Autophagy in Cellular Stress Responses

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Abstract

Autophagy is an essential cellular mechanism involving the lysosomal degradation of cytoplasmic organelles or cytosolic components. Autophagy can be induced by various stress stimuli including oxidative stress, hypoxia, pathogen infection, and osmotic pressure, which in turn affects a variety of cellular biological functions and plays a role of double-edged sword in determining the fate of cells depending on different stress conditions, degrees of damage, and cell model. We have summarized the molecular events involved in the process of autophagy induced by cellular stress in this chapter.

Keywords

Autophagy · Cellular stress · Endoplasmic reticulum stress

Abbreviation

3-MA	3-Methyladenine
AAC	Abdominal aortic constriction
AEG-1	Astrocyte elevated gene-1

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AMP	Adenosine monophosphate
AMPK	AMP-activated protein kinase
ATF	Activating transcription factor
ATF4	Activating transcription factor 4
ATG101	Autophagy-related gene 101
ATG12	Autophagy-related gene 12
ATG13	Autophagy-related gene 13
ATG14L	Atg14-like protein
ATG5	Autophagy-related gene 5
ATG9A	Autophagy-related gene 9A
ATP	Adenosine triphosphate
Bcl-2	B cell lymphoma-2
BH3	B cell lymphoma-2 homology domain 3
BNIP3	BCL2/adenovirus E1B-interacting protein 3
cGAS	Cyclic GMP-AMP synthase
CHOP	C/EBP homologous protein
CMA	Chaperone-mediated autophagy
CQ	Chloroquine
CRACs	Ca^{2+} release-activated channels
CXCR4	C-X-C chemokine receptor type 4
E1	Ubiquitin activating
E2	Ubiquitin conjugating
E3	Ubiquitin ligase
eIF2α	Eukaryotic translation initiation factor 2 alpha
ER stress	Endoplasmic reticulum stress
ER	Endoplasmic reticulum
F6P	Fructose-6-phosphate
FIP200	FAK family kinase interacting protein of 200 kDa
FYCO1	FYVE and coiled-coil domain-containing 1
G6P	Glucose-6-phosphate
G6PDH	Glucose-6-phosphate dehydrogenase
GRP78/BiP	78 kDa glucose-regulated protein/binding immunoglobulin protein
HCV	Hepatitis C Virus
HIF-1	Hypoxia-inducible factor-1
HK II	Hexokinase II
HSP	Heat shock protein
HSPA8/HSC70	Heat shock 70 kDa protein 8
HSV-1	Herpes simplex virus type 1
ICS model	Intermittent cold stress in C57BL/6 J mouse model
ICS	Intermittent cold stress
IH	Intermittent hypoxia
IRE1	Inositol-requiring enzyme 1
IRE1α	Inositol-requiring enzyme 1α
IRF3	Interferon regulator 3

IRGM	Immunity-related GTPase family M
K-48	Lysine residue 48
K-63	Lysine residue 63
KFERQ	Recognizes the signal peptide
LAMP2A	Lysosomal-associated membrane protein 2A
LC3	Microtubule-associated protein light chain 3
LC3-II	Microtubule-associated protein light chain 3-II
LIR	LC3 interacts
LUBAC	Linear ubiquitin chain assembly complex
MAP 1LC3B	Microtubule-associated protein 1 light chain 3B
MAVS	Mitochondrial antiviral signaling proteins
MeV	Measles virus
mTOR	Mammalian target of rapamycin
mTORC1	Mammalian target of rapamycin complex 1
NADPH	Nicotinamide adenine dinucleotide phosphate
NDP52	Nuclear dot 10 protein 52
NLRP3	Nucleotide-binding oligomerization domain receptor, pyrin domain-containing 3
NS4B	Nonstructural protein 4B
NS5ATP9	Nonstructural protein 5A upregulation gene
OPTN	Optineurin
OXPHOS	Oxidative phosphorylation
p62	Protein sequestosome 1/p62
PAMPs	Pathogen-associated molecular patterns
PE	Phosphatidylethanolamine
PERK	Protein kinase RNA-like ER kinase
PI3K	Phosphatidylinositol 3-kinase
PI3P	Phosphatidylinositol 3-phosphate
PINK1	Putative kinase protein 1
PKR	Double-stranded RNA-dependent protein kinase
PLEKHM1	Pleckstrin homology and RUN domain containing M1
PRRS	Pattern recognition receptors
R5P	Ribulose-5-phosphate
RIG-I	Retinoic acid-inducible gene I
ROS	Reactive oxygen species
SINV	Sindbis virus
SnRK1	Snf1-related protein kinase 1
SQSTM1	Sequestosome 1
TANK1	TANK-binding kinase 1
TAX1BP1	3'-UTR of Tax1-binding protein 1
TAX1BP1	Tax1-binding protein 1
TBC1D5	Tre-2/Bub2/Cdc16 domain family member 5
TIAM1	T-lymphoma invasion and metastasis-inducing protein 1
TLR	Toll-like receptors
TOR	Target of rapamycin

TRIF	Toll/IL-1R domain-containing adaptor-inducing IFNβ
TRPV1	Transient receptor potential vanilloid 1
TSC1	Tuberous sclerosis complex subunit 1
TSC2	Tuberous sclerosis complex subunit 2
ULK1	UNC-51-like kinase 1
UPR	Unfolded protein reaction
UPR	Unfolded protein response
UPS	Ubiquitin-proteasome system
UVRAG	UV irradiation resistance-associated gene
Vps34	Vacuolar protein sorting 34

