Review article

Autophagy, dysglycemia and myocardial infarction

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1. Introduction

Myocardial infarction (MI) remains a leading cause of morbidity and mortality worldwide [1]. MI occurs when myocardial ischemia, a diminished blood supply to the heart, exceeds a critical threshold and overwhelms myocardial cellular repair mechanisms designed to maintain normal operating function and homeostasis [2]. Ischemia at this critical threshold level for an extended period results in irreversible myocardial cell damage or death. Autophagy is thought as a novel cell death mechanism involving in the pathophysiological process of myocardial infarction (MI), and modulation of autophagy may be considered as a promising treatment modality for MI. Dysglycemia was associated with higher mortality in patients with MI. We hypothesize that autophagy may be a potential pathway through which dysglycemia has an impact on the outcomes of MI. In this review, we summarize the function of autophagy in the conditions of MI and the regulatory effects of dysglycemia on autophagy. Four main impacts of autophagy on MI under dysglycemia have been revealed. The first one is that autophagy limits the infarct size via inhibited mTOR. The second one is that autophagy promotes the survival of cardiomyocytes through depleted ATP. The third one is that autophagy protects cardiac myocytes from impairing by way of degradation. The last one is that autophagy maintenance of LV function through FoxO1.

Therefore, the ability to modulate autophagy may represent as a potential and promising therapeutic strategy in limiting MI caused by dysglycemia. However, elucidation of precise ways of autophagy in mediating MI caused by dysglycemia, as well as when and how autophagy is manipulated remains us to research.
Lysosomal degradative machinery [19–21]. Since cardiac myocytes are terminally differentiated, the role of autophagy is essential to maintain the homeostasis of the myocardium [19,22]. Autophagy supplies nutrients for the synthesis of essential proteins during starvation and thus helps to extend cell survival. Although autophagy is non-selective, under oxidative conditions it effectively removes oxidatively damaged mitochondria, peroxisomes and endoplasmic reticulum [19–21]. Thus, autophagy can protect the cells from apoptosis and other major injuries, and it is considered to be in the cross-road between cell death and survival. However, excess autophagy can destroy essential cellular components and lead to cell death.

There are three main autophagic pathways: macroautophagy, microautophagy and chaperon-mediated autophagy [23–28]. Macroautophagy, hereafter referred to as autophagy, is the most common form of autophagy. Microautophagy is a form with few features. The notable difference between macroautophagy and microautophagy is that in the latter the cytoplasm is directly up taken into the lysosome/vacuole. Chaperone-mediated autophagy is activated by physiological stresses such as prolonged starvation. No vesicular traffic is required for this protein degradation pathway, so it differs from microautophagy and macroautophagy.

2.2. Molecular machinery of autophagy

Autophagy process is divided into mechanistically distinct steps, including induction, cargo recognition and selection, vesicle formation, autophagosome-vacuole fusion, and breakdown of the cargo followed by release of the degradation products back into the cytosol [19–21]. Different sets of Atg proteins are involved in these steps and consist of the core autophagic machinery [29–35]. Beclin1 (Atg6) and class III PI3K are needed for the vesicle (called isolation membrane) nucleation step of autophagy. The vesicle elongation process features two conjugation systems that are well-conserved among eukaryotes. One pathway involves the conjugation of Atg12 to Atg5 with the help of Atg7 and Atg10. The second pathway involves the conjugation of phosphatidylyl-ethanolamine to Atg8 [microtubule-associated protein 1 light chain 3; LC3] by the sequential action of Atg4, Atg7 and Atg3. The conjugation leads to the conversion of the soluble form of LC3 (LC3-I) to the autophagic vesicle-associated form (LC3-II). And it is used as a marker of autophagy.

2.3. Signaling pathways regulating autophagy

There are a number of signaling complexes and pathways involved in the initiation and maturation of autophagy. The main signaling pathways of regulating autophagy, based on the existing literature, are nutrient signaling insulin/growth factor pathways, energy sensing, stress response and pathogen infection [36].

