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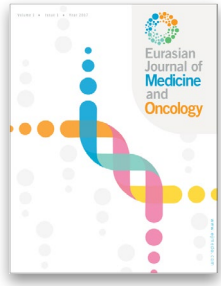

Review

The Role of Autophagy in Myocardial Ischemia and Reperfusion

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Abstract

Autophagy is a process in which lysosome-mediated intracellular damage or aging organelles and proteins are degraded to produce amino acids, fatty acids, ATP, etc., and then reused by cells. Under normal physiological conditions, cardiomyocytes maintain low levels of autophagy. However, autophagy is activated during myocardial ischemia-reperfusion (MI/R), and autophagosomes increase significantly, indicating that autophagy plays an important role in myocardial ischemia-reperfusion injury (MI/RI). Studies have shown that autophagy has protective and detrimental effects on MI/RI and is regulated by a variety of factors. This article reviews the relationship between autophagy and MI/RI.

Keywords: Autophagy, cardiomyocytes, hypoxia-reoxygenation injury, myocardial ischemia-reperfusion injury

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The incidence of acute myocardial ischemia is increasing year by year, which seriously endangers people's health. Effective and rapid recovery of blood flow reperfusion in ischemic myocardium can reduce myocardial infarct size, rescue dying heart muscle, and improve cardiac remodeling. In recent years, with the gradual maturity and popularization of coronary intervention, arterial bypass, etc., ischemic myocardium can restore blood supply in the shortest possible time. However, some patients have MI/RI, and severe patients develop heart failure, heart remodeling, and even death. Therefore, MI/RI is an obstacle to ischemic myocardial reperfusion therapy, limiting the optimal clinical outcome. Cardiomyocytes in MI/RI can undergo physiological and pathological changes such as autophagy, apoptosis and necrosis, which eventually lead to irreversible cell death and affect the development and outcome of the disease.[1] Autophagy is an important mechanism of cell necrosis in addition to death from apoptosis and necrosis.[2] Studies have shown that autophagy plays a double or even opposite role in MI/RI,[3] which depends mainly on different stimuli.[4] Autophagy in the basal state can eliminate damaged organelles in cells, which is of great significance for maintaining cell homeostasis.[5] Moderate levels of enhanced autophagy, such as transient hypoxia and low levels of oxidative stress,[6, 7] can promote cell survival. But excessively activated autophagy can cause cell death.[8, 9] Therefore, autophagy is considered a therapeutic target for ischemic heart disease, but the specific mechanism is still clear.[10, 11] In recent years, the role of autophagy in MI/RI has been paid more and more attention. This paper will review the role of autophagy in MI/RI.

Overview of Autophagy

The Concept of Autophagy

In 1962, Ashford and Porter first discovered autophagy when observing hepatocytes using an electron microscope. Autophagy is a stress regulation and defense mechanism unique to eukaryotic cells. It is an adaptive response to changes in stress, metabolism, and environment. It is the degradation of lysosomes or the removal of abnormal components such as organelles, proteins, carbohydrates, lipids, etc.[12-14] Reuse of the above substances not only provides raw materials for cell repair and regeneration, but also maintains the homeostasis of the cells, which is a normal physiological process and defense system prevalent in

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cells. Under normal physiological conditions, autophagy is at a basal level. When cells encounter exogenous factors such as nutrient deficiencies, ischemia, hypoxia, infection, etc., they can activate autophagy. Cells use autophagy to degrade intracellular substances, such as organelles and proteins, to provide raw materials and energy for cell reconstruction, repair and even regeneration, which maintains the normal structure and function of the cells.[15] However, insufficient autophagy or excessive autophagy can lead to disease in the body.[16]

Classification of Autophagy

At present, autophagy is divided into three categories: macroautophagy, microautophagy, and chaperone-mediated autophagy. Macroautophagy is generally autophagy and also the most important form of autophagy in cells.[17] Macroautophagy refers to the process in which autophagosomes fuse with lysosomes to form autophagic lysosomes, while degrading intracellular substances encapsulated in autophagy bodies. Microautophagy refers to the process in which lysosomes directly encapsulate, digest and degrade cytoplasmic components. Chaperone-mediated autophagy refers to the process in which some molecular chaperones such as Hsp70 can help unfolded proteins to be transported to the lysosomes for digestion and degradation. The autophagy discussed herein refers to the form of macroautophagy.