6.1 Introduction

Autophagy is a process of dynamic changes of subcellular membrane structure in eukaryotes and lysosome-mediated degradation of intracellular proteins and organelles. There are three types of autophagic degradation, including macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA), mainly differing in the mechanism of cargo delivery to the lysosome, which have been elaborated in these reviews [1, 2]. During macroautophagy, usually referred to as "autophagy", autophagosomes encapsulate part of the cytoplasm and organelles, proteins, and other components that need to be degraded in the cell and fuse with the lysosome to form an autophagolysosome, which degrades the contents of the lysosome under the action of lysosomal enzymes and achieves the energy metabolism needs of the cell itself as well as the renewal of certain organelles.

The autophagosome is a vacuole structure with a diameter of about 100 nm composed of a double-layer phospholipid molecular membrane, the formation of which marks the initiation of autophagy. The processing of phosphatidylethanolamine (PE), phosphatidylinositol 3-phosphate (PI3P), and other phospholipid molecules is the key molecular event in autophagosome formation [3], which is achieved by high-dimensional protein complexes due to large volume of phospholipid molecules containing two 14–18 carbon fatty acid tails. The formation of autophagosomes is a process precisely regulated by multiple protein complexes such as ULK1, ATG14L, and ATG16L1, which can be divided into three stages, including initial signaling stage, functional protein recruitment stage, and membrane extension stage. During the initial signaling stage, ULK1 (autophagy-related gene 1, Atg1) stimulated by upstream signals forms a "ULK1 complex" with FIP200, ATG13, and ATG101, which in turn significantly activates ULK1 and subsequently triggers the functional protein recruitment stage. The activation of ULK1 can further activate beclin-1 (Atg6), Vps34, ATG14L, UVRAG, and other proteins to form "class III PI3K complex." As a PI3P synthase, Vps34 is activated by formation of the complex and thereby synthesizes a large amount of PI3P to recruit more autophagy-related functional proteins, thus laying the foundation for the formation and

extension of autophagosome membranes. In response to activated PI3P synthesis, ATG16L1, ATG5, and ATG12 form a three-element "ATG16L1 complex" that further transforms into a higher-dimensional 12-element complex. The complex subsequently promotes the lipidation reaction of LC3 (Atg8) via connecting it to a PE molecule, thus leading to formation of LC3-II anchored to the autophagosome membrane. As a linker protein, LC3-II can assist in transporting the substances that need to be degraded into the autophagosomes, which is also considered as a distinguishable feature of autophagosomes.

When exposed to external stress stimuli, cells initiate a series of reactions in response to cell pressure and protect themselves from potential damage. Autophagy is one of the core pathways that mediates cellular stress response. In 1992, Ohsumi's team reported for the first time that nutrient-deficient conditions stimulated extensive autophagic deg radation of cytosolic components in the vacuoles of yeast cells [4]. Subsequent studies have shown that as a cellular stress response, a utophagy can be induced by various stimuli, including oxidative stress, hypoxia, pathogen infection, and osmotic pressure. In this chapter, we will discuss molecular events involved in the process of autophagy induced by cellular stress.

6.2 Oxidative Stress and Autophagy

Oxidative stress refers to the imbalance between oxidation and antioxidation states in the body, and the production of a large number of reactive oxygen species (ROS) as well as the tendency to oxidation will damage organelles, especially mitochondria [5]. So far, the only known mechanism for mitochondrial renewal is autophagy. Current studies have shown that cellular ROS levels increase under stress conditions, and H_2O_2 and $O_2^{\bullet -}$ in ROS are early inducers of autophagy [6–12].

The mammalian target of rapamycin complex 1 (mTORC1) is involved in the synthesis of proteins [13]. Under nutrient-rich conditions, mTORC1 is activated and phosphorylates Atg13 (Ser258) and ULK1 (Ser757) to inhibit catalytic activation of ULK1 complex (containing ULK1, Atg13, FIP200, and Atg101), thereby inhibiting autophagy [7]. When glucose deficiency and glucose-6-phosphate (G6P) levels are reduced, the glycolytic pathway and pentose phosphate pathway are inhibited, resulting in reduced NADPH and ATP levels. Since NADPH is the common substrate of glutathione reductase and thiol regeneration-related reductase and provides the electrons needed for thiol redox homeostasis, the cellular antioxidant capacity is reduced, and ROS production accordingly increases (Fig. 6.1) [6, 14, 15].

The exposed H_2O_2 and $O_2^{\bullet -}$ actively regulate autophagy through at least three different pathways. Excessive exposure of H_2O_2 and $O_2\bullet -$ can induce the activation of AMP-dependent protein kinase (AMPK) [16, 17]. AMPK stabilizes TSC1–TSC2 complex and shuts down mTORC1 signaling by phosphorylating TSC2, which removes the inhibition of mTORC1 on autophagy induction [18] (1). AMPK also directly phosphorylates ULK1 (Ser777 and Ser317) and activates the catalytic function of ULK1, which subsequently phosphorylates its interaction factors (Atg13 and FIP200) at other residues different from mTORC1. Activated ULK1

