



REVIEW

The Autophagy-Oxidative Stress Circuit: A Conductor of Cell Fate

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ABSTRACT: Autophagy and oxidative stress form a bidirectional and dynamic regulatory network governing cell fate. Dysregulation of this crosstalk contributes to the pathogenesis of various diseases, including cancer, neurodegeneration, inflammation, metabolic disorders, and aging. Therefore, a deep understanding of the molecular mechanisms underlying the interplay between autophagy and oxidative stress provides a theoretical foundation for developing therapeutic strategies targeting this axis. This review synthesizes recent literature on the underlying molecular mechanisms. Oxidative stress drives autophagic initiation through multiple interconnected pathways, including direct oxidative modification of core autophagy-related proteins, modulation of canonical signaling cascades, activation of nuclear transcription factors, and induction of selective autophagy. In turn, autophagy acts as a pivotal cytoprotective mechanism by eliminating reactive oxygen species (ROS) generated by damaged organelles, sustaining metabolic homeostasis, and reinforcing antioxidant signaling, thereby counteracting oxidative damage. The balance between these two processes determines whether cells adapt and survive, undergo programmed cell death, or enter senescence.

KEYWORDS: Autophagy; oxidative stress; reactive oxygen species; selective autophagy; cell fate

1 Introduction

Autophagy is a highly conserved catabolic process that generally plays an essential role in maintaining cellular homeostasis [1,2]. Based on the different pathways by which materials are delivered to lysosomes, autophagy is generally categorized into macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA) [3]. Among these, macroautophagy is the most extensively studied and is often simply referred to as autophagy [4]. The process of autophagy mainly includes the initiation of autophagy, the engulfment of cellular components such as organelles to form autophagosomes, the fusion of autophagosomes with lysosomes, and the degradation within autolysosomes [5,6]. Through this process, cells can eliminate deleterious materials and obtain energy, thereby contributing to their survival [7,8]. However, autophagy can also mediate cell death or even exert detrimental effects on cells [9,10]. Therefore, autophagy may play a decisive role in determining whether cells survive or die [11,12].

Oxidative stress is the result of an imbalance between the generation of reactive oxygen species (ROS) and the cellular antioxidant defense mechanisms [13,14]. Under conditions such as tumors, inflammation,

and neurodegenerative diseases, cells primarily produce large amounts of ROS through two pathways. These include the mitochondria and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which trigger oxidative stress and contribute to disease progression [15–17]. Excessive ROS can lead to mitochondrial dysfunction and DNA damage, which in turn promote further ROS generation, ultimately resulting in cellular impairment and cell death, thus forming a vicious cycle [18–20].

Recent studies have revealed that autophagy and oxidative stress interact and are closely intertwined [21]. Together, they co-regulate cell fate and influence disease progression [22–24]. This review summarizes recent advances in the molecular regulatory mechanisms underlying the crosstalk between oxidative stress and autophagy. It also discusses their decisive role in determining cell fate under various conditions, aiming to provide a theoretical basis for the clinical management and research of related diseases.

2 Regulatory Mechanism of Oxidative Stress on Autophagy

Current research has revealed that oxidative stress can regulate autophagy through multiple pathways to eliminate oxidatively damaged proteins and organelles (Fig. 1). In terms of regulatory mechanisms, these can be broadly categorized into direct modification of core autophagy-related proteins by ROS, indirect regulation mediated by signaling pathway networks, regulation of autophagy gene expression mediated by nuclear transcription factors, and selective autophagy.

2.1 Modification of Core Autophagy-Related Proteins

The direct regulation of autophagy by oxidative stress primarily relies on the oxidative modification of cysteine residues in proteins by ROS [25]. This process is rapid and site-specific, serving as the core mechanism for the swift initiation of autophagy under oxidative stress. During oxidative stress, sensitive oxidative sites on autophagy-related proteins are progressively oxidized by ROS, ultimately altering the original protein functions and triggering autophagy [26].

