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REVIEW ARTICLE

Potential relationship between autophagy and ferroptosis in myocardial ischemia/reperfusion injury

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Abstract Autophagy is an evolutionarily conserved process involved in the degradation of long-lived proteins and excessive or dysfunctional organelles. As a pivotal cellular response, autophagy has been extensively studied and is known to be involved in various diseases. Ferroptosis is a recently discovered form of regulated cell death characterized by iron overload, leading to the accumulation of lethal levels of lipid hydroperoxides. Recently, an increasing number of studies have revealed a link between autophagy and ferroptosis. Myocardial ischemia/reperfusion injury (MIRI) is an urgent dilemma after myocardial infarction recanalization, which is regulated by several cell death pathways, including autophagy and ferroptosis. However, the potential relationship between autophagy and ferroptosis in MIRI remains unexplored. In this study, we briefly review the mechanisms of autophagy and ferroptosis, including their roles in MIRI. Moreover, we provide an overview of the potential crosstalk in MIRI. Clarifying the relationship between different cell death pathways may provide new ideas for the treatment of MIRI in the future.

Introduction

Ischemic heart disease (IHD) remains a major threat to public health with its overall burden increasing globally.[1] Many deaths occur during an acute ischemic event, such as an ST-elevation myocardial infarction. Proper and timely restoration of blood flow through anti-thrombolytic drugs or mechanical interventions is the primary treatment.[2] However, these treatments are restricted by narrow time frames and side effects. Moreover, reperfusion may induce a secondary injury. Restoring blood circulation to the myocardium may still incur further damage, such as

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myocardial cell necrosis and tissue structure disorder, namely myocardial ischemia/reperfusion injury (MIRI). Hence, finding ways to limit cardiomyocyte death during MIRI has been the focus of extensive studies over the past 30 years.[3] Several cell death pathways, including apoptosis, necrosis, and autophagy, have been identified to be involved in MIRI pathophysiology. Among these, necrosis has been generally regarded as a passive and uncontrolled form of cell death; however, certain types of regulated necrosis have recently been found, such as necroptosis, ferroptosis, parthanatos, pyroptosis, and CypD-mediated necrosis. Therefore, targeting these specific types of regulatory necrosis pharmacologically or genetically has provided new ideas for the treatment of MIRI.[4]

Autophagy is a conserved cellular degradation process in which damaged cellular organelles are recycled, cellular nutrients are provided, and basal homeostasis is maintained.[5] Autophagy is a common phenomenon *in vivo* that exists under both physiological and pathological conditions. It is mainly executed by multiple autophagy-related genes (ATGs) and is regulated by a complex signaling network. Recent investigations have suggested that autophagy plays a dual role, depending on the degree of activation in MIRI.[6]

Ferroptosis is an iron-dependent form of regulated cell death that is characterized by the accumulation of lethal levels of lipid hydroperoxides, resulting in oxidative damage to cell membranes, and is recognized to differ from apoptosis, necroptosis, and autophagy in several aspects.[7] Different from the above types of cell death, ferroptosis does not lead to changes in cell morphology, mainly manifested as mitochondrial shrinking and mitochondrial membrane density increase.[8] Table 1 lists the characteristics of autophagy and ferroptosis. Emerging evidence shows that ferroptosis is closely associated with the occurrence and progression of various diseases in organs including the brain,[9] liver,[10] kidney,[11] and heart.[12]

While autophagy and ferroptosis are mechanistically and morphologically distinct cell death pathways, several recent studies have reported significant crosstalk between them.[13,14] This identification not only provides a deeper understanding of cell death but also provides new insights on diseases regulated by autophagy and ferroptosis. In this review, we introduce autophagy and ferroptosis in MIRI, including the pathways that mediate their interactions. Furthermore, we discuss their potential relationships in MIRI.

Autophagy and myocardial ischemia/reperfusion (I/R)

The introduction of autophagy

Autophagy is a dynamic *in vivo* process that exists in both physiological and pathological conditions, relying on specific membrane structures, such as phagophores, autophagosomes, and autolysosomes.[15] The formation and maturation of specific membrane structures are controlled by ATG and other proteins. Different ATG protein synthesis systems are involved in the autophagy process, including the ATG1 (ULK1) protein kinase complex, type III phosphatidylinositol 3-kinase (PI3KC3) complex, ubiquitin-like conjugated protein system (ATG8 and ATG12), and ATG9 circulatory system. Among them, the ATG1 (ULK1) protein kinase complex regulates the level of autophagy according to changes in environmental stimulus. PI3KC3 complex recruits important downstream ATG proteins and vesicle nucleation function. The ubiquitin-like conjugated protein system is involved in autophagosome membrane elongation. The ATG9 cycle system provides a membrane lipid source for autophagosome membrane extension.[16,17] Autophagy is divided into three main types: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). Macroautophagy (hereafter referred to as autophagy) can be further divided into nonselective and selective autophagy (e.g., mitophagy, pexophagy, lipophagy, and ferritinophagy).[18]