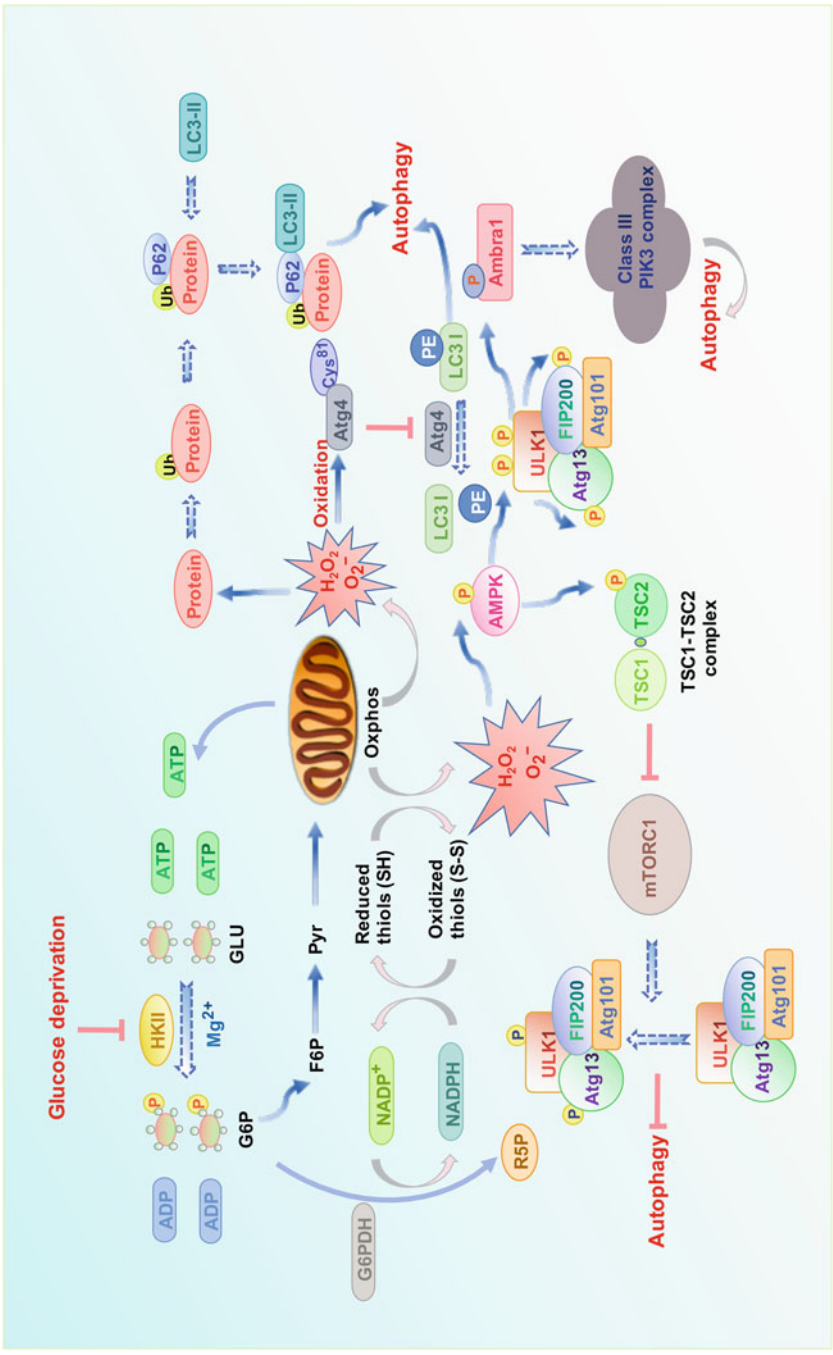

Fig. 6.1 Overview of the oxidative stress and autophagy. Upon glucose deficiency, NADPH and ATP levels are reduced, which results in ROS production. ROS induces autophagy by acting on AMPK, Atg4, and other autophagy pathway-related proteins. *F6P* fructose-6-phosphate, *Pyr* pyruvate, *OXPHOS* oxidative phosphorylation, *G6PDH* glucose-6-phosphate dehydrogenase, *R5P* ribulose-5-phosphate, *HK II* hexokinase II, mitochondrial isoform

complex recruits class III PI3K complex through activating molecules in beclin-1-regulated autophagy Ambra1, which contributes to the extension of autophagic bubble membrane [19, 20] (2). Adaptor molecule p62 has been shown to bind to ubiquitinated proteins and target them to LC3-II to induce autophagy [21, 22], and the study has indicated that p62 may be regulated by redox signaling [23]. In addition, ROS can also promote ubiquitination of the substances to be degraded, which promotes their recognition by p62 and targeted transport to the autophagosomes via binding to LC3-II [7] (3). ROS also causes oxidation of Cys81 on Atg4, resulting in inactivation of its "delipidating" activity on LC3, which facilitates accumulation of LC3-II and helps to extend autophagy (Fig. 6.1) [6, 24].