2.1.1 Autophagy-Related Proteins (ATG)

The orderly progression of this complex process depends on the synergistic action of a series of ATG, which are central to ensuring the successful formation of autophagosomes [27]. The direct oxidative modification of ATGs by ROS mainly targets key enzymes involved in the lipidation process of ATG8/microtubule-associated protein 1 light chain 3 (LC3), thereby regulating the initiation and progression of autophagy by altering their catalytic activities [28]. ATG4 is the primary target in this regulatory network. As a cysteine protease, ATG4 processes newly synthesized LC3 precursors to expose the C-terminal glycine residue. In the later stages of autophagosome formation, it also cleaves and recycles the LC3-PE conjugate (i.e., lipidated LC3-II) bound to the autophagosome membrane [29]. Under oxidative stress conditions, ROS can directly oxidize cysteine residues near the catalytic site of ATG4, leading to reversible inhibition of its enzyme activity [30,31]. This inhibition prevents ATG4 from prematurely cleaving LC3-II from the expanding autophagosome membrane. As a result, the binding of LC3-II to the membrane is stabilized. This ensures the extension, expansion, and eventual maturation of the autophagosome membrane [32]. Thus, the oxidation of ATG4 by ROS acts as a key switch that promotes autophagosome formation.

In addition to ATG4, other core enzymes involved in the LC3 lipidation cascade are also direct targets of ROS. The conversion of LC3-I to LC3-II requires a ubiquitination-like cascade, in which ATG7 acts as an E1-like activating enzyme and ATG3 as an E2-like conjugating enzyme, working together to catalyze the covalent linkage of LC3-I to PE [33,34]. Studies have shown that ROS can directly oxidize cysteine residues

at the catalytic site of ATG3, inhibiting its E2 enzyme activity and consequently affecting the generation of LC3-II [35,36]. Similarly, ROS can directly oxidize ATG7, promoting the formation of inactive oxidized dimers and thereby inhibiting autophagy initiation [36]. As mentioned above, the oxidative effects of ROS on ATG4 antagonize those on ATG3 and ATG7. This may be due to the higher oxidative sensitivity of ATG3 and ATG7, meaning that low levels of ROS preferentially oxidize ATG3/7 to inhibit excessive activation of autophagy, maintaining ROS's role as signaling molecules [37]. However, when ROS concentrations exceed the cellular antioxidant buffering capacity, oxidative modification of ATG4 becomes dominant, initiating autophagy to clear oxidatively damaged products [37]. In addition to direct oxidative modification, recent studies have found that ROS can also ubiquitinate ATG7 and ATG9A through E3 ubiquitin ligases, thereby modulating the process of autophagy [38,39].

