Progress in the Study of Cardiomyocyte Autophagy in the Course of Heart Failure

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Abstract: Autophagy is a general physiological process that occurs in all eukaryotic cells. It can be induced by starvation, myocardial infarction and heart failure. Rational autophagy in cardiac cells heart failure helps to keep cellular homeostasis, and inhibit the cell loss. However, inappropriate activation of autophagy leads to cell death. This paper intends to review the progress of research on cardiomyocyte autophagy in the course of heart failure.

Key words: autophagy; heart failure; cardiac myocyte

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Cellular autophagy is a life phenomenon widely found in eukaryotic cells and is a highly conserved cellular degradation process and self-protection mechanism during evolution. Autophagy at the background level removes damaged organelles and prolongs cell life; autophagy during nutrient limitation and oxidative stress, often induced as an adaptive cellular response; autophagy during apoptosis, involved in type II programmed cell death; autophagy also plays a major role in the exploration of the pathogenesis of many diseases, including cardiovascular diseases. Heart failure is the final pathophysiological process of severe cardiac diseases, in which autophagy is also involved. Therefore, this paper is intended to review the role of autophagy in the process of heart failure.

1. Overview of Cellular Autophagy

Cellular autophagy is an autophagy at the subcellular level, which refers to a series of degradation processes carried out by lysosomes to isolate parts of the cytoplasm and organelles of cells into vesicles with double membranes. In total, more than 30 autophagy-associated genes (Atg) have been identified, which affect the non-specific autophagy of protein renewal, autophagy of peroxisomal degradation and the hydrolase delivery pathway from the cytoplasm to the lysosome. These dynamic pathways can usually be divided into the following steps: induction of autophagy; recognition of carriers; nucleation, expansion and closure of vesicles to form autophagosomes; recycling of Atg proteins; fusion of vesicles with lysosomes to form autophagic lysosomes; degradation of vesicle contents after disassembly; recycling of macromolecules.

There are three main types of autophagy in eukaryotic cells: macro autophagy, micro autophagy, and chaperone-mediated autophagy (CMA). Among them, macro autophagy, which is often referred to as autophagy, wraps degradable proteins and degenerated necrotic organelles in the cell plasma with its non-

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lysosomal origin bilayer membrane structure to form an autophagosome, which fuses with the lysosome and releases the monolayer inner membrane vesicles into the lysosome for degradation and processing, and the hydrolases in the lysosome can effectively hydrolyze the degraded materials therein The lysosomal hydrolases can effectively hydrolyze the degraded material in it and generate macromolecules for reuse after translocation to the cytosol via membrane permease. Small autophagy is the direct phagocytosis of degradates on the lysosomal surface through lysosomal invagination, protrusion and segregation, and CMA can directly allow unfolded soluble proteins to enter the lysosome across the membrane.

The regulation of cellular autophagy focuses on the upstream signaling pathways involved in autophagosome formation, the Atg system involved in autophagosome formation, and the regulation of mature late autophagy. At the first level, there are mainly mammalian target of rapamycin (mTOR) dependent pathways, non mTOR dependent pathways and other pathways such as eIF2α, MAPK, PKC and NF-κB involved in autophagy regulation. At the second level, Atg1 and Beclin 1 are involved, in addition to post-translational modifications of Atg proteins and transcriptional regulation. At the third level, ERK1/2 activation may stimulate the formation and maturation of autophagosomes, while p38 has an inhibitory effect on early autophagy.

2. Heart Failure and Cellular Autophagy

Heart failure is a pathophysiological process of cardiac insufficiency and progressive loss of cardiomyocyte function due to various cardiac diseases such as coronary artery disease, hypertension, cardiomyopathy and arrhythmia, which manifests as compensatory hypertrophy of the myocardium, and when compensatory hypertrophy occurs in the heart, left ventricular hypertrophy further promotes irreversible loss of cardiomyocyte compensation, eventually leading to ventricular dilation and systolic dysfunction. The thinning of the ventricular wall is caused by protein hydrolysis and myocardial cell death. The pathological mechanisms are: failure of blood function to meet the demands of the hypertrophied myocardium; changes in contractile proteins; extracellular matrix remodeling; and altered adrenergic signaling. This ultimately leads to the development of heart failure.

In heart failure, apoptosis occurs in cardiomyocytes, promoting myocardial remodeling. A recent study found that in heart failure, cardiomyocyte autophagy appears with increase. In the observation that cardiomyocytes from patients with Danon's cardiomyopathy contain many autophagic vesicles, deletion of the lysosomal membrane protein Lamp2 can lead to impaired autophagy, suggesting that autophagy plays an important role in maintaining myocardial structure and function. In advanced heart failure caused by ischemic or dilated cardiomyopathy, autophagic death of cardiomyocytes is 0.3%, while apoptosis occurs in up to 0.002% of cardiomyocytes. Cardiomyocyte autophagy was found to be one of the major causes of cardiomyocyte death in patients with compensated cardiac hypertrophy due to aortic stenosis. Cardiomyocyte apoptosis and autophagic death were found in patients with primary dilated heart disease. When myocardial hypertrophy occurs, blood supply is also relatively inadequate, and autophagy can be involved in myocardial tolerance to chronic ischemia. Thus, autophagy is involved in the pathological process of cardiomyocyte death during the progression of heart failure, although it is still unclear how autophagy acts as a signaling mechanism for the limitation of myocardial repair and the death of hypertrophic cardiomyocytes. Autophagy is also a major contributing factor for cardiomyocytes throughout the occurrence of hemodynamic stress.