6.3 Endoplasmic Reticulum Stress and Autophagy

Endoplasmic reticulum (ER) stress involves accumulation of misfolded and unfolded proteins in the endoplasmic reticulum and disturbance of calcium ion balance [25]. The unfolded protein reaction (UPR) is the main pathway of ER stress response, which can help misfolded and unfolded proteins return to normal structure [26, 27]. UPR is mainly regulated by three ER membrane-associated sensor proteins, namely, inositol-requiring enzyme 1α (IRE1α), protein kinase RNA-like ER kinase (PERK), and activating transcription factor (ATF) 6 [28]. Under physiological conditions, the ER chaperone GRP78/BiP binds to ER membrane-located ATF6, IRE1, and PERK proteins. When misfolded proteins accumulate in the ER lumen, BiP/GRP78 dissociates from the three proteins and binds to unfolded proteins, thus activating these sensors and triggering UPR system to clear the accumulated proteins [25]. However, when the accumulation exceeds the UPR clearance capacity, cells may initiate autophagy as a scavenger to the point of protecting cells from damage [29]. Emerging evidence has shown that UPR sensors, PERK and IRE1, are implicated in mediating ER stress-induced autophagy [30, 31]. On the other hand, Ca^{2+} plays a vital role in ER stress-induced autophagy. During ER stress, Ca^{2+} is released from the ER lumen to the cytosol, thereby leading to the activation of AMPK and inducing autophagosome formation via CaMKKβ [32]. ER stress can also mediate autophagy by enhancing the interaction between Ca^{2+} binding protein caldendrin and LC3, which in turn reduces ER stress [33]. Taken together, autophagy can be induced through Ca^{2+}- and UPR-dependent mechanism under ER stress (Fig. 6.2).

6.4 Hypoxia-Induced Autophagy

Oxygen plays an important role in cellular respiration and energy metabolism. It was found that the number of autophagosomes increased under the condition of hypoxic culture [34]. HIF-1 is a hypoxia-inducible factor closely related to hypoxia-induced autophagy [35]. HIF-1 enhances the activity of BNIP3 by acting on BH3 site, so as

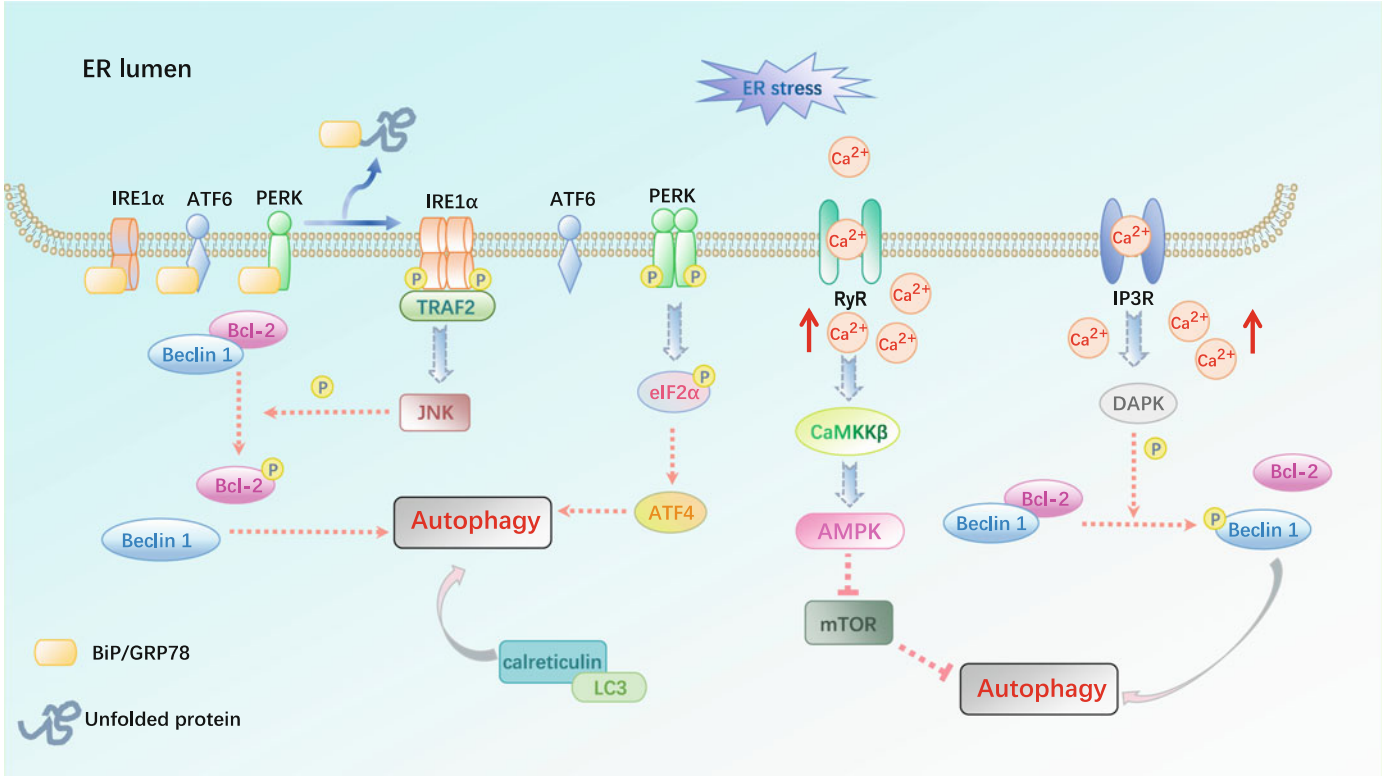

Fig. 6.2 Schematic presentation of ER stress-induced autophagy. IP3R and RyR receptors are ER membrane located in Ca^{2+} release-activated Ca^{2+} channels (CRACs). The PERK-eIF2α or the IRE-TRAF2-JNK pathway is implicated in ER stress-induced autophagy. In addition, the ER stress-induced increase in cytosolic Ca^{2+} can stimulate autophagy via CaMKKβ- or DAPK-mediated pathway