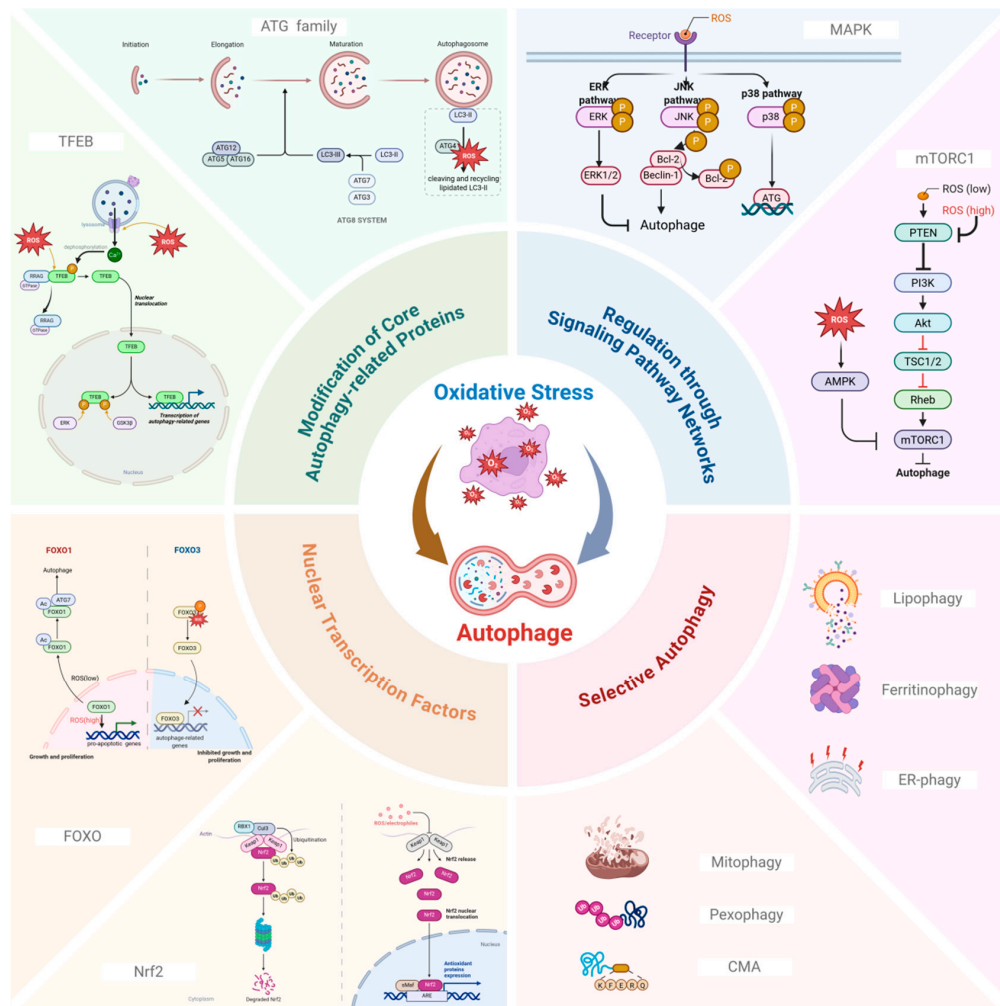


Figure 1: Regulatory mechanism of oxidative stress on autophagy. Oxidative stress mediates and exacerbates autophagic processes through four interconnected regulatory modules: direct modification of core autophagy-related proteins, signaling pathway networks, nuclear transcription factors, and selective autophagy (Created in BioRender. Zhang D. (2026) <https://BioRender.com/hk2a2ol>). Abbreviations: ROS, reactive oxygen species; TFEB, transcription factor EB; mTORC1, mechanistic target of rapamycin complex 1; MAPK, mitogen-activated protein kinase; FOXO, forkhead box O; Nrf2, nuclear factor erythroid 2-related factor 2; CMA, chaperone-mediated autophagy; ER, endoplasmic reticulum.

2.1.2 Transcription Factor EB (TFEB)

TFEB is recognized as a master regulator of autophagy and lysosomal biogenesis, driving the large-scale expression of genes including ATGs and lysosomal proteins [40]. Importantly, beyond its transcriptional role, TFEB is also subject to rapid post-translational modifications that allow it to respond swiftly to oxidative stress. Previous studies have found that TFEB activity is primarily finely regulated by post-translational modifications: the mechanistic target of rapamycin complex 1 (mTORC1) and extracellular signal-regulated kinase 2 (ERK2), located on the lysosomal surface, phosphorylate specific serine residues on TFEB [41,42]. Phosphorylated TFEB then binds to the cytoplasmic chaperone protein 14-3-3, thereby being retained in the cytoplasm and unable to translocate to the nucleus to perform its transcriptional function [43,44]. When cells face conditions such as oxidative stress or starvation, TFEB is rapidly dephosphorylated and translocates into the nucleus, activating autophagy and promoting lysosomal biogenesis [45].

In addition to the aforementioned classical signaling pathways, recent studies have revealed that ROS can also directly oxidize the TFEB protein itself, thereby rapidly initiating the autophagic process. Specifically, the direct oxidation of TFEB by ROS primarily targets a specific cysteine residue within its protein structure, Cys-212 [46]. Treatment with H₂O₂ induces significant oxidation of TFEB, whereas mutating Cys-212 to alanine (C212A) almost completely abolishes this oxidative signal, indicating that Cys-212 is the ROS-driven oxidation site [46]. In mouse TFEB, the corresponding sole cysteine residue is Cys-211, whose oxidation similarly promotes TFEB nuclear translocation [47]. Functionally, the oxidative modification of Cys-212 disrupts the interaction between TFEB and RRAG GTPases [48]. RRAG GTPases are GTPases located on the lysosomal surface responsible for recruiting mTORC1 to the lysosomal surface and activating it, while also participating in anchoring TFEB to the lysosomal membrane [49]. ROS-mediated oxidation disrupts this interaction, causing TFEB to be released from the lysosomal surface, achieving rapid nuclear accumulation even without inhibiting mTORC1 kinase activity [46]. Live-cell imaging experiments demonstrate that H₂O₂ treatment induces rapid nuclear translocation of TFEB within 8 min. This speed is significantly faster than that induced by starvation or mTORC1 inhibitor treatment, providing kinetic evidence for this direct oxidation mechanism [46].