The Process of Autophagy

The typical process of autophagy is divided into four stages:[18] (1) initiation induction: formation of separation membrane; (2) extension: formation of autophagosomes; (3) mature fusion: autophagosomes and Lysosomal fusion to form autophagosomes; (4) degradation: degradation and reuse of contents.[19, 20] The development of autophagy requires regulation of a number of evolutionarily conserved autophagy-related gene (Atg).[21, 22] After autophagy initiation induces signal transfer to cells, Atg12 is activated by Atg7 and covalently binds to Atg5 via Atg10, thereby forming an Atg5-Atg12 complex, an autophagy precursor (phagophore), which has a flat shape like that of a two-layer lipid. The "bowl" formed by the double layer of the membrane can be observed under electron microscope. The autophagy precursor further binds Atg16 in a non-covalent form to form the Atg5-Atg12-Atg16 complex to recruit LC3-PE to form a separation membrane.[23] The autophagy precursor gradually expands and encapsulates the intracellular material, eventually forming a closed circular autophagosome. It has two distinct features: one is a two-layer membrane structure, and the other is an intracellular component, such as organelle fragments, proteins, etc. LC3-PE formation is also regulated by Atg protein. First, Atg4 cleaves pro-LC3 to form cytoplasmic soluble LC3-I,[24] while Atg3 and Atg7 cause LC3-I to covalently bind PE (phosphatidylethanolamine) to form LC3-PE complex (LC3-II).[25] The Atg5-Atg12-Atg16 complex binds to LC3-II and is then isolated from mature autophagosomes. LC3-II acts as a marker molecule for autophagosomes on its membrane.[25, 26] Autophagosomes and lysosome fusion further produce autolysosomes, and LC3-II is degraded. Substances in autophagosomes are also degraded into fatty acids, amino acids, ATP, etc.[27, 28] These substances are reused by cells, and the residue remains in the cytosol or excretes extracellularly. The autophagosome and lysosomal fusion further produce autolysosome, and LC3-II is degraded. The substance in autophagosomes is also degraded into fatty acid, amino acid, and ATP. These substances are used again by the cells, and the residue remains in the cytosol or excretes extracellularly.

Autophagy of Myocardial Ischemia Autophagy

Mechanism of Autophagy

Cardiomyocyte autophagy is increased during the ischemia. Mainly through the following ways: (1) activation of AMPK signaling pathway: in ischemia, the lack of energy supply in cardiomyocytes increases oxygen consumption, while ATP consumption decreases and AMP level increases, and then ATP/AMP ratio decreases, activating AMPK signaling pathway. At the same time, ULK1 (Atg1 homolog) is modified to induce autophagy.[29, 30] In addition, AMPK can directly phosphorylate and activate ULK1, which initiates autophagy.[31] (2) ROS increase: When cardiomyocytes are in ischemia and hypoxia, intracellular ROS content is increased. ROS can increase autophagy level through a series of pathways, mainly through Beclin1 protein. (3) Up-regulation of HIF-1α: In ischemia and hypoxia, Bnip3 up-regulates HIF-1α expression, and cardiomyocyte autophagy is activated, but the mechanism is still unclear.

The Role of Autophagy

Favorable Effects

Some basic experiments have proved that ischemia promotes autophagy of cardiomyocytes and plays a favorable role. As early as 2005, Yan et al. used small pigs to make chronic myocardial ischemia model, and found that chronic ischemia increased autophagy and inhibited apoptosis of cardiomyocytes, indicating that autophagy can alleviate chronic myocardial ischemic injury.[32] Liang et al found that 3,3'Diindolylmethane activates autophagy in H9c2 cells during hypoxia, attenuating hypoxia-induced inflammation and apoptosis, and attenuating hypoxia-induced damage.[33] Zhang et al. found that down-regulation of MicroRNA-122 can promote autophagy in H9c2 cells and attenuate hypoxia-induced