to regulate the interaction between Bcl-2 and beclin-1 as well as inhibit the activity of mTOR, thus stimulating the occurrence of autophagy [36, 37]. Moreover, hypoxia can also cause an increase in intracellular AMP/ATP ratio, thus stimulating AMPK that can promote autophagy by inhibiting the activity of mTOR [38]. Other studies have shown that mRNA levels of autophagy genes *LC3* and *ATG5* increase under hypoxia, which are regulated by PERK-dependent ATF4 and CHOP [39]. In addition, intermittent hypoxia (IH) activates endoplasmic reticulum stress and induces autophagy through the PERK/eIF2/ATF4 signaling pathway, thereby reducing IH-induced apoptosis [40] (Fig. 6.3).

6.5 Osmotic Stress and Autophagy

Normal osmotic pressure is crucial for maintaining cellular homeostasis. However, osmotic stress may occur under both physiological and pathological conditions [41]. As an important stress response, how does autophagy respond to cellular osmotic pressure? Hypertonic stress has been shown to induce autophagy in some organisms [42, 43]. Jiang et al. found that hyperosmotic stress could activate autophagy of nucleus pulposus cells through Ca^{2+}-dependent AMPK/mTOR pathway, thereby promoting the degradation of SQSTM1/p62 and inhibiting apoptosis under hyperosmotic condition, so as to ensure the survival of nucleus pulposus cells [44]. Similarly, Daniel et al. found that polycystin-2, a membrane protein of the polycystin family, downregulated mTOR pathway and thus promoted autophagy to act as an adaptive mechanism of cell survival under hyperosmotic stress [41]. In plants, osmotic stress also inhibits the TOR complex by activating an ortholog of mammalian AMPK and Snf1-related protein kinase 1 (SnRK1) and hinders the inhibitory effect of TOR on Atg1 or other unknown downstream regulatory factors and finally induces autophagy [45, 46]. The above findings indicate that autophagy tends to be activated as a protective mechanism response to osmotic stress.

6.6 Infection-Induced Autophagy

6.6.1 Bacterial Pathogen Infection

Selective autophagy is an important pathway to remove intracellular pathogens (e.g., *Mycobacterium*, *Salmonella*, *Escherichia coli*) [47–49]. In the case of pathogen invasion, host cells respond to the warning signals and damaged cell membranes through the family of galectins [50]. This will help the specific pathogens coated in ubiquitin by E3 ligases to generate a “kill-me” signal within the cells [50–52]. Subsequently, the autophagy receptor proteins (p62, NDP52, OPTN, TAX1BP1) recognize ubiquitinated pathogens and deliver them to autophagosomes for subsequent degradation [53–56].

Ubiquitination of pathogens needs three enzyme cascade effects: ubiquitin activating (E1), ubiquitin conjugating (E2), and ubiquitin ligating (E3) [57]. The