Cellular autophagy also plays a very important role in the progression of cardiac hypertrophy to heart failure. In an animal model of heart failure due to pressure overload induced by ligation of the aorta, a significant increase in cardiac autophagic activity was found. The autophagic activity induced by pressure overload peaked at 2 days and persisted for 3 weeks. The level of autophagy was not identical in all parts of the heart, with the highest level of autophagy in the ventricular septum. By inhibiting Beclin1 expression, cardiomyocyte autophagy can be effectively reduced and pathological myocardial remodeling due to severe stress can be attenuated. However, when Beclin1 was overexpressed, autophagic activity was instead enhanced, promoting stress overload-induced myocardial hypertrophy and ventricular remodeling.

A recent researcher found that RNA interference by Atg7 in primary isolated cultures of mammary rat cardiomyocytes inhibited autophagy-induced myocardial hypertrophy, and the cross-sectional area of cardiomyocytes was increased in Atg5 knockout mice. In addition, myocardial hypertrophy induced by thyroid hormone induction or ligation of the aorta can be prevented with rapamycin. Rapamycin, an mTOR inhibitor, can effectively activate autophagy via the type III PI3K pathway due to the close association of non mTOR dependent pathways with Beclin1 and type III PI3K, thus regressing pressure overload mediated myocardial hypertrophy and thus improving cardiac function. Autophagy can counteract myocardial hypertrophy by enhancing protein degradation and reducing cardiomyocyte volume.

The PI3K signaling pathway plays an important role in the regulation of myocardial hypertrophy. Three of the type I PI3Ks are expressed in the heart. Growth factors and insulin activate the type I PI3K pathway to generate phosphatidylinositol 3,4 biphosphate and phosphatidylinositol 3,4,5 trisphosphate. the main effector of type I PI3K is the serine/threonine kinase Akt/PKB. phosphatidylinositol binds to PKB and forms a complex, which in turn inhibits the downstream small G protein Rheb, thereby inhibiting mTOR activity and inducing autophagy. Akt signaling is associated with a variety of cellular responses that regulate metabolism and cellular hypertrophy. Under stress overload, PI3Kα activates and regulates cardiac hypertrophy. It may be caused by activation of the insulin-like growth factor 1 receptor (IGF-1R). When cardiac-specific IGF-1R is overexpressed, it can lead to myocardial hypertrophy.

Qin et al demonstrated an increase in reactive oxygen species (ROS) clusters in heart failure; Scherz et al found that ROS released from mitochondria could further come to regulate nutrient deficiency-induced autophagy by inhibiting the activity of Atg4 through oxidation. In addition to post-translational modifications such as ubiquitination and acetylation to regulate Atg protein activity, ROS may also have similar regulatory functions or may influence the development of cellular autophagy through the NF-κB pathway.

Whether cardiomyocyte autophagy plays a protective or detrimental role in the myocardium depends on the level of autophagy. Intramyocardial injection of diphtheria toxin in transgenic mice expressing diphtheria toxin receptors in the heart was observed to degenerate cardiomyocytes within 1 weeks after injection, and almost mice developed heart failure and died within 2 weeks, with the heart showing autophagic cell death characteristics, upregulation of lysosomal marker LAMP expression, and accumulation of autophagosomes. Autophagy levels are significantly elevated in heart failure, suggesting that excessive autophagy can lead to autophagic cardiomyocyte death. An increasing number of studies have shown that in heart failure due to dilated cardiomyopathy, valvular heart disease, hypertensive heart disease, and coronary heart disease, cardiomyocyte autophagy is significant,

whereas this feature is absent in normal hearts.

This shows that cardiomyocyte autophagy plays an important role in maintaining the stability of the internal environment and cardiomyocyte size, cardiac structure and function. Autophagy has cardioprotective effects by removing protein aggregates and damaged organelles, protecting the heart from starvation, reducing excessive adrenergic stimulation, and attenuating damage caused by local ischemia. However, during post-ischemic reperfusion or during heart failure, Beclin1 protein expression increases excessively and excessive autophagy leads to autophagic death of cardiomyocytes, exacerbating ischemia-reperfusion injury or promoting the progression of heart failure.

Recently, it has been shown that upregulation of Bnip3 expression correlates with autophagy induction. Bnip3, a member of the bcl-2 family, is susceptible to hypoxia induction and can promote the formation of autophagosomes in nutrient-deficient states. Its increased levels can be observed in animal models of chronic heart failure. During the development of heart failure, oxidative stress leads to mitochondrial permeability conversion and mitochondrial damage. Meanwhile, Bnip3 overexpression leads to increased mitochondrial damage, which enhances autophagy. And in its knockout mice, it prevents apoptosis in cardiomyocytes due to ischemia and overload. Therefore, it can be concluded that Bnip3 has a role in promoting cardiomyocyte survival, reducing ventricular remodeling and enhancing myocardial function.

In conclusion, the study of the relationship between cardiomyocyte autophagy and heart failure has become a new hotspot. The understanding of cellular autophagy and autophagic cell death is still in its infancy, and further research is needed on issues such as whether cardiomyocyte autophagy is a marker of heart failure. Therefore, to strengthen the study of cardiomyocyte autophagy, to explore the mechanism of the occurrence and development of cardiomyocyte autophagy and its regulatory factors and pathways, and to grasp the interrelationship between cardiomyocyte autophagy, apoptosis and cell necrosis, may provide new ideas for the clinical prevention and treatment of heart failure.

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