Autophagy in myocardial I/R

Physiological autophagy is believed to be the mechanism of cells for self-protection. This protects cells from damage and maintains cell homeostasis while excessive autophagy can lead to cell damage and autophagic death.[19] Since cardiomyocytes have a very limited ability to regenerate, autophagy seems to be critical for cardiomyocytes. Studies have shown that autophagy is involved in both stages of myocardial ischemia and reperfusion, and appears to have different mechanisms and manifestations.[20,21]

Several studies have suggested that autophagy usually plays a protective role in myocardial ischemia and in cell damage through three mechanisms as follows: (a) Autophagy may provide an energy source through the autophagosome pathway, increasing ATP production.[22] (b) Autophagy activation may be involved in the removal of damaged proteins that are harmful to cells.[23] (c) Autophagy of cardiomyocytes plays an important role in reducing reactive oxygen species (ROS) and removing damaged organelles (i.e., mitochondria) which may release pro-apoptotic factors.[24]

During the reperfusion phase, however, the energy crisis is partially resolved because cardiomyocytes have access to oxygen and nutrients, and autophagy takes on different forms. ROS accumulation is the main promoter of autophagy during reperfusion, leading to mitochondrial damage, opening of the mitochondrial permeability transition pore (MPTP), and fragmentation of mitochondria.[25] Studies have shown that ROS can oxidize and inhibit the cysteine protease activity of Atg4, leading to LC3 lipidation and autophagy.[26] Additionally, recent studies have shown that ROS plays an important role in mediating Beclin 1 upregulation in mice hearts during ischemia/reperfusion (I/R).[27] Studies show that an increased autophagic flux during reperfusion may be beneficial or harmful. This dual role of autophagy may be attributed to the dual role of Beclin 1 in ischemia-reperfusion injury (IRI).[21] Activation of Beclin 1 during early ischemia is necessary to initiate autophagy. However, continued Beclin 1 activity during reperfusion leads to excessive catabolic activity and cell death.[28] Since Beclin 1 can be inhibited by the anti-apoptotic protein, B-cell lymphoma (Bcl)-2, this interaction may play a role in regulating the ratio of cell survival to cell death. Similarly, Bcl-2/adenovirus E1B-19KD interacting protein 3 (BNIP3) is involved in regulating MPTP opening and activating

Table 1 Characteristics of autophagy and ferroptosis.

	Autophagy	Ferroptosis
Presented time	1963	2012
Definition	Autophagy is a highly conserved self-digestion process.	Ferroptosis is an iron-dependent form of regulated cell death.
Morphological characteristics	Autophagosomes, a double membrane vesicle containing multiple cytoplasmic contents. The autophagosomes fuse with lysosomes to form autolysosomes.	Atrophy of mitochondria with increased membrane densities, reduced even disappeared mitochondria crista and ruptured outer membrane, normal nucleus
Mechanisms	Initiation and nucleation, maturation of autophagosomes and fusion with the lysosome and degradation. Controlled by Atgs and several complicated signaling pathways.	Iron overload, GSH depletion and GPX 4 inactivation, impaired system Xc-, lipid peroxidation.
Key regulators	AMPK,mTOR,Beclin1, PI3K,ULK1,P62,P53,STAT3 and other Atgs	Positive:ACSL4,TfR1, LPCAT3, ALOX15, NCOA4, Beclin1, GLS2, VDAC2/3, RAB7A, P53 and HSP90 Negative:GPX4,SLC7A11, Nrf2, HSPB1, HSPA5, P53, NFS1 and OTUB1
Inducers	Simvastatin, Rapamycin, Metformin, Resveratrol, sodium,Everolimus,Brefeldin A	Erastin, Sorafenib, Glutamate, Artesunate, RSL3, FIN56, FINO2, iFSP1, Fluvastatin, Hemoglobin
Inhibitors	3-MA,LY294002,SBI-0206965,NSC185058, Chloroquine, Compound C, Nocodazole, Bafilomycin A1, Pepstatin A, Spautin-1,Hydroxychloroquine	Deferoxamine, Vitamin E, Ferrostatin-1, Liproxstatin-1, CoQ10, Baicalein, GSH, Rosiglitazone, Selenium

AMPK, Adenosine 5′-monophosphate (AMP)-activated protein kinase; PI3K, Phosphatidylinositol 3-kinase; ULK1, unc-51-like kinase 1; STAT3, Signal transducer and activator of transcription 3; Atgs, Autophagy-related genes; RSL3, Ras-selective lethal small molecule 3; iFSP1, inhibitor of FSP1; GSH, Glutathione; ACSL4, Acyl-CoA synthetase long chain family member 4; TfR1, Transferrin receptor 1; LPCAT3, Lysophosphatidylcholine acyltransferase 3; ALOX15, Arachidonate-15-Lipoxygenase; NCOA4, Nuclear receptor coactivator 4; GLS2, Glutaminase 2; VDAC, voltage-dependent anion channels; HSP90, Heat shock protein 90; GPX4, Glutathione peroxidase 4;;SLC7A11, solute carrier family 7 member 11; Nrf2, nuclearfactorerythroid-2-relatedfactor2; HSPA5, Heat shock 70 kDa protein 5; NFS1, Cysteine desulfurase; OTUB1, ovarian tumor family member deubiquitinase; 3-MA, 3-Methyladenine.