Furthermore, ROS may also induce the release of Ca²⁺ through the lysosomal transient receptor potential mucolipin 1 (TRPML1) channel or mucolipin 1 (MCOLN1) channel, leading to calcineurin-dependent dephosphorylation of TFEB [50,51]. Meanwhile, oxidatively modified TFEB is more sensitive to the dephosphorylation mediated by this pathway, suggesting that the two mechanisms can synergistically initiate the autophagic response more efficiently [51,52]. In hepatocellular carcinoma, the endogenous antioxidant enzyme sulfiredoxin-1 (SRXN1) promotes tumor cell proliferation by scavenging ROS and inhibiting TFEB nuclear translocation and its mediated autophagy-lysosome biogenesis [53]. This indicates that maintaining an appropriate level of ROS-mediated TFEB oxidation is crucial for normal autophagic function. Additionally, the corresponding cysteine residues in TFEB family members TFE3 and microphthalmia-associated transcription factor (MITF) exhibit similar oxidative sensitivity and jointly participate in ROS-mediated autophagy activation [46,54,55].

2.2 Signaling Pathway Networks

Oxidative stress can transmit and amplify oxidative signals through multiple classical signaling pathways, thereby achieving indirect regulation of autophagy.

2.2.1 Mechanistic Target of Rapamycin Complex 1 (mTORC1)

As discussed earlier, mTORC1 plays a central regulatory role in autophagy [41,42]. Current research has identified multiple pathways centered on mTORC1 through which oxidative stress regulates autophagy.

Firstly, oxidative stress can activate AMP-activated protein kinase (AMPK), which sits at the apex of these pathways [56,57]. The classical view holds that an increased AMP/ATP ratio resulting from energy deprivation activates AMPK [58–60]. However, recent studies have found that under conditions such as glucose deprivation or metformin treatment, elevated intracellular ROS levels can induce S-glutathionylation of protein kinase C ζ (PKC ζ) [61]. This modification promotes its interaction with the nuclear transporter karyopherin α 2 (KPNA2) and subsequent nuclear translocation, where it phosphorylates the AMPK upstream kinase liver kinase B1 (LKB1) at Ser428 [61]. This triggers LKB1's export from the nucleus, enabling it to phosphorylate AMPK at Thr172 in the cytoplasm, thereby activating AMPK [61]. Furthermore, ataxia-telangiectasia mutated kinase (ATM) is also recognized as playing a significant role in this process. Traditionally, ATM is regarded as a DNA damage response kinase localized within the nucleus, responsible for sensing DNA double-strand breaks and initiating repair mechanisms and cell cycle checkpoints [62]. However, when ROS levels rise, a conserved cysteine residue, Cys2991, within the ATM protein can be oxidized to form an intermolecular disulfide bond [63,64]. This induces a conformational change in the ATM dimer and activates its kinase activity, a mode of activation independent of its mechanism for sensing DNA damage in the nucleus [64,65]. Following activation, cytoplasmic ATM phosphorylates LKB1, initiating the downstream signaling cascade. Relevant studies have shown that an LKB1 mutant lacking the ATM phosphorylation site loses the ROS-induced inhibitory function on mTORC1, directly demonstrating that LKB1 is a key downstream effector of ATM [65]. Activated AMPK can then phosphorylate tuberous sclerosis complex 2 (TSC2), enhancing the GTPase-activating protein activity of the TSC1/2 complex and inactivating mTORC1 [66]. Concurrently, AMPK can also directly phosphorylate the key mTORC1 subunit Raptor (regulatory-associated protein of mTOR), inducing its dissociation from the mTORC1 complex and further inhibiting mTORC1 kinase activity [67]. The inhibition of mTORC1 activity directly relieves its constraint on the downstream Unc-51-like kinase 1 (ULK1) complex, promoting autophagosome formation [68,69]. Additionally, activated AMPK can directly phosphorylate multiple activating sites on ULK1, such as Ser317 and Ser777, independently of mTORC1, thereby promoting the activation of the ULK1 complex [68]. In recent years, it is noteworthy that some studies have also challenged the traditional view that AMPK invariably inhibits mTORC1 and promotes autophagy. In a kidney injury model, exercise preconditioning restores energy homeostasis by activating AMPK, but this is accompanied by moderate activation of mTORC1 to suppress excessive autophagic flux, thereby protecting renal function [70]. Kazyken et al. [71], however, discovered that AMPK suppresses autophagy during prolonged amino acid deprivation and supports mTORC1 signaling through a new but unknown mechanism.

