiac function. Thus, there is ongoing debate about whether up-regulated autophagy is the cause of cardiomyocyte death or whether it is actually an attempt to protect cells against cardiac stress conditions, including diabetes and ischemic heart disease.

Suppression of Cardiac Autophagy in Type 1 Diabetes

Recently, we have established the role of autophagy in the development of diabetic cardiomyopathy in type 1 diabetic animal models [3,4]. At six months of age, OVE26 mice, an established type 1 diabetic mouse model generated through targeted overexpression of calmodulin in β cell, exhibit very high blood glucose concentrations, reduced serum insulin values, and elevated serum triglyceride levels [5], and they also exhibit cardiomyopathy characterized by clear morphological abnormalities and impaired cardiac performance. Evidence for diabetes-induced suppression of autophagic activity is uncovered by western blotting and electron microscopy, which demonstrate that diabetes decreases accumulation of lipidated microtubule-associated protein1 light chain 3 (LC3-II) and autophagosome formation in the heart. Moreover, streptozotocin (STZ) - induced diabetes also suppresses cardiac autophagy and impairs cardiac function.

Mechanistically, AMP-activated protein kinase (AMPK) activity is significantly inhibited in diabetic OVE26 mice, chronic activation of AMPK by metformin restores cardiac autophagy in wild type diabetic hearts, but this effect is abolished in mice deficient of AMPKα2, indicating that AMPK regulates cardiac autophagy in diabetic cardiomyopathy. In addition, Diabetic hearts display activation of the tuberous sclerosis complex mammalian target of rapamycin (TSC-mTOR) signaling pathway, as reflected by decreased phosphorylation of raptor, as well as increased phosphorylation of mTOR and its downstream effectors, 4 E binding protein 1 (4EBP1) and p70 ribosomal protein S6 kinase 1 (p70 S6K1). Activation of AMPK by metformin inhibits the TSC-mTOR pathway and restores cardiac autophagy in OVE26 mice. Finally, we demonstrate that AMPK activation attenuates diabetic cardiomyopathy through regulation of the switch between autophagy and apoptotic machinery (He C, et al. [3] unpublished data). This effect is attributable to c-Jun N-terminal kinase (JNK)-mediated Bcl-2 (B-cell lymphoma 2) phosphorylation and subsequent Beclin1-Bcl-2 disassociation. In STZ-induced diabetic mice, hyperglycemia enhances the interaction between Beclin1 and Bcl-2 through inhibition of JNK1 and Bcl-2 phosphorylation and results in suppression of autophagy and induction of apoptosis. Activation of AMPK stimulates JNK1, which mediates Bcl-2 phosphorylation and subsequent Beclin1-Bcl-2 disassociation, leading to restoration of Cardiac autophagy and protection against cardiac apoptosis. As a result, cardiac structure and function are improved in diabetic mice. These data suggest that hyperglycemia suppresses cardiac autophagy, leading to cell death and cardiac dysfunction. Restoration of autophagy by activated AMPK prevents diabetic cardiomyopathy. However, a recent study demonstrates that high glucose directly inhibits autophagic flux in neonatal rat cardiomyocytes and in these cells the reduction of autophagy appears to be an adaptive response that functions to limit high glucose induced cardiomyocyte injury [6]. Neonatal cardiomyocytes have been reported to behave substantially different from adult cardiomyocytes [7]. Especially, autophagy is up-regulated in the neonatal cardiac tissue during perinatal period of relative starvation [8]. Thus, autophagy could be either protective or detrimental depending on the cell type and cellular environment.

Autophagy in Metabolic Syndrome

Metabolic syndrome is a collection of medical disorders, including obesity, insulin resistance, and dyslipidemia, which can lead to diabetes and cardiovascular disease. Under these energy-rich conditions, the Akt signaling pathway is activated. In turn, Akt phosphorylates and activates the mTOR kinase, a negative regulator of autophagy. Inhibition of mTOR has been linked to autophagy induction in metabolic syndrome. For instance, obesity was reported to inhibit autophagy in the liver. In addition to activation of Akt-mTOR signaling, obesity also induces the calcium dependent protease calpain, eading to cleavage and degradation of autophagy related protein 7 and ultimately inhibition of autophagy [9]. Similarly, a recent study in *Drosophila* demonstrated that high fat diet induced obesity and cardiac dysfunction through activation of TOR signaling pathway and suppression of TOR signaling protected the heart against high fat diet induced cardiac dysfunction [10]. Because TOR is a primary inhibitor of the autophagic pathway, it is reasonable to propose that high fat diet may inhibit autophagy in this model. However, Mellor et al. reported that up-regulation of autophagy was associated with decreased phosphorylation of Akt and S6 kinase, an mTOR downstream molecule, in a type 2 diabetic mouse model [11]. In this animal model, twelve weeks of 60% fructose diet treatment induced systemic insulin resistance, as signified by impaired glucose tolerance and hyperglycsmia. Concomitantly downstream signaling of the class I Phosphatidylinositol 3-kinases (PI3K) pathway

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was inactivated and the autophagic markers, lipidated LC3B (LC3B-II/ LC3B-I) and p62, were up-regulated. The activation of myocardial autophagy was accompanied by elevated production of reactive oxygen species (ROS), fibrosis and cardiomyocyte loss (without indication of apoptosis induction). These results suggest that in insulin-resistant myocardium, suppression of Akt and S6 kinase as well as activation of autophagy have detrimental impact on cardiomyocyte viability in high fructose-induced diabetic mouse model. It is not yet clear how these contradictions may be explained. More investigations are warranted to determine how the PI3K-Akt signaling pathway can both promote and suppress autophagy in metabolic syndrome.

Conclusions

In summary, there is persuasive evidence that diabetes affects cardiac structure and function through regulating autophagy and its upstream signaling pathways, but further studies are needed to better explain the inconsistent data published thus far. For example, the precise role of autophagy in the development of diabetic cardiomyopathy has to be determined individually within the specific contexts. Differential role for mTOR and AMPK in regulation of autophagy in type 1 and type 2 diabetic hearts should be better explored. Elucidation of the role of autophagy in mediating either cell survival or cell death during the development of diabetic cardiomyopathy, as well as when and how autophagy is manipulated, would have a significant impact on the treatment of diabetes and its complications.

Acknowledgements

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