apoptosis.[34] In the MI model of C57J/BL6 mice and the OGD (Oxygen-Glucose Deprivation) model of H9c2 cells, Chiang et al found that aliskiren improves myocardial damage, reduces apoptosis and necrosis, and enhances cell survival rate by increasing the formation of autophagosomes.[35] Du et al.[36] found that shock wave therapy can regulate AMPK/mTOR pathway to promote cardiac autophagy, protect cell function and increase survival rate in H9c2 myocardial cell hypoxia. Wu et al. found that DRAM1 (Damage-regulated autophagy modulator 1) overexpression promotes autophagosome formation, autolysosome degradation and recovery of autophagic flow in myocardial infarction (MI) model of Sprague-Dawley (SD) rats induced by ligation of left anterior descending coronary artery (LAD) and OGD model of H9c2 cardiomyocytes, indicating that autophagy has anti-ischemic damage.[37] SUNG et al. found that Lcn2 (lipocalin-2) can inhibit cardiomyocyte autophagy in myocardial ischemia during ligation of LAD-induced MI model of Lcn2-KO mice, C57BL/6 mice and hypoxia model of H9c2 cells, which increased ischemia-induced cell death and cardiac dysfunction.[38] Zhang et al. found that overexpression of BAG3 in the hypoxia model of H9c2 cells activates autophagy via the NF-κB pathway, attenuating apoptosis and promoting proliferation.[39] Gu et al. found that pre-treatment of sanggenon C can promote autophagy and attenuate hypoxia-induced inflammatory response and ROS production in the hypoxia model of H9c2 cells, which indicates that autophagy enhances cardiomyocytes against hypoxia injury.[40] Wu et al. found that metformin protected cardiomyocytes against oxygen-glucose deprivation injury by promoting autophagic flux through AMPK pathway.[41] Based on the above basic studies of different animal models and cell models, it is proved that autophagy is beneficial in the period of myocardial ischemia. Promoting autophagy can reduce the injury of myocardial cells induced by ischemia and hypoxia, while inhibiting autophagy further aggravates the injury.

Harmful Effects

Other basic experimental studies have shown that the effect of autophagy during myocardial ischemia is harmful. Jia et al. found that berberine can reduce apoptosis and increase cell survival rate by inhibiting hypoxia-induced autophagy of H9c2 cells.[42] Wang et al. found that lactone component from ligusticum chuanxiong can significantly improve the survival rate of rat cardiomyocytes by inhibiting autophagy in the iso-induced myocardial ischemia model of SD rats and the OGD model of H9c2 cells, which enables myocardial ischemic injury recovered.[43] Liu et al. found that MicroRNA-223 protected SD rat cardiomyocytes and H9c2 cells from hypoxia-induced excessive autophagy by targeting PARP-1 and through the Akt/mTOR pathway, thereby reducing apoptosis, showing that reduced autophagy could protect cells.[44] Wang et al. found that shuangshen ningxin capsule can protect coronary artery and increase the stability of plaque by inhibiting myocardial autophagy in the coronary artery balloon injury model of miniature swines and OGD model of H9c2 cells.[45] The above experimental studies reveal that autophagy is harmful during myocardial ischemia, while inhibiting autophagy plays a role in protecting cardiomyocytes.