autophagy in I/R cells. In addition, increased intracellular calcium through the depletion of sarcoplasmic reticulum stores increases autophagy activity in cardiomyocytes.[29] Previous studies have shown that under myocardial I/R conditions, an increase in Beclin 1 expression increases the formation of autophagosomes, and autophagy seems to increase at this stage. However, a novel explanation has emerged, namely that autophagy flux is partially impaired during reperfusion rather than further activation.[30] In this light, the researchers concluded that autophagosome clearance in cardiomyocytes significantly reduces with reperfusion, impinging on the survival of reperfusion cardiomyocytes. This suggests that increased cell death during I/R is due to defects in autophagosome clearance.[31] This indicates the importance of LAMP2 in the removal of autophagosomes. Therefore, the increase in autophagosomes may be caused by two different phenomena: autophagy up-regulation or autophagy degradation blocking.[32] Therefore, inhibition of autophagy at different stages may have different effects on I/R damage.

Accumulating evidence suggests that I/R causes an imbalance in the mitophagy process, causing further cytotoxic damage potentially leading to cell death. It is worth noting that whether the main mechanism of "autophagy death" is excessive mitophagy or large-scale accumulation of autophagosomes remains controversial.[33,34] There is an emerging consensus that cell damage causes changes consistent with autophagosome formation and autophagy initiation in cardiomyocytes, which are processes that lead to cell death. Early findings on the role of autophagy in IR-induced cardiomyocyte death have been somewhat contradictory, suggesting that autophagy can protect cells but can also guide cells toward apoptosis.[35] Both *in vitro* and *in vivo* evidence suggests that damage to *ATG* gene expression leads to reduced cell death, possibly triggering cell death in a Caspase-independent manner.[36,37] Rigorous kinetic analysis is required to determine whether autophagy death is independent of apoptotic or necrotic processes and whether it represents a step in these processes that ultimately leads to cell destruction.[38]

Since the molecular mechanism of autophagy playing dual roles in I/R is not fully understood, further study is necessary for many conditions, whether autophagy can play a protective or harmful role needs to be further studied. Studies have demonstrated the direct relationship of the severity of myocardial ischemia to autophagy in myocardial I/R. Increased autophagy activity may lead to the digestion of proteins and organelles that protect the myocardium due to the partially nonspecific characteristics of autophagy degradation. It can be seen that early I/R induces protective autophagy, while in the late I/R stage, autophagy has a damaging effect.[39]

Due to the conflicting reports and debates on the benefits and harmful functions of autophagy in myocardial I/R, many scientists have begun to focus on the double-sided role of autophagy in myocardial protection, which will help

identify new therapeutic strategies in reducing MIRI. To evaluate the pharmacological regulation of autophagy flux as an effective strategy against MIRI, a number of preclinical studies have been conducted with very interesting results obtained. Modulation of autophagy intensity has been reported as a feasible strategy in the treatment of MIRI. Many pharmacologic interventions (e.g., visnagin, alliin, resveratrol, and hydrogen-rich saline) have been found to protect the heart from IRI by enhancing autophagy flux.[40–43] Some medications (e.g., calreticulin, geniposide, berberine, and tetramethylprazine) have been found to protect the heart by inhibiting autophagy or improving impaired autophagy flux.[28,44–46] In addition, some noncoding RNAs targeting autophagy have also been shown to play important roles in MIRI.[47,48]

Therefore, further identification of specific cellular mechanisms, maintenance of appropriate autophagy flux, and control of excessive autophagy are priorities of therapeutic interest and may contribute to the development of new cardiac protection strategies for MIRI in the future.

Ferroptosis and myocardial I/R

The introduction of ferroptosis

Ferroptosis is a regulatory cell death induced by iron-dependent lipid peroxidation. Iron is an essential trace element in the human body, playing an important physiological role. However, excessive iron accumulation generates ROS through the Fenton reaction, leading to lipid peroxidation and mediating ferroptosis.[49] Glutathione peroxidase 4 (GPX4) catalyzes the oxidation of glutathione (GSH) and the removal of lipid peroxides to protect cells. GPX4 is a key regulatory factor in the ferroptosis signaling pathway. Direct or indirect inactivation of GPX4 is a classic induction mechanism of ferroptosis. RSL3, ML162, FINO2, and solanine A can directly inactivate or deplete GPX4 to induce ferroptosis.[50] The cystine/glutamate antitransporter Xc system mediates cystine uptake and glutamate release to promote GSH synthesis, while GSH acts as a co-promoter of GPX4 in assisting the removal of lipid peroxide-protecting cells. Erastin inhibits the Xc system and indirectly inactivates GPX4, resulting in the accumulation of lipid peroxides that promote ferroptosis.[51] In addition to the classical GPX4-dependent ferroptotic pathway, recent studies have uncovered some new regulatory pathways independent of GPX4, including the ferroptosis suppressor protein (FSP1)—CoQ10 pathway and guanosine triphosphate cyclohydrolase 1- tetrahydrobiopterin (GCH1-BH4) pathway.[52,53]

