

Autophagy: a potential therapeutic target in cardiac lipotoxicity?

Editorial

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Under physiological conditions, the heart preferably utilizes free fatty acid for energy generation. Normally the lipid uptake and oxidation are finely balanced and little lipid accumulation is present within the heart. However, in response to chronic overnutrition, the plasma free fatty acids are elevated probably due to insulin resistance of adipose tissue, leading to lipid accumulation in non-adipose tissues including the heart. The excessive amounts of free fatty acids are converted into triglycerides and stored as lipid droplet. Chronic accumulation of lipid droplets and lipid metabolic intermediates in the heart may disrupt normal cell signaling, leading to cardiac dysfunction and in some cases apoptotic cell death, a process termed cardiac lipotoxicity. Clinical studies have suggested that myocardial lipid accumulation is associated with ventricular systolic dysfunction, diastolic dysfunction and cardiomyopathy in people with obesity and type 2 diabetes [1,2]. Animal studies have shown that cardiac lipid accumulation directly contributes to abnormalities of cardiac structure and function [3]. Therefore, target lipid accumulation in the heart may represent a potential therapeutic strategy for the treatment of heart disease associated with obesity and diabetes. Indeed, several approaches aiming to limit or prevent lipotoxicity are developed [4]. However, given that the prevalence of diabetes grows rapidly and heart disease is the leading cause of mortality among individuals with diabetes, identification of novel molecular mechanisms governing lipid accumulation in the heart is urgently needed for the development of more effective therapeutic approaches to fight against cardiac lipotoxicity. Recently, macroautophagy (hereafter refer to as autophagy) is emerging as a potential target for cardiac lipotoxicity therapy.

Autophagy is an evolutionarily conserved pathway that degrades cytoplasmic components in lysosomes. Under normal conditions, autophagy occurs at low levels in the heart, which is essential to maintain cardiac structure and function by removing misfolded protein, protein aggregates and damaged mitochondria [5]. Cardiac autophagy is up-regulated in response to a variety of stresses such as hypoxia, endoplasmic reticulum stress, nutrient starvation, inflammation and oxidative stress [6]. Dysregulation of autophagy contributes to the pathogenesis of many forms of heart disease including ischemia heart disease, hypertensive heart disease and heart failure [7].

It has been well established that autophagy regulates protein and glycogen metabolism. Recently, a growing body of evidence has shown that autophagy also regulates lipid metabolism, a process termed lipophagy. In this pathway, the triglyceride and cholesterol in lipid droplet are selectively sequestered by autophagosomes and then delivered to lysosomes, followed by degradation of the substrates by lysosomal acid lipase, leading to decrease in lipid droplet content [8]. Lipophagy is most extensively studied in hepatocyte because lipid is actively metabolized there. Inhibition of autophagy leads to lipid accumulation while activation of autophagy reduces lipid accumulation in the liver. It is of particular interest that in alcoholic and non alcoholic liver disease, pharmacological induction of autophagy by carbamazepine or rapamycin ameliorates hepatic steatosis and liver injury. Conversely, pharmacological inhibition of autophagy by chloroquine aggravates fatty liver condition and liver injury [9]. These findings suggest that autophagy modulation may be a therapeutic target for lipotoxicity in the liver. In the heart, there is little direct evidence linking autophagy to lipid accumulation. However, several lines of research have suggested the association of cardiac autophagy with lipid accumulation. One study has shown that high-fat diet induces lipid accumulation in the heart. Rapamycin treatment improves lipid deposition in the heart, which is associated with enhanced autophagy and improved cardiomyocyte contractility [10]. Another study conducted by Asli et al has demonstrated that high-fat diet causes cardiac hypertrophy and dysfunction, which is attenuated by apelin, an adipokine important for the regulation of energy metabolism. Meanwhile, apelin reduces high-fat diet induced myocardial lipid accumulation, which is associated with recovered high-fat diet-induced suppression of autophagy [11]. These studies implicate autophagy in the treatment of cardiac dysfunction caused by lipid accumulation. Interestingly, hepatic steatosis is commonly associated with cardiac steatosis and cardiovascular disease because of the metabolic crosstalk between the heart and liver [12]. Thus, systemic pharmacological manipulation of autophagy is potentially useful to simultaneously treat lipid accumulation both in the heart, liver and more broadly, human disorders

that lipid accumulation plays a role in the pathogenesis. However, a few questions and concerns regarding autophagy as a therapeutic alternative for lipotoxic heart disease are posed.

- i. Lipid and autophagy have unexpected impacts on each other. On the one hand, lipid modulates autophagy, either stimulatory or inhibitory depending upon lipid type and context. For instance, saturated fatty acid myristate, but not palmitate stimulates autophagy in adult primary cardiomyocytes [13]. On the other hand, the light chain-3 conjugation system in autophagy participates in the formation of lipid droplet [14]. The interaction between lipid and elements of autophagy needs to be further understood.
- ii. Although autophagy is a protective mechanism in the heart under normal conditions, overactivation of autophagy can be detrimental to the heart [15]. Thus, autophagy should be fine-tuned to selectively regulate lipid metabolism for therapeutic purpose.
- iii. Acute lipid droplet accumulation or appropriate amount of lipid droplet is considered to be an adaptive response in the heart under overnutrition conditions. Autophagy activation may disrupt the compensatory response. In addition, overactivation of autophagy is capable of hydrolyzing the triglyceride pool in cardiomyocyte without restriction, leading to excessive production of lipid intermediates such as ceramide, which causes harmful effects to the heart [16].
- iv. The functional relationship between lysosomal acid lipase and adipose triglyceride lipase in lipid droplet hydrolysis in the heart is not clear. It remains to be determined if individual cellular lipid droplets have preferential pathway targeted for degradation.
- v. Adverse effects of autophagy on the cells other than cardiomyocytes should be considered. For instance, autophagy mediates apoptosis induced by trans fatty acid in primary cardiac myofibroblast [17].

In conclusion, chronic lipid accumulation contributes to the pathogenesis of lipotoxic heart disease. Autophagy regulates lipid metabolism. Although more preclinical and clinical studies are required to provide further insight into lipophagy in the heart,

modulation of autophagy may represent a promising therapeutic avenue for prevention and treatment of not only cardiac lipotoxicity, but other organ disorders as a whole under pathological conditions such as obesity and type 2 diabetes.

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