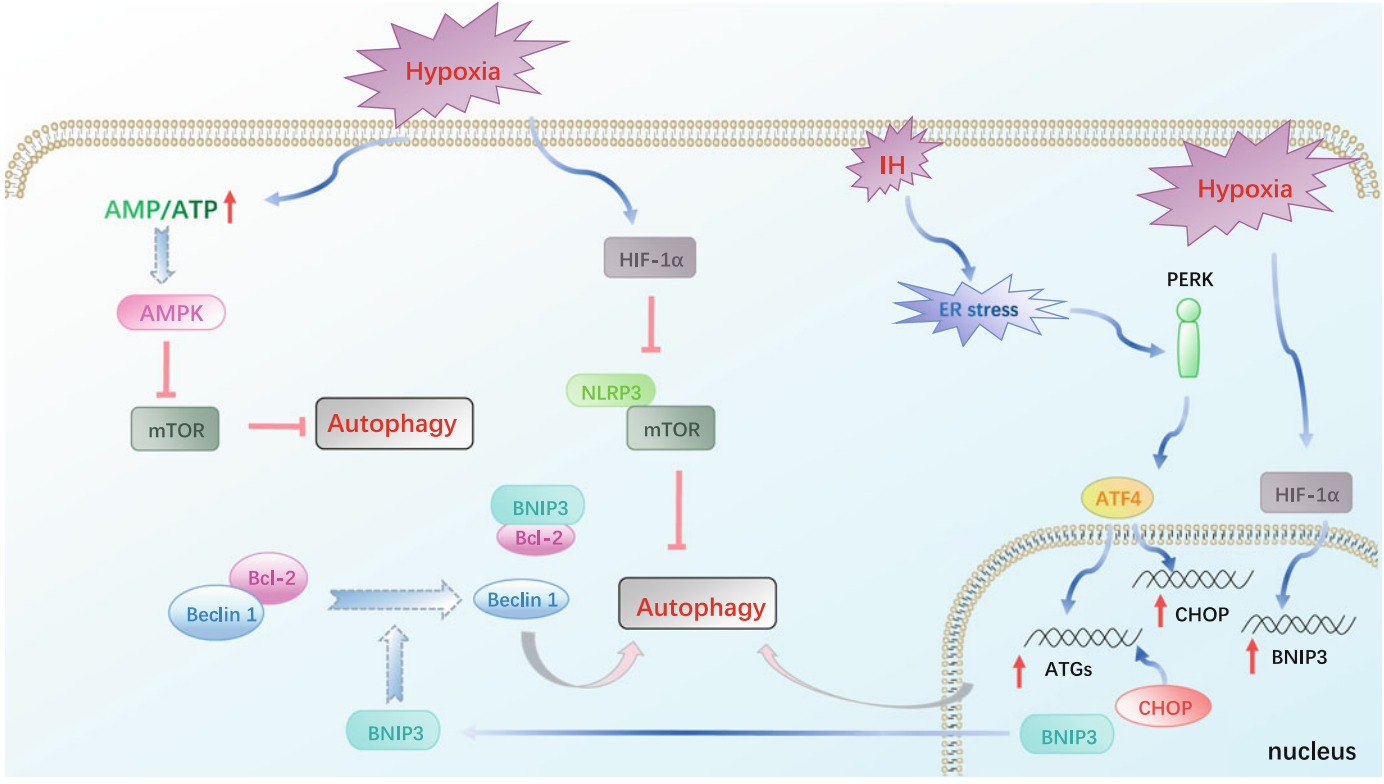

Fig. 6.3 Schematic presentation of hypoxia-induced autophagy. Hypoxia enhanced the activity of BNIP3 by promoting HIF-1α, which dissociates the interaction between Bcl-2 and beclin-1. On the other hand, hypoxia induces autophagy by inhibiting the activity of mTOR. An increase in AMP/ATP ratio is also observed in hypoxic cells. Meanwhile, mRNA levels of autophagy genes are increased through the regulation of ATF4 and CHOP. IH can stimulate ER stress and promote the PERK/eIF2α/ATF4 signaling pathway to induce autophagy

ubiquitin coat produced by E3 ligases can attract autophagy receptor proteins (p62, NDP52, OPTN, TAX1BP1), which increases the ability of autophagy to eliminate pathogens and limit bacterial proliferation [48, 58]. The ubiquitin coat consists of several different linkages such as linear K-63 and K-48, and all the linkages can perform as "eat me" signals in triggering autophagy to remove the pathogens [48, 59]. However, for proteins, the way of ubiquitin connection will affect subsequent degradation pathways of these proteins. The proteins wrapped by K-63 ubiquitin chains are mainly cleared by autophagy, while the proteins wrapped by K-48 ubiquitin chains are subjected to be degraded by proteasomes [60, 61]. Several E3 ligases have been identified to be involved in ubiquitinating bacterial pathogens and targeting them for selective autophagy [62–65]. Parkin is one of the most thoroughly studied E3 ligases, which is required for the ubiquitination of *Mycobacterium tuberculosis* and *Salmonella typhi* as well as subsequent autophagy-mediated degradation [49, 62]. The E3 ligase LRSAM1 is an important ligase in the process of clearing many intracellular bacterial pathogens such as *S. typhimurium*, *Escherichia coli*, and a *Shigella flexneri* [63]. Other E3 ligases such as ARIH, HOIPI, and LUBAC are also involved in the ubiquitination of bacterial pathogens [64, 65].

In selective autophagy, the autophagy adaptor proteins are a bridge between the ubiquitinated cargoes to be degraded and the newborn autophagosomes. The autophagy adaptor proteins, including ULK1/2, FYCO1, TBC1D5, PLEKHM1, and TIAM1, target the ubiquitinated substrate degradation by driving autophagy-lysosome pathway without degradation of themselves [66–71]. However, under the conditions caused by bacterial pathogen infection, the autophagy receptor proteins (such as p62, NDP52, OPTN, TAX1BP1) can act as the adaptor proteins to promote the maturation of autophagosomes and degrade along with the pathogens [53–56, 72, 73]. For example, during the *Salmonella* infection, (1) **p62** recognizes the targets of the E3 ligase ARIH, HOIP1, and LRSAM1 and then is recruited into *Salmonella* and used as a target for autophagy degradation [74]. (2) **NDP52** interacts with galectin 8 to help recruit TANK-binding kinase 1 (TNK1) to phosphorylate NDP52. NDP52-TBK1 is the first responder before E3 ligase LSRAM1 ubiquitinates bacteria, which can help NDP52 target bacterial autophagy [50, 75]. LC3 interacts with the (LIR) domain of NDP52 to deliver bacteria into autophagosomes and limit its proliferation [54]. (3) M1 polyubiquitination on the surface of bacteria is recruited by the E3 ligase complex LUBAC, and then **OPTN** recognizes LUBAC and targets the bacteria for autophagy degradation [64]. (4) **TAX1BP1** interacts with myosin VI to induce the fusion of autophagosome and lysosome in *Salmonella* [56].

The E3 ligase and autophagy receptor proteins are important in the selective autophagy of bacterial pathogens. Different autophagy receptor proteins display similar functions in targeting bacterial species for autophagy degradation. However, there are relatively few types of E3 ligase that have been clarified, and the ubiquitination (single ubiquitin or polyubiquitination) degree of ubiquitin chains (K-63, K-48, K-27) and the mechanisms in different infectious bacteria remain to be further studied.