Ferroptosis in myocardial I/R

Gao et al[54] first found that ferroptosis plays a key role in the development of MIRI. Studies have shown that deferramine (an iron chelator and inhibitor of ferroptosis) can effectively reduce the size of myocardial infarction after I/R and improve myocardial systolic function. Tang et al[55] also confirmed the role of ferroptosis in MIRI; however, ferroptosis may occur mainly in the reperfusion phase but not in ischemia in rat hearts. Baba et al[56] further found evidence of iron overload in cardiomyocytes after I/R. The stimulation of Fe^{3+}, Erastin, and RSL3 can significantly increase the level of ROS in cardiomyocytes, induce ferroptosis in the cells while the mammalian target of rapamycin (mTOR) plays a key regulatory role. Overexpression of mTOR inhibits ROS production and reduces ferroptosis. Fang et al[57] found iron overload in the cardiomyocyte mitochondria of a mouse in a MIRI model. Ferrostatin 1, a ferroptosis inhibitor, can reduce I/R-induced myocardial remodeling and fibrosis in mice, resulting in a long-term protective effect on MIRI. At the same time, mt-Cytb and mt-Atp6 were upregulated, suggesting that the myocardial protection induced by inhibiting ferroptosis may be related to the recovery of mitochondrial function. Ma et al[58] found that overexpression of ubiquitin-specific protease 22 (USP22) could inhibit ferroptotic cardiomyocyte death for protection against IRI. Tang et al[59] found that USP7 (another deubiquitinase family member) promotes ferroptosis via activation of the p53/TfR1 pathway in rat hearts after I/R. Most recently, Stamenkovic et al[60] demonstrated that oxidized phosphatidylcholines (OxPCs) increased during MIRI, leading to decreased GPX4 activity and increased ferroptosis. Notably, cell death induced by OxPCs was suppressed by Fer-1 treatment. Recently, Chen et al[14] found that the expression of embryonic lethal abnormal vision-like protein 1 (ELAVL1) was upregulated during MIRI. After further study, the authors showed that ELAVL1 was transcriptionally activated by forkhead box C1 (FOXC1) and promoted ferroptosis in MIRI by regulating autophagy. To the best of our knowledge, this is the first study directly involving the relationship between autophagy and ferroptosis in MIRI.

Ferroptosis is also involved in MIRI with diabetes as a comorbidity. Li et al[61] investigated the effect of ferroptosis in the process of MIRI in patients with diabetes and revealed that inhibition of ferroptosis could reduce endoplasmic reticulum stress (ERS), myocardial injury, and cell injury in H9c2 cells in the rat I/R model. Additionally, Wang et al[62] found that diabetes exaggerates myocardial IRI by activating Nox2-related oxidative stress and ferroptosis.

Although the above studies have confirmed the key role of ferroptosis in MIRI, the pathways involved remain unclear and need to be further elucidated (Table 2). Recently, an increasing number of studies have reported significant crosstalk between autophagy and ferroptosis. This recognition not only favors a deeper understanding of cell death but also provides new ideas for diseases regulated by autophagy and ferroptosis. Thus, we provide an overview of the crosstalk between autophagy and ferroptosis, especially their potential relationship with MIRI.

The crosstalk between autophagy and ferroptosis in MIRI

Recent studies have shown that the occurrence of ferroptosis is dependent on autophagy, and many ferroptosis regulators have been identified as potential regulators of autophagy. Since autophagy and ferroptosis have been found to play important roles in MIRI, the molecular mechanisms of the association between autophagy and

Table 2 Ferroptosis in myocardial I/R injury.