Autophagy of Myocardial Ischemia and Reperfusion

Mechanism of Autophagy

In the process of MI/R, the autophagy of cardiomyocytes in the early stage of ischemia increased and was further aggravated in the reperfusion period, but the induction pathway was different from the ischemia period. There are mainly the following ways: (1) Activation of Beclin1: The state of myocardial ischemia and hypoxia is corrected during reperfusion, so the autophagy induced by activation of AMPK is inhibited during the ischemia period. Autophagy was mainly induced by up-regulation of Beclin1 during reperfusion.[46] Beclin1 is a key protein regulator for autophagosome formation and promoting autophagy process, and its up-regulation directly participates in autophagy activity during reperfusion period.[47] (2) Large amount of ROS production: ROS accumulates in the mitochondria during MI/R, damaging the main organelles in the cells and causing lipid peroxidation, and promoting autophagy. At the same time, a large amount of ROS production promotes oxidation of mitochondrial proteins and abnormality of mitochondrial function, further enhancing oxidative stress of mitochondria itself. In addition, ROS can also promote the formation of autophagosomes by direct oxidative stress. (3) Mitochondrial Ca^{2+} overload: The Na^{+}-Ca^{2+} channel on the cell membrane is open during myocardial ischemia, which increases the intracellular Ca^{2+} concentration. The membrane potential is also restored due to the rapid recovery of potential energy by mitochondria during reperfusion. At this time, Ca^{2+} can enter the mitochondria along the concentration gradient, causing Ca^{2+} overload, which aggravates MI/RI. Intracellular Ca^{2+} can induce autophagy via the mTOR pathway.[48] Increased mitochondrial Ca^{2+} concentration during reperfusion will aggravate cell damage by enhancing autophagy activity.[20] (4) MPTP opening: MPTP, acting as a permeability transport channel on the mitochondrial membrane, spans the inner and outer membranes of the mitochondria. Under physiological conditions, MPTP is turned off, and MPTP opens when cells are subjected to external stress, thus damaging cells. During reperfusion, MPTP activates autophagy due to opening, inhibiting MPTP from blocking its opening and reducing autophagy activity.[49]

The Role of Autophagy

Favorable Effects

Some basic studies have confirmed that autophagy plays a protective role in MI/RI. Qian et al. found that blocking

Hsp20 phosphorylation inhibits autophagy, increases cardiac cell death, and aggravates MI/RI in mice, which suggests the beneficial role of autophagy in MI/R.[50] Hu et al. found that congenital heart disease patients living at high altitude had better anti-MI/RI ability during cardiac surgery than those living at low altitude, which may be due to chronic hypoxia up-regulated cardiomyocyte autophagy.[51] In the MI/R model of rabbits, Xie et al. reported that the cardioprotection of histone deacetylase inhibitor SAHA in reducing myocardial infarction area was at least partially achieved by inducing autophagy flow.[52] Li et al. revealed that autophagy may protect cardiomyocytes from MI/RI by clearing CLP36.[53] Wu et al. reported that inhibition of MicroRNA-101 alleviated H/R-induced apoptosis by inducing autophagy in H9c2 cells.[54] Mo et al. found that pramipexole decreased MI/RI by up-regulating autophagy via AMPK pathway in the MI/R model of C57BL/6 mice and H/R model of H9c2 cells.[55] Duan et al. found that spermine-induced autophagy reduced H/R injury in SD neonatal rat cardiomyocytes, and rapamycin could enhance this effect.[56] Song et al. proved that CREG (Human cellular repressor of E1A-stimulated genes) was down-regulated in MI/RI, and recombinant protein CREG activated autophagy to reduce MI/RI, which may be a new therapeutic target for MI/RI patients.[57] Hao et al. found that myocardial ischemic postconditioning promoted autophagy by activating nNOS/AMPK/mTOR pathway to resist MI/RI in the MI/R model of C57BL/6 mice and H/R model of H9c2 cells.[58] Zhang et al. found that hongjingtian injection alleviated H/R injury of H9c2 cells by promoting autophagy and inhibiting apoptosis.[59] Liu et al. found that exosomes derived from mesenchymal stem cells induced myocardial autophagy through AMPK and Akt pathways, reducing MI/RI.[60] Zhang et al. found that coenzyme Q10 pretreatment can enhance autophagy and anti-oxidative stress of cardiomyocytes in MI/RI rats, which reduces apoptosis and death and improves cardiac function.[61] Huang et al. demonstrated that inhibition of mTOR/NF-κB pathway and enhancement of autophagy can enhance the protective effect of HTEA (high thoracic epidural anesthesia) on MI/RI in rats and reduce apoptosis.[62] Fu et al. found that Visnagin coated with NIPAAm-MMA nanoparticles improved MI/RI by promoting autophagy and inhibiting apoptosis in rats.[63] Meng et al. found that silencing NLPR3 inflammasome promoted autophagy and proliferation of cardiomyocytes, inhibits inflammatory response and apoptosis, and alleviates MI/RI in rats. This suggests that NLPR3 may be a new therapeutic target for MI/RI.[64] Meng et al. found that heme oxygenase-1 inhibited H9c2 cells apoptosis through the Sirt3 pathway, promoted autophagy and cell proliferation, and improved H/R injury.[65] Xiao et al. found that thymoquinone activated autophagy, exerted antioxidant and anti-apoptosis effects, and reduced MI/RI in rats.[66] The above experimental studies have confirmed that autophagy plays a favorable role in the process of MI/R. Promoting autophagy can reduce MI/RI, while inhibiting autophagy aggravates MIRI.