In addition to the pathways mentioned above, the class I phosphatidylinositol 3-kinase (PI3K) also plays a significant role in this process. Under normal conditions, class I PI3K recruits and activates downstream AKT serine/threonine kinase (AKT) protein by catalyzing the conversion of phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3) on the plasma membrane [72]. Under conditions of PIP3 accumulation, Akt auto-activates and inhibits the activity of TSC2, thereby activating mTORC1 and suppressing the occurrence of autophagy [73,74]. However, when ROS levels increase, phosphatase and tensin homolog (PTEN) can dephosphorylate PIP3 to regenerate PIP2, thereby antagonizing PI3K signaling and inhibiting excessive AKT activation [75,76]. This, in turn, activates TSC2 and inhibits mTORC1 activity, promoting autophagy [77]. It is important to note, however, that excessively high levels of ROS can conversely lead to the oxidative inactivation of PTEN, resulting

in sustained AKT activation and the inhibition of autophagy via mTORC1 [74,76]. Additionally, further upstream, relevant studies have found that oxidative stress can induce the modification of sirtuin 1 (SIRT1), thereby reducing its enhancing effect on PI3K and mTORC1 activity and promoting autophagy [78,79].

2.2.2 Mitogen-Activated Protein Kinase (MAPK)

The MAPK family comprises a group of serine/threonine protein kinases activated by various extracellular stimuli and plays a key role in linking oxidative stress signals to autophagy initiation [80]. This family mainly includes classical MAPK members and atypical MAPKs. Classical MAPK members are best characterized, including extracellular signal-regulated kinases 1/2 (ERK1/2), c-Jun amino (N)-terminal kinases 1/2/3 (JNK1/2/3), p38, and ERK5 [81]. In recent years, numerous therapeutic studies have indicated that drugs can alleviate disease progression through oxidative stress-activated MAPK signaling pathways [82–84]. Regarding the specific mechanisms of action, early studies have shown that oxidative stress conditions can increase p38 phosphorylation and activate JNK, as well as induce the expression of multiple ATGs [85,86]. Further research revealed that the anti-apoptotic protein B-cell lymphoma 2 (Bcl-2) can bind to Beclin-1, a core component of the autophagosome nucleation complex, consequently inhibiting its ability to provide the nucleation signal for autophagosome formation [87]. JNK primarily disrupts the inhibitory binding between Bcl-2 and Beclin-1 by phosphorylating multiple sites on Bcl-2, releasing Beclin-1 to promote autophagosome nucleation [88]. p38, on the other hand, upregulates the transcription of autophagy-related genes by phosphorylating ATG5 or regulating the expression of transcription factors [89].

Research on the mechanism of ERK in regulating autophagy under oxidative stress is relatively limited, with studies focusing more on its role in the tumor environment or on autophagy itself. However, it is currently relatively clear that ERK1/2 plays an inhibitory role in autophagy [90,91]. Whether ERK5 directly regulates autophagy remains a subject of debate [92].