References	Interventions	Subjects	Targets	Effects
Li et al (2020) [61]	/	Rat DM + I/R and HHR cells	ER Stress	Ferroptosis is involved in Diabetes MIR through ER Stress.
Ma et al (2020) [58]	USP22	MI/R rats	SIRT1/p53/SLC7A11 axis	USP22 protects against MIRI via the SIRT1-p53/SLC7A11-dependent Inhibition of ferroptosis-Induced cardiomyocyte Death.
Li et al (2019) [105]	/	IRI mice	TLR4/Trif/Type I interferon pathway	Ferroptotic cell death triggers initial inflammatory responses after heart transplantation.
Tang et al (2021) [59]	USP7	MI/R rats	p53/TfR1 pathway	Ubiquitin-specific protease 7 promotes ferroptosis via activation of the p53/TfR1 pathway in the rat hearts after ischemia/reperfusion
Wang et al (2020) [62]	Diabetes	Rat DM + I/R and HHR cells	AMPK, Nox2	Diabetes aggravates MIRI via activating Nox2-related programmed cell death in an AMPK-dependent manner
Tang et al (2021) [55]	Iron chelator (deferoxamine)	MI/R rats	ACSL4, GPX4, iron, and malondialdehyde	Ferroptosis occurs in phase of reperfusion but not ischemia in rat heart following ischemia or ischemia/reperfusion
Feng et al (2019) [97]	Lip-1	IRI mice	VDAC1, GPX4	Liproxstatin-1 protects the mouse myocardium against ischemia/reperfusion injury by decreasing VDAC1 levels and restoring GPX4 levels
Chen et al (2021) [14]	ELAVL1	IRI mice	Autophagy	ELAVL1 is transcriptionally activated by FOXC1 and promotes ferroptosis in myocardial ischemia/reperfusion injury by regulating autophagy
Lv et al (2021) [72]	Etomidate	MI/R rats	SOD content, GSH activity and GPX4; MDA and iron and ACSL4; Nrf2 pathway	Etomidate attenuates the ferroptosis in myocardial Ischemia/Reperfusion rat model via Nrf2 pathway
Fan et al (2021)[106]	Baicalin	MI/R rats	ACSL4-controlled ferroptosis	Baicalin prevents myocardial Ischemia/Reperfusion Injury Through inhibiting ACSL4 mediated ferroptosis
Shan et al (2021) [84]	Cyanidin-3-glucoside (C3G)	MI/R rats (OGD/R) model	USP19, Beclin1, NCOA4, and LC3II/LC3I、FTH1 and GPX4	The protective effect of Cyanidin-3-Glucoside on myocardial Ischemia-Reperfusion Injury through ferroptosis
Stamenkovic et al (2021) [60]	/	rat cells (OGD/R) model	OxPCs	Oxidized phosphatidylcholines trigger ferroptosis in cardiomyocytes 2 during ischemia/reperfusion injury

I/R, Ischemic/Reperfusion; ER, Endoplasmic reticulum; OGD/R, oxygen-glucose deprivation reoxidation.
USP22, Ubiquitin-specific protease; SIRT1,sittuin1; SLC7A11, solute carrier family 7 member 11; Type I TfR1,transferrin recepter1; GPX4, glutathione peroxidase 4; VDAC1, voltage dependent anion channel 1; SOD, superoxide dismutase; MDA, Malondialdehyde; Nrf2, Nuclear factor erythroid 2-related factor 2; OxPCs, Oxidized phosphatidylcholines; LC3, light chain 3; FTH1, ferritin heavy chain 1; FOXC1, Forkhead box protein C1.