Harmful Effects

However, some experimental studies have shown that autophagy plays a harmful role in MI/RI. Zhang et al. showed that Ginsenoside Rg1 inhibited H/R-induced formation of autophagosomes and apoptosis in H9c2 cells, which was beneficial to cell survival.[67] Cao et al. showed that alpha-lipoic acid pretreatment could inhibit H/R-induced autophagy of H9c2 cells, improve cell survival rate and reduce cell death.[68] Cheng et al. showed that H/R-induced autophagy in H9c2 cells lead to cell death, while hypothermia significantly reduced H/R-induced autophagy and decreased death.[69] Jian et al. found that *Bauhinia championii* flavone played a cardiac protective role by activating PI3K/Akt pathway to inhibit apoptosis and excessive autophagy during MI/R process.[70] Huang et al. showed that berberine protected cardiomyocytes by inhibiting autophagy activation during MI/R process.[71] Xiao et al. found that hydrogen sulfide alleviated H/R injury of cardiomyocytes by activating mTOR pathway to inhibit autophagy.[72] Wang et al. showed that N-n-butyl haloperidol iodide alleviated H/R injury of cardiomyocytes by inhibiting autophagy.[73] Wang et al. showed that U0126 prevented H/R-induced apoptosis and autophagy of cardiomyocytes through MEK/ERK/EGR-1 pathway in MI/R model of C57BL/6 mouse and H/R model of cardiomyocytes of C57BL/6 newborn mice, thereby protecting myocardium from H/R injury. This may be a potential treatment for reducing MI/RI.[74] Xuan et al. found that MHBFC activated PI3K/Akt pathway to inhibit apoptosis and autophagy, and improved MI/RI of rat.[75] The results of Fan et al. in MI/R model of SD rat and H/R model of SD neonatal rat cardiomyocytes showed that danshensu reduced MI/RI by activating mTOR pathway to inhibit excessive autophagy and apoptosis.[76] Wang et al. found that N-acetylcysteine exerted a protective effect on MI/RI in diabetic SD rats by inhibiting excessive autophagy.[77] Wang et al. found that coptisine alleviated H/R injury in H9c2 cells by inhibiting autophagy.[78] Shi et al found that xuefuzhuyu decoction protected H9c2 cells from H/R injury by inhibiting autophagy.[79] Li et al. showed that thioredoxin-2 protected H9c2 cells from oxygen-glucose deprivation/reperfusion injury by inhibiting autophagy and apoptosis.[80] Huang et al found that MicroRNA-21 inhibited excessive autophagy in H9c2 cells by activating the Akt/mTOR pathway and reduced H/R injury.[81] Zheng et al. found that berbamine inhibited MI/R-induced autophagy and restored the process