6.6.2 Virus Infection

During viral infection, autophagy may be induced by adsorption, invasion, membrane fusion, protein synthesis, and other steps in the viral replication cycle [76–78]. At first, the adsorption of virions can induce autophagy [79]. For example, in measles virus (MeV) infection, human surface pathogen receptor CD46 induces autophagy by interacting with the Vps34-beclin-1 complex via the CD46-Cyt1/GOPC pathway [80–82]. MeV can also activate autophagy by targeting immunity-related GTPase family M (IRGM) [83, 84]. Moreover, autophagy is also activated during viral membrane fusion. The fusion of HIV-1 envelope glycoproteins gp120 and gp41 with the CD4 and CXCR4 receptors of uninfected $CD4^+$ T cells induces autophagy [78, 85]. Studies have shown that CXCR4 phosphorylates and activates p53, which increases the expression of Bax and activates the mitochondrial death pathway, thereby resulting in the death of uninfected $CD4^+$ T cells [86]. Another study suggested that autophagy activation may be also associated with increased bioactive lipids and ROS during membrane fusion [87].

After the membrane fusion, the viral genome activates different pattern recognition receptors (PRRs) such as retinoic acid-inducible gene I (RIG-I) and toll-like receptors (TLRs), and PRR induces autophagy by recognizing pathogen-associated molecular patterns (PAMPs) [88–90]. After TLRs recognize viral genome, the myeloid differentiation primary response protein MYD88 and adaptor molecule 1 (TRIF) will be recruited. TLR then stimulates MYD88 or TRIF to bind to beclin-1, which dissociates beclin-1 from the inhibitory complex Bcl-2 and induces autophagy [89, 91]. After being stimulated by viral dsRNA, RIG-I transmits signals to mitochondrial antiviral signaling proteins (MAVS) to activate interferon regulator 3 (IRF3), inducing the expression of IFNα/β and IFN target genes [88]. Double-stranded RNA-dependent protein kinase R (PKR) is activated by interferon and binds to beclin-1 in the Vps34-beclin-1 complex to initiate autophagosome formation. PKR can also induce autophagy by inhibiting protein translation through phosphorylating and inactivating eukaryotic initiation factor 2 (eIF2) [89, 92]. During DNA virus infection, the DNA sensor cyclic GMP-AMP synthase (cGAS) competes with the autophagy inhibitor Rubicon to bind to beclin-1, thereby triggering autophagy and stimulating the degradation of cytoplasmic viral DNA [93].

The viruses can induce autophagy not only directly through the interaction between its own proteins and autophagy-related proteins but also indirectly by inducing cellular stress [85, 94]. Take hepatitis C virus (HCV) infection as an example: the NS3/4A protease of HCV can bind to the autophagy-related protein IRGM to induce autophagy [95]. The NS4B protein of HCV has been shown to induce LC3 lipidation and autophagosome accumulation and may form complexes with Rab5, hVps34, and beclin-1 to induce autophagy [96, 97]. NS5ATP9 is a functional protein involved in DNA damage response, cellular signal transduction, and cell death. It has been reported that HCV NS5A upregulates the expression of beclin-1 via NS5ATP9 and may therefore induce autophagy [98–100]. A recent study shows that the host endoplasmic reticulum transmembrane protein SCOTIN

interacts with NS5A of HCV and induces autophagic degradation, thereby inhibiting virus replication [101].

On the other hand, HCV infection may induce ER stress, which enables the unfolded protein response (UPR) to induce autophagy and enhance protein degradation, thus alleviating ER stress [102, 103]. At the same time, ER stress releases calcium ions from the endoplasmic reticulum, which increases the activity of mitochondria, leading to the production of excessive ROS and causing oxidative stress. The damaged mitochondria are then degraded by targeted mitophagy [104, 105]. Another study has shown that HCV infection induces the expression of the protein kinase PINK1 and its substrate parkin (an E3 ubiquitin ligase), which are meanwhile recruited to the mitochondrial membrane to induce mitophagy [94, 106].

In the autophagy induced by viral infection, a few viruses such as HSV-1 and SINV are targets of xenophagy [107, 108]. The mechanism is that the host recognizes the ubiquitin chain on the virus and targets the virus particles to the autophagosome for degradation [109]. This is similar to the mechanism by which a bacterial pathogen infection induces autophagy. But in most cases, autophagy is induced by viral components such as nucleic acids and proteins or indirectly stimulated by viral infection-mediated cellular stress.

6.7 Autophagy Under Heat and Cold Stress

Autophagy and the heat shock response are two cellular protein homeostasis systems, the former occurring only in eukaryotes while the latter existing in all prokaryotes and eukaryotes [110]. The heat shock protein (HSP) chaperone system can regulate the folding of newborn peptides and the transport of mature proteins [111, 112]. When cells are under heat stress, the expression of the molecular chaperone HSP increases. HSP promotes the degradation of irreversible protein aggregation during heat stress through ubiquitin-proteasome system (UPS) and chaperone-mediated autophagy pathways [111, 113]. For example, in chaperone-mediated autophagy, heat shock 70 kDa protein 8 (HSPA8/HSC70) recognizes the signal peptide (KFERQ) at the N-terminal of the cytosolic protein and then binds it to lysosomal-associated membrane protein 2A (LAMP2A) followed by subsequent degradation in lysosomes [114].