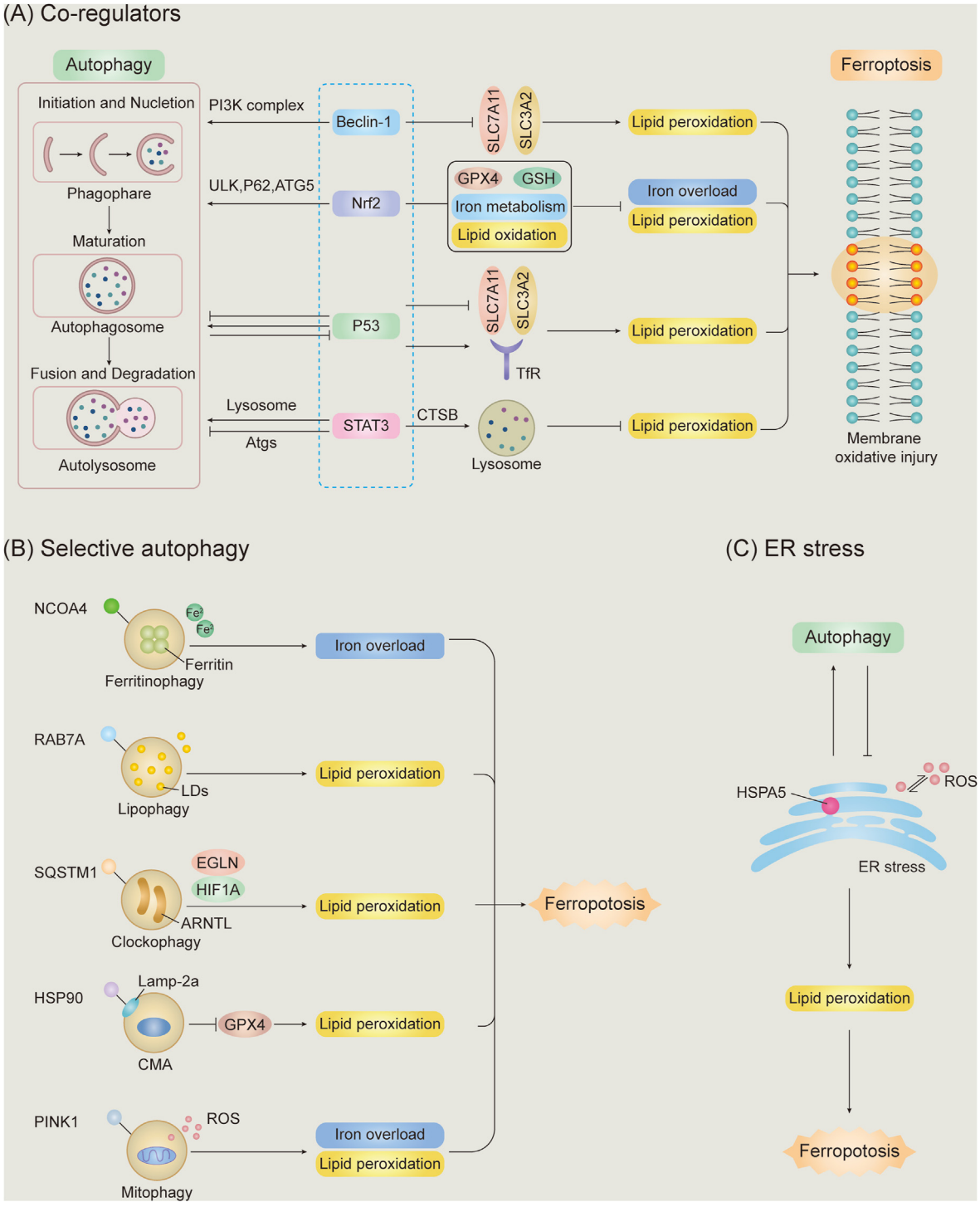

Figure 1 The possible crosstalk between autophagy and ferroptosis in MIRI. **(A)** Co-regulatory proteins (eg.,Beclin1,Nrf2,P53,-STAT3), **(B)** Selective autophagy (eg.,NCOA4-mediated ferritinophagy, RAB7A-mediated lipophagy, SQSTM1-mediated clockophagy, HSP90-mediated CMA, PINK1-mediated mitophagy) and **(C)** ER stress. NCOA4, Nuclear factor erythroid 2-related factor 2; STAT3, signal transduction and activator of transcription 3; CTSB, cathepsin B; SLC7A11,solute carrier family 7 member 11; GPX4, glutathione peroxidase 4; GSH, glutathione; TfR, transferrin recepter; NCOA4, nuclear receptor coactivator 4; RAB7A, RAS-related GTP-binding proteins 7A; LDs, lipid droplets; SQSTM1, Sequestosome 1; HSP90, heat shock protein 90; HSPA5, heat shock 70 kDa protein 5.

ferroptosis, as well as their potential relationship in MIRI, are significant (Fig. 1A—C).

Regulatory proteins shared by autophagy and ferroptosis

Recently, ferroptosis regulatory pathways and regulatory factors have been reported. To date, as many as 27 ferroptosis regulatory proteins are known, some of which play an important role in autophagy pathways, such as regulating autophagy activity or regulating autophagy substrate degradation.[7] Next, we will focus on several important regulatory proteins and their possible relationships in MIRI.

Beclin 1

Beclin 1 is a key regulator of autophagy and is involved in the regulation of mammalian autophagosome formation.[63] Beclin 1 has been widely identified as an important modulator of autophagy in MIRI.[46,64] Studies have shown that Beclin 1 can be involved in the regulation of cell ferroptosis as an inhibitor of System Xc, an important regulatory pathway for ferroptosis.[65] Beclin 1 is phosphorylated by protein kinase (AMPK) at Ser90/93/96. The Beclin 1-SLC7A11 results from the formation of SLC7A11 with System Xc-core protein, directly inhibiting the activity of System Xc, promoting ferroptosis. At the same time, Beclin 1 knockdown attenuates the inhibition of System Xc activity by ferroptosis inducers such as erastin.[66] Additionally, Chen et al demonstrated that Beclin-1 mRNA regulates autophagy to induce ferroptosis in MIRI.[14] These studies suggest that Beclin 1 may play a crucial role in the relationship between ferroptosis and autophagy in MIRI.

Nrf2

Nrf2 is a key regulator of intracellular oxidation homeostasis that participates in the control of lipid peroxidation.[67] Under physiological conditions, Nrf2 degradation is mainly mediated by Kelch-like ECH-associated protein 1 (Keap1) via the ubiquitin proteasome pathway. Under oxidative stimulation, Nrf2 transactivates the *SQSTM1* gene encoding P62 protein, while P62 accumulation promotes P62-dependent autophagy degradation of Keap1 and inhibits KEAP1-mediated Nrf2 degradation.[68] In addition, Nrf2 is activated to induce the expression of autophagy-related genes such as *P62*, *ATG5*, and *ULK1*, and improves autophagy to eliminate damaged proteins and organelles in cells.[69] As a transcription factor, Nrf2 can also directly regulate some important genes in the process of ferroptosis, thereby regulating intracellular iron metabolism, GSH level, GPX4 synthesis, lipid oxidation, and other processes. Therefore, Nrf2 also plays an important role in the regulation of ferroptosis.[70] Recent studies have found that Nrf2/HO-1 participates in the prevention of ferroptosis, autophagy, and apoptosis in many cardiovascular diseases.[71] Lv et al confirmed that the activation of Nrf2 can prevent ferroptosis in MIRI.[72] Thus, Nrf2 may act as an important bridge between autophagy and ferroptosis in the content of MIRI.