of impaired autophagy by activating the PI3K/Akt pathway.[82] Qiu et al. found that MicroRNA-204 inhibits autophagy and apoptosis by regulating Sirt1, protecting H9c2 cells from H/R injury.[83] Deng et al found that bifunctional supramolecular hydrogel can significantly inhibit excessive autophagy in the M/R model of C57BL/6 mice and H/R model of SD neonatal rat cardiomyocytes, thereby inhibiting cardiomyocytes apoptosis, attenuating MI/RI, which may be a promising biomaterial for the treatment of MI/RI.[84] Dang et al. found that Soluble receptor for advance glycation end-products (sRAGE) inhibited I/R-induced myocardial autophagy through the STAT3 pathway in MI/R model of C57BL/6 mice and H/R model of SD neonatal rat cardiomyocytes, playing a protective role of myocardium.[85] Hu et al. found that FGF21 protected MI/RI by reducing miR-145-mediated autophagy in the MI/R model of SD rats and H/R model of H9c2 cells.[86] Liu et al found that inhibition of autophagy can enhance the protective effect of ischemia preconditioning on MI/RI in diabetic rats.[87] Li et al. confirmed that hesperidin reduced MI/RI of SD rats by activating PI3K/Akt/mTOR pathway to inhibit excessive autophagy.[88] Chen et al found that melatonin inhibited autophagy by inhibiting AMPK/mTOR signaling pathway, protecting cardiac microvascular endothelial cells (CMECs) and reducing MI/RI in rats.[89] Zheng et al. showed that inhibition of miRNA-30e enhanced autophagy by activating Notch1/Hes1/Akt signaling pathway, reduced H9c2 cell apoptosis and oxidative stress damage, and reduced H/R injury.[90] Li et al. study have shown that propofol postconditioning induced autophagy through the SAPK/JNK pathway, promoting cell survival and protecting H9c2 cells from H/R injury.[91] Yu et al. found that down-regulation of lncRNA AK139328 attenuated MI/RI in diabetic mice by modulating miR-204-3p and inhibiting autophagy[92] Lu et al. showed that sevoflurane attenuated H/R-induced apoptosis of human induced pluripotent stem cell-derived cardiomyocytes by inhibiting PI3KC3-mediated autophagy.[93] Tong et al. found that exposure to particulate matter (PM2.5) aggravated MI/RI of rats by up-regulating farnesoid-X receptor-induced autophagy.[94] Guo et al. showed that RP105 inhibited autophagy by activating TLR4/NF-κB pathway, and reduced apoptosis of cardiomyocytes in MI/RI rats, thus protecting the heart, which may be an innovative therapeutic target for reducing MIRI.[95] Zhou et al. found that circRNA ACR inhibited autophagy and reduced MI/RI in C57BL/6 mice by regulating Pink1/FAM65B pathway.[96] Ye et al. showed that vascular smooth muscle cells activated PI3K/Akt pathway by secreting basic fibroblast growth factor to inhibit autophagy, reduce apoptosis and MI/RI.[97] We found that trimetazidine (TMZ) can inhibit MI/RI-induced excessive autophagy by activating AKT/mTOR pathway, improve cell viability and reduce cell apoptosis in the MI/R model of SD rat and H/R model of H9c2 cell, which suggests that TMZ can inhibit autophagy and resist MI/RI.[98] The above experimental studies confirm that activation of autophagy in MI/R is harmful from different animal models and cell models, while inhibition of autophagy was beneficial to reduce MI/RI.

Summary and Prospect

As one of the body's normal physiological responses and adaptive regulatory responses under stress, autophagy of cardiomyocytes is regulated by a variety of pathways in the process of ischemia and reperfusion. Moreover, autophagy plays a dual role and has a double-edged sword effect. Through the above literature, we can clearly understand its beneficial and harmful effects. On the one hand, moderately activated autophagy in MI/R provides essential nutrients for reuse by removing intracellular harmful substances. Therefore, autophagy plays an important role in myocardial protection.[99] On the other hand, over-activated autophagy can degrade normal organelles and proteins, disrupt normal physiological processes of cells and lead to irreversible death. However, complete inhibition of autophagy is also harmful.[100] In short, the protective or destructive effects of autophagy induced by myocardial ischemia and reperfusion are environmentally dependent. Therefore, autophagy manipulation for treatment should be confirmed according to the MI/R time stage.[101] Zeng et al. found that crocin can play an anti-MI/RI role by regulating autophagy, and can induce autophagy by activating AMPK pathway during ischemia. However, it inhibits autophagy by activating AKT pathway in reperfusion period.[102] The study showed that there existed contradictory mechanism in the role of autophagy in different stages. Crocin in different periods through different signaling pathways controlled autophagy and reduced MI/RI. At present, although researches of autophagy mechanism in myocardial ischemia and reperfusion have achieved great progress, monitoring autophagy level in different stages such as excessive or insufficient, discovering autophagy control targets, and finding suitable selective autophagy regulatory drugs will need to be further explored. These will also become new targets for prevention and treatment of MI/RI, and provide more adequate theoretical guidance for clinical prevention and treatment.

Disclosures

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