The central player in these signaling pathways is TOR/mTOR in nutrient signaling insulin/growth factor pathways [37,38]. TOR, the target of rapamycin, is a serine/threonine kinase involved in most regulatory pathways that control the response to changes in nutrient conditions and energy metabolism. TOR acts as a good gate-keeper in autophagy and exerts an inhibitory effect on autophagy. In the presence of growth factors and abundant nutrients, it is the major inhibitory signal that shuts off autophagy. The mTOR pathway is regulated by the 5′-AMP-activated protein kinase (AMPK).

In addition to that, energy sensing signaling pathway also plays a role in autophagy regulation [39,40]. It has been reported that reduced cellular content of ATP would induce autophagy. In cultured cardiac myocytes, glucose deprivation caused significant reduction in the levels of ATP. Moreover, because of adenylate kinase equilibrium in the cell, a fall in ATP is often associated with an increase in AMP. AMPK, which serves as a general integrator of metabolic responses to changes in energy availability, is activated in response to elevations of the AMP/ATP ratio. Thus, autophagy can be upregulated by AMP through activation of AMPK.

FoxO (forkhead box transcription factor class O) functions is another signaling pathways of regulating autophagy in parallel to the mTOR pathway, whilst both pathways are downstream of IGF-1-insulin-PtdIns3K-PKB/Akt signaling [41,42]. Thus, autophagy is regulated by two different mechanisms: nontranscriptional inhibition by mTOR and transcription-dependent upregulation through FoxO. Thereinto FoxO1 is the first transcription factor that is shown to be necessary and sufficient to induce autophagy in the drosophila larval fat body. However, not much is known about the underlying transcriptional machinery.

21. Function of autophagy in the conditions of MI

MI, caused by occlusion of an epicardial coronary artery, leads within hours to irreversible death of the cardiomyocytes in the distribution supplied by that artery [2]. MI also initiates a cascade of neurohumoral changes such as myocardial remodeling that attempt to compensate for the lack of contractile function caused by the MI. This initially maintains cardiac output and perfusion to the vital organs, but with time, these compensatory mechanisms fail, and there is progressive deterioration of cardiac function. The end result is a dilated, poorly functioning ventricle, and the clinical syndrome of heart failure ensues. Thus, one of the most important factors for improving the prognosis after MI is the attenuation of adverse myocardial remodeling. However, currently, therapeutic strategies that inhibit remodeling are limited to inhibition of neurohumoral activation. There is increasing evidence suggest that autophagy, as a mechanism for the degradation of damaged long-lived proteins and organelles, plays an important role in the process of cardiac remodeling [43–46]. Thus, autophagy, which is one of the cell death mechanisms, seems to be essential in MI.

3.1. Limit infarct size

Of note is that, induction of autophagy by inhibition of mTOR with everolimus (RAD) prevents adverse LV remodeling and limits infarct size following MI [47]. mTOR-dependent signaling mechanisms of autophagy are centrally involved in the myocardial remodeling process [37,38]. One or three days following MI, Wistar rats were treated with RAD (3.0 mg/kg/day) [48]. After one month, treatment with RAD leads to a significant decrease of infarct size, improvement of systolic and diastolic LV function and reduced LV dimensions as compared to vehicle treatment. In the clinical setting, frequently patients present in subacute stages of MI. Also, when initiated three days after MI, significant attenuation of myocardial remodeling is observed in the RAD group, although the beneficial effect is smaller as compared to the earlier administration. Therefore, mTOR inhibition reduces post-MI remodeling and limits infarct size. mTOR inhibition increases autophagy and concomitantly decreases proteasome activity especially in the border zone of the infarcted myocardium. The induction of autophagy via mTOR inhibition is a novel potential therapeutic approach to limit infarct size and to attenuate adverse left ventricular remodeling following MI.

3.2. Promote the survival of cardiomyocytes

Autophagy also promotes the survival of cardiomyocytes [22,49]. In hearts subjected to reperfused MI, autophagy is activated first by the AMP activated protein kinase (AMPK)-dependent mechanism during the ischemic period, followed by Beclin-1-dependent autophagy after reflow is established. In this model, autophagy promotes the survival of cardiomyocytes during the AMPK dependent (ischemic) phase, but becomes detrimental during the Beclin-1 dependent (reflow) phase.
3.3. Cardioprotective

Autophagy has been shown to be cardioprotective [50]. At the same time, Gurusamy et al. [51] also reported that preconditioning enhanced autophagy and that inhibition of autophagy abolished the cardioprotective effects of preconditioning. Based on these results, we conclude that autophagy is cardioprotective is because the cellular autophagosome–lysosomal complexes degrade proteins to generate a large number of free amino acids and fatty acids to maintain the mitochondrial energy supply, and improve the survival cells. Secondly, autophagy protects cardiac myocytes from necrosis by removing damaged mitochondria. Thirdly, autophagy protects cardiac myocyte by degrading disordered structural proteins, which are harmful to cardiac myocytes.