P53

P53 is the most studied tumor-suppressing protein and its regulation of autophagy has two sides. On one hand, p53 activates autophagy by upregulating the expression of some related genes promoting autophagy or inhibiting the activity of mTOR.[32] In contrast, p53 can also inhibit autophagy.[73] In addition, autophagy can regulate p53 and mTOR pathways in cells.[74] During ferroptosis, p53 promotes ferroptosis by inhibiting SLC7A11 expression or by promoting ROS accumulation.[75] Previous studies have found that p53 plays an important role in regulating autophagy in MIRI. USP22 protects against MIRI via Sirt1-p53/SLC7A11-Dependent inhibition of ferroptosis-induced cardiomyocyte death.[58] USP7 promotes ferroptosis via activation of the p53/TfR1 pathway in rat hearts after I/R.[59] Therefore, as a co-regulatory molecule between autophagy and ferroptosis in MIRI, p53 deserves further investigation.

STAT3

Autophagy is a lysosome-dependent, self-digestion process. Recently, studies have found that lysosomal activity can also be impaired by ferroptosis, which provides new insights into the relationship between autophagy and ferroptosis. Signal transduction and activator of transcription 3 (STAT3) play a role in maintaining lysosomal function during autophagy.[76] STAT3 is also an inhibiting protein in autophagy. Inhibiting STAT3 expression can activate the expression of autophagy-related genes and thus activate autophagy.[77] STAT3 induces the expression and release of cathespin B (CTSB) to increase the permeability of lysosomal membranes, resulting in lysosomal dysfunction and the promotion of ferroptosis.[78] These findings suggest a potential role for autophagy in ferroptosis via the regulation of the lysosomal pathway. To the best of our knowledge, there is still inadequate research regarding this and its relationship in MIRI. Further studies are needed.

Autophagy regulates ferroptosis

Increasing evidence has shown that ferroptosis is autophagy-dependent and excessive activation of autophagy or abnormal increase in lysosome activity can lead to the accumulation of iron ions and lipid peroxides in cells, thus promoting ferroptosis.[79] The process by which autophagy regulates ferroptosis mainly manifests in the following aspects.

Ferritinophagy

The process by which autophagy degrades the iron-storage macromolecule ferritin is termed ferritinophagy.[80] Ferritinophagy is mediated by nuclear receptor coactivator 4 (NCOA4), an autophagy cargo receptor that binds FTH1 (the main iron storage protein) and transfers the complex to the autolysosome for degradation, leading to the release of free iron.[81] Studies have shown that activated autophagy releases free iron through the degradation of ferritin, increases labile iron levels in cells, promotes ROS production, and leads to ferroptosis.[82,83] Similarly, myocardial I/R challenge or OGD/R treatment promoted ROS-induced lipid peroxidation and caused iron accumulation by activating

TfR1 signaling and NCOA4-medicated ferritinophagy, indicating the activation of ferroptosis after I/R.[84] These studies suggest that ferritinophagy regulates ferroptosis by degrading ferritin in MIRI.

Lipophagy

Lipophagy refers to the process of lipid droplets (LDs) in cells that are selectively transmitted by autophagosomes to lysosomes for degradation.[85] Lipophagy plays an important role in ferroptosis. LDs are lipid-rich organelles that regulate the storage and hydrolysis of neutral lipids in cells. Studies have shown that intracellular LD levels are negatively correlated with oxidative stress-induced ferroptosis.[13] RAB7A, a member of the *Ras* oncogene family and a cargo protein, plays an important role in regulating autophagosome-lysosome fusion and autolysosome maturation. In the process of lipophagy, RAB7A can mediate lipophagy to degrade LDs, increase intracellular lipid levels, promote lipid peroxidation, and further promote RSL3-induced ferroptosis.[86] Studies have found a reshaping of neutral lipids and generation of LDs alongside the induction of lipophagy in an I/R injury model of the blood—brain barrier, which leads to lipid degradation.[87] Thus, it can be assumed that in MIRI, activated lipophagy might promote lipid peroxidation, which then contributes to ferroptosis.

Clockophagy

Clockophagy is a selective autophagy process that was discovered in 2019. Sequestosome 1 (SQSTM1) is used as cargo protein to selectively depress aryl hydrocarbon receptor nuclear translocator-like protein (ARNTL), which is the core of circadian rhythm regulation.[88] Liu et al demonstrated that clockophagy, namely, the selective autophagic degradation of the circadian clock regulator ARNTL promotes ferroptosis *in vitro* and *in vivo*.[89] These studies indicate that clockophagy can promote ferroptosis via the Egl 9 homolog 2- hypoxia-induced factor 1A (EGLN2-HIF1A) pathway. In conclusion, the activation of the dependent SQSTM1-ARNTL-EGLN2-HIF1A pathway can mediate lipid peroxidation and promote ferroptosis. Yang et al indicated that clockophagy is an endogenous oscillating mechanism, as it controls various cellular processes, including iron metabolism, oxidative stress, and cell death.[88] As ferroptosis can affect MIRI, it is closely associated with clockophagy. We suggest that there is a relationship between ferropotosis and clockophagy in MIRI.