A new research suggests that in response to cellular stress, cells prioritize the heat shock response over autophagy in order to ensure protein homeostasis. When the two systems are activated, the heat shock response can inhibit autophagy [115]. Overexpression of HSP70 protein is the main executor of heat shock response [116]. In the cell culture model, overexpression of HSP70 inhibits starvation-mediated increase of LC3 and the degradation of p62, because LC3 and p62 are respectively involved in the elongation of autophagosome membranes and the degradation of autophagosomes, suggesting that overexpression of HSP70 significantly inhibits starvation-induced autophagy [115, 117, 118]. Moreover, this inhibition may be related to the activation of Akt/mTOR pathway. HSP70 phosphorylates

mTOR by inducing the phosphorylation of Akt, leading to the inhibition of autophagy [19]. Knockdown of heat shock transcription factor 1 (HSF1) leads to accumulation of misfolded proteins, which increases the lipidation of LC3 associated with autophagosome formation and promotes hunger-induced autophagy [115].

According to the researches on cold stress, severe cold exposure can promote the oxidative stress of organisms and induce the increase of ROS and the damage of mitochondria. Meanwhile, cold stress also plays an important role in the regulation of autophagy [119–122]. Transient receptor potential vanilloid 1 (TRPV1) is a nonselective cation channel with high permeability to calcium ions, which can be activated by a variety of endogenous and exogenous physical or chemical stimuli and plays a key role in pain and temperature perception [123, 124]. In a study of cold stress and pressure overload [122], it was found that pressure overload produced by abdominal aortic constriction (AAC) treatment of mice led to upregulated TRPV1 expression, phosphorylated autophagy regulator AMPK, downregulated autophagy marker protein p62, and increased ratio of LC3 II/LC3 I. And subsequent continuous cold exposure not only did promote autophagy by significantly enhancing the regulation of TRPV1, AMPK, and p62 by AAC surgery but also increased the production of ROS and mitochondrial damage induced by pressure overload. Under pressure overload, cold stress-induced ROS production may help induce AMPK activation [125]. Moreover, TRPV1 promotes autophagy dependent of ROS and AMPK [126]. Therefore, it is speculated that in the state of pressure overload, the upregulation of TRPV1 expression induced by cold stress may promote excessive autophagy [122].

A study found that the mice exposed to intermittent cold stress (ICS) demonstrated induced mitochondrial dysfunction and autophagy, reflected by significantly increased transcription levels of autophagy-related genes *MAP 1LC3B* and *BECN1* that respectively encodes LC3 and beclin-1 [121]. Accordingly, another study showed increased LC3 II/LC3 I ratio and observable marks of autophagosome vesicles in cells exposed to mild cold shock, suggesting that the autophagy pathway can also be activated under mild cold stress [127].

There are few studies on autophagy-related cold stress, and the regulation of autophagy may not be directly affected by cold stress. Some have been accompanied by a combination of oxidative stress. For example, in studies on cold stress and pressure overload, cold exposure itself has little impact on the generation of autophagy regulators and ROS as well as can only enhance the effect of pressure overload on autophagy promotion. However, the mechanism of heat stress-induced autophagy is more complex. It has been reported that autophagy and the heat shock response are two systems in protein homeostasis complementing each other under certain conditions, but the underlying molecular mechanisms remain to be further explained.

6.8 Autophagy Inducers or Inhibitors

At present, some typical autophagy inhibitors including 3-methyladenine (3-MA), chloroquine (CQ), and hydroxychloroquine have been clearly clarified [128]. 3-MA inhibits autophagy by inactiviting PI3K [129], and CQ exerts inhibitory effect by disrupting the fusion of autophagy lysosomes and blocking autophagy flux [130]. Chemicals that target the autophagy-related gene themselves or key upstream autophagy regulatory proteins may alter the levels of autophagy. Sulfosalicylic acid has been shown to reduce autophagy of cachectic cancer mice in vivo [131]. On the contrary, there are also some chemicals or drugs showing a promotive effect on autophagy. For example, inflammatory bowel disease drug corticosteroids [132] could induce autophagy of bone cells, L6 myoblasts, and lymphocytes through mTORC1 inhibition [133–135]. By inhibiting mTOR, Akt, and ERK1/2 phosphorylation, harmaline can regulate B16 cell autophagy [136]. Similarly, sinomenine inhibits the PI3K/Akt/mTOR signaling pathway in melanoma cells, which reduces the proliferation of melanoma cells by stimulating autophagy and promoting the apoptosis of melanoma cells [137]. In conclusion, different chemicals or drugs have dual effects on regulation of autophagy, and the treatment of some diseases by targeting autophagy has already become the focus of researches.

6.9 Conclusions and Perspectives

As an important stress response, autophagy is closely related to the development of various diseases. In traditional view, autophagy serves as a pro-survival mechanism. However, there is also large quantity of evidence demonstrating that the excessive activation of autophagy is disadvantageous for cell survival. For example, hypoxia promotes autophagy by inhibiting the mTOR/NLRP3 pathway, which reduces the expression of inflammatory genes in Crohn's disease and improves the inflammatory response [138]. Another study also demonstrates that autophagy may play a protective role in ischemic hypoxia injury [139]. In a variety of tumor cells, autophagy is usually induced through HIF-1 [140, 141], ATG9A [142], AEG-1 [143], and other pathways under hypoxia environment, thereby promoting the proliferation and metastasis of tumor cells and reducing the chemical sensitivity of tumor cells. In summary, autophagy plays a role of double-edged sword in determining the fate of cells, which may change depending on different stress conditions, degrees of damage, and cell models. Nevertheless, the manipulation of stress-induced autophagy can become a treatment strategy for related diseases.

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