3.4. Maintenance of left ventricular function

In addition, autophagy can also maintain the LV function during starvation by functional FoxO1. FoxO1 is an inducer of autophagy especially in the border zone of myocardial cell [49]. Many studies have reported that autophagy principally has a cardioprotective effect during MI. However, some studies have demonstrated that upregulation of autophagy can lead to myocyte death after ischemia/reperfusion, excessive autophagy may facilitate death of myocytes during MI [52]. So, all of these need us to make further research. But for now, we think that autophagy principally has a cardioprotective effect during MI according to the reports.

Although functional autophagy is crucial for normal functioning of cardiomyocytes, the effects of MI on autophagy, and conversely the effects of autophagy on the heart following MI, remain incompletely described.

4. Regulatory effects of dysglycemia on autophagy

4.1. Hyperglycemia and MI

Several studies have reported that acute hyperglycemia is related to a higher incidence of mortality [53–58]. Most of the older and smaller studies (predominantly from the 1980s and ’90s) were summarized in the meta-analysis by Capes et al. [55]. These combined results demonstrated that the relative risk of in-hospital mortality in non-diabetic MI patients with admission glucose level > 6.1 mmol/L was 3.9, as compared with non-diabetic MI patients who were euglycemic [55]. Among MI patients with diabetes, those with admission glucose level > 10.0 mmol/L had a 70% increase in the relative risk of in-hospital mortality, as compared with diabetic patients with normal admission glucose level [55]. More recent studies have confirmed these findings, showing significant increases in the risk of short- and long-term mortality, as well as heart failure, in hyperglycemic MI patients both with and without known diabetes [11,12]. These findings extend to the entire range of acute coronary syndromes, including ST-segment elevation MI, non-ST segment elevation MI and unstable angina [58]. Several studies also have documented a clear relationship between elevated FPG level during MI hospitalization and increased mortality risk [59,60]. In contrast to a random glucose level on admission, an elevated FPG level may better reflect abnormalities in underlying glucose metabolism, and thus may be a better predictor of outcomes. In one of the earlier studies on this issue, Suleiman et al. [61] demonstrated that while both admission and fasting glucose levels predicted 30-day mortality in non-diabetic patients with MI, fasting glucose level was the better discriminator. In a subsequent study by the same group, using a larger patient sample size and a longer follow-up period, fasting glucose level also was shown to be a strong predictor of 2-year mortality and left ventricular systolic function post-MI. FPG also added significantly to the discriminability of the Global Registry of Acute Coronary Events (GRACE) risk score (a validated tool used to estimate all-cause mortality risk in patients with acute coronary syndromes) [62].

4.2. Hypoglycaemia and MI

The prognostic significance of hypoglycemia after MI is controversial. Svensson et al. [61] conducted a study in 713 diabetic patients with unstable angina or non-Q-wave MI and found a significantly higher mortality at 2 years in subjects with hypoglycemia (admission glucose level ≤ 3.0 mmol/L) than in those with euglycemia; however, a causal link between in-hospital hypoglycemia and clinical outcomes ascertained 2 years later was difficult to establish. Kosiborod et al. [62] showed that hypoglycemia (admission glucose level < 3.3 mmol/L) was associated with increased mortality in patients with MI, but this risk was confined to patients who had spontaneous hypoglycemia (i.e., not including iatrogenic hypoglycemia). A more recent analysis by Goyal et al. [63] revealed that both admission and post-admission hyperglycemia (admission glucose level ≤ 3.8 mmol/L) could predict 30-day death in MI patients. However, only hypoglycemia on admission predicted death, and this relationship dissipated after admission. Another report from the DIGAMI-2 (Diabetes mellitus, Insulin Glucose infusion in Acute Myocardial Infarction 2) trial [64] showed that hypoglycemia (admission glucose level < 3.0 mmol/L) during the initial hospitalization was not an independent risk factor for future morbidity or mortality in patients with type 2 diabetes and MI. Hypoglycemic episodes were, however, more prevalent in patients at high risk for other reasons. All trials mentioned above used a much lower threshold to define hypoglycemia, and nondiabetic subjects were not included in some trials [63–66]. In our previous study, we observed that mild to moderately decreasing FPG levels (≤ 5 mmol/L) were associated with a relative increase in risk of mortality [65–67]. There was a U-shaped relationship between admission FPG levels and short- and long-term mortality.