Chaperone-mediated autophagy

Chaperone-mediated autophagy (CMA) is an autophagy process in which substrate proteins in the cytoplasm are selectively bound by molecular chaperone proteins, transported to the lysosomal lumen, and then digested and degraded by lysosomal enzymes.[90] Recent studies have found that CMA is highly activated during oxidative stress.[91] Heat shock protein 90 (HSP90) is widely expressed in cells and is evolutionarily conserved, and is an important molecular chaperone that maintains the function and stability of cells.[92] Studies have shown that HSP90 regulates the protein stability of lysosome-associated membrane protein-2a (Lamp-2a) in the process of CMA, which enhances the degradation of antioxidant proteins such as Gpx4 and promotes ferroptosis. Both HSP90 inhibitors and knockdown of *HSP90* gene expression reversed erastin-induced ferroptosis in mouse neurons.[93] Since oxidative stress is a critical event during MIRI, we assumed that CMA might be activated under MIRI, which then participates in ferroptosis by inducing GPX4 degradation.

Mitophagy

Mitophagy is a special type of autophagy that can dictate mitochondrial turnover by degrading damaged mitochondria.[94] Mitochondrial dysfunction is a major pathological process of MIRI and is an important therapeutic target. It is regulated by a complex mechanical network and forms a vicious cycle that destroys mitochondrial homeostasis.[95] Mitophagy can be considered a beneficial cellular process that enhances cell viability following stressful stimuli by eliminating dysfunctional mitochondria. In addition, ferroptosis has been found to be involved in mitochondrial dysfunction.[96] Morphologically, ferroptosis is characterized by mitochondrial atrophy, increased membrane density, decreased or even disappeared mitochondrial crista, and rupture of the outer membrane.[49] The mitochondria are central in iron metabolism, as well as substance and energy metabolism. It is the major organelle in iron utilization and catabolic and anabolic pathways. Interference of key regulators of mitochondrial lipid metabolism (e.g., ASCF2 and CS), iron homeostasis (e.g., ferritin, mitoferrin1/2, and NEET proteins), glutamine metabolism, and other signaling pathways are different from ferroptosis.[97,98] Ferroptosis seems to converge on the BCL2-family protein member BID, promoting its translocation to the mitochondria, where it causes profound mitochondrial fragmentation and dysfunction.[99] This suggests a major role for mitochondria during ferroptosis. Thus, we speculated that the induction of mitophagy in MIRI may modulate ferroptosis by regulating mitochondrial function.

ER stress and other potential crosstalk

Endoplasmic reticulum (ER) stress has been confirmed as an essential factor contributing to the pathogenesis of MIRI.[100] Previous studies have demonstrated that the ER stress response can activate the autophagy-lysosome signaling pathway, which plays a major role in the cardiac stress response.[101] Autophagy functions as a cellular stress signaling pathway and can assist in the degradation of proteins to restore ER homeostasis.[102] Recently studies have also found a relationship between ER stress and ferroptosis in MIRI. Li et al suggested that MIRI regulated by ferroptosis can change the oxidative stress level of cardiomyocytes, causing myocardial cell damage through the interaction of ROS with ER stress.

Heat shock 70 kDa protein 5 (HSPA5) is an important molecular chaperone expressed primarily in the ER. It has been shown to effectively protect against cell death in response to ER stress-induced autophagy through P62 binding.[103] A recent study demonstrated that overexpression of HSPA5 can negatively regulate ferroptosis by limiting Gpx4 degradation and lipid peroxidation.[104] In the future, additional studies are needed to clarify the relationship between ER stress and cell death in MIRI.

Conclusions

MIRI is regulated by several cell death pathways and is an urgent challenge in cardiovascular diseases. Both autophagy and ferroptosis are involved in the mechanism of MIRI. Autophagy seems to play a dual role, depending on the degree of activation. Ferroptosis is a newly discovered way to regulate cell death, producing lipid peroxidation leading to cell death. It also plays a key role in the development of MIRI. Recently, the crosstalk between autophagy and ferroptosis has attracted increasing attention, providing a novel idea regarding the regulation of cell death. Studies have universally shown that ferroptosis is an autophagy-dependent cell death through the following patterns: ferritinophagy, lipophagy, clockophagy, CMA, and mitophagy. Ferroptosis and autophagy share the same regulatory proteins (e.g., Beclin 1, Nrf2, P53, and STAT3). ER stress might also be involved in the connection. However, their potential effects on MIRI have not yet been discussed. In this review, we provide an overview of their potential interrelationships in MIRI. Clarifying the relationship between these factors may provide ideas for new treatments of MIRI in the future. Interventions targeting both autophagy and ferroptosis simultaneously could provide new ideas for the future treatment of MIRI.

Notably, some studies have shown that ferroptosis can exist independently of autophagy. Moreover, they can influence each other and form a feedback loop in MIRI. Moreover, since autophagy plays a dual role in MIRI, it is critical for future interventions to modulate autophagy to find a balance between ferroptosis and autophagy and minimize myocardial damage. To date, the relationship between ferroptosis and autophagy in MIRI is still in the preliminary stage of research, and further studies will reveal the relationship between them.

Conflict of interests

The authors have no conflicts to declare.

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