The exact mechanisms behind the association of hyper-/hypoglycemia and higher mortality have not been definitively established. However, prior physiological studies show that higher glucose levels in patients with MI are associated with higher free fatty acid concentrations, insulin resistance, and impaired myocardial glucose use, thus increasing the consumption of oxygen and potentially worsening ischemia [68]. Hypoglycemia and rapid changes in blood glucose have been shown to increase levels of counter regulatory hormones such as epinephrine and norepinephrine, which may induce vasoconstriction, platelet aggregation, and thereby ischemia [69].

5. Autophagy, dysglycemia and MI

5.1. mTOR inhibition

Firstly, mTOR is an important negative regulator of autophagy in cardiomyocytes and integrates intracellular signals including glucose. The AMPK-mTOR pathway is an important regulator of autophagy in response to glucose deprivation in neonatal myocytes as inhibition of AMPK reduced autophagy and increased cell death in cardiomyocytes [37].

5.2. ATP depletion

Secondly, in cultured cardiac myocytes, glucose deprivation caused significant reduction in the levels of ATP. A decrease in ATP levels is accompanied by an increase in the AMP/ATP ratio, resulting in activation of the AMP-activated protein kinase (AMPK). Matsui et al. [72] reported that glucose deprivation induced autophagy via activation of AMPK in isolated cardiac myocytes. Meanwhile, autophagy also promotes the survival of cardiomyocytes by this signaling pathways.
5.3. Autophagy degradation

Thirdly, higher glucose levels in patients with MI are associated with higher free fatty acid concentrations. The cellular autophagosomes–lysosomal complexes in autophagy degrade a large number of free fatty acids to maintain the mitochondrial energy supply, and improve the survival cells.

5.4. FoxO induction

Lastly, it was recently reported that glucose deprivation of cardiac myocytes induced translocation of FoxO1 to the nucleus where they activated transcription of genes involved in autophagy [49,71–73]. FoxO1 is highly expressed in the heart and regulate autophagy by activating transcription of the Atg genes. Another study recently reported that deacetylation of FoxO1 by Sir1 was an essential step for autophagy in glucosedeprieved cardiac myocytes as FoxO1 mutants that cannot be deacetylated by Sir1 inhibited induction of autophagy [74]. Therefore, FoxO1 is required for glucose deprivation-induced autophagy. At the same time, autophagy can also maintain of LV function during starvation by functional FoxO1. Consequently, we can maintain of LV function when dysglycemia by way of autophagy which is induced by FoxO1.

6. Conclusions

Recently, there has been considerable interests in defining the molecular signaling pathways that govern autophagy in MI. In this review, we summarize the function of autophagy in the conditions of MI and the regulatory effects of dysglycemia on autophagy. Four main impacts of autophagy on MI under dysglycemia have been revealed (Fig. 1). The first one is that autophagy limits the infarct size via nontranscriptional inhibition of mTOR. The second one is that autophagy promotes the survival of cardiomyocytes through depleted ATP. The third one is that autophagy protects cardiac myocytes from impairing by way of degradation. The last one is that autophagy maintenance of LV function through FoxO1. Therefore, the ability to modulate autophagy may represent as a potential and promising therapeutic strategy in limiting MI caused by dysglycemia. However, elucidation of precise ways of autophagy in mediating MI caused by dysglycemia, as well as when and how autophagy is manipulated remains us to research.

Ethical statement

We adhere to the statement of ethical publishing as appears in the International of Cardiology [70].

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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