2.2.3 Ca^{2+}

During oxidative stress, ROS can directly modify key cysteine residues on intracellular calcium channels and pumps. This activates the inositol trisphosphate receptor (IP₃R) and ryanodine receptor (RyR) on the endoplasmic reticulum, promoting calcium release from stores, while simultaneously inhibiting the calcium re-uptake function of the sarco/endoplasmic reticulum calcium ATPase (SERCA) [93–95]. This results in a sustained increase in cytosolic calcium concentration. Mitochondria, as the core organelles for calcium buffering, take up cytosolic calcium via the mitochondrial calcium uniporter (MCU) [96]. However, calcium overload can induce the opening of the mitochondrial permeability transition pore (mPTP), further amplifying oxidative damage and initiating autophagic signals [96,97]. At the mechanistic level, elevated Ca^{2+} binds to calmodulin (CaM) and can activate AMPK through direct phosphorylation at Thr172 by Ca^{2+} /calmodulin-dependent protein kinase kinase 2 (CaMKK2), subsequently initiating the pathways previously described to promote autophagy [98]. Furthermore, as mentioned earlier, cytosolic calcium can activate calcineurin, inducing the calcineurin-dependent dephosphorylation of TFEB to promote autophagy [50,51]. Lerner et al. [99] reported that calcium signaling can weaken the inhibitory binding between Beclin-1 and Bcl-2 via death-associated protein kinase (DAPK). This releases Beclin-1 to activate vacuolar protein sorting 34 (Vps34) and initiate autophagy. At the mitochondrial level, calcium signals activate Ca^{2+} /calmodulin-dependent protein kinase I α (CaMKI α) [100] and calcineurin [101]. Through phosphorylation (at Ser600) and dephosphorylation (at Ser637), respectively, these molecules modify DRP1 to promote mitochondrial fission, which primes mitochondria for autophagic degradation. A recent study by Nguyen et al. [102] also links calcium signaling to the mTORC1 pathway, revealing that oxidative stress

can induce lysosomal Ca^{2+} release and sustained activation of mTORC1 on the lysosomal membrane in pancreatic β -cells, ultimately inhibiting autophagy.

2.3 Nuclear Transcription Factors

Oxidative stress can upregulate the expression of autophagy-related genes at the transcriptional level by activating nuclear transcription factors, thereby achieving long-term regulation of autophagy. These transcription factors initiate transcriptional programs by binding to specific response elements in the promoter regions of autophagy genes. Meanwhile, some transcription factors can mediate the coordinated activation of autophagy and the antioxidant system, forming a cellular defense network under oxidative stress.

2.3.1 Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2)

Nrf2 is the master transcriptional regulator of the cellular antioxidant defense [103]. Under basal conditions, Nrf2 binds to its inhibitor protein, kelch like ECH associated protein 1 (Keap1), and is continuously degraded via ubiquitination mediated by the Cullin3 (Cul3) ubiquitin ligase, maintaining it at a low level [104]. When cells are exposed to oxidative stress, ROS can oxidize sensitive sites on Keap1, thereby inhibiting Cul3 activity and suppressing the ubiquitination and degradation of Keap1 [105,106]. Concurrently, relevant studies have found that the autophagy receptor protein sequestosome 1 (SQSTM1/p62) can competitively hinder the interaction between Keap1 and Nrf2 [107]. This may be related to the activation of the DNA damage response kinase pathway ATM-checkpoint kinase 2 (CHK2) by ROS, which phosphorylates p62, enhancing its binding ability to Keap1 [108]. Once stabilized, Nrf2 translocates into the nucleus and binds to the antioxidant response element (ARE) in the promoter regions of target genes such as Beclin-1, p62, and ATG5, initiating the transcription of a series of autophagy-related and antioxidant genes [109]. Notably, this transcription promotes the accumulation of p62 protein. p62 then continues to competitively inhibit the Keap1-Nrf2 interaction. This leads to further stabilization and activation of Nrf2, thus forming a positive feedback amplification loop [110,111]. Furthermore, Nrf2 is closely associated with multiple pathways mentioned previously. Relevant studies indicate that activation of the PI3K/AKT pathway allows activated AKT to directly phosphorylate Nrf2 or Keap1, promoting the dissociation of Nrf2 from Keap1 and its translocation to the nucleus [112–114]. Concurrently, the PI3K/AKT pathway can inactivate glycogen synthase kinase-3 (GSK-3) through phosphorylation, relieving the inhibitory effects of GSK-3 on Nrf2 degradation and nuclear translocation [115,116]. The p38/MAPK pathway, however, functions similarly to GSK-3. Upon activation by oxidative stress, it can phosphorylate Nrf2, inhibiting its nuclear translocation and transcriptional activity [117,118].

2.3.2 The Forkhead Box O (FOXO) Family

FOXO family mainly includes FOXO1, FOXO3, FOXO4, and FOXO6 [119,120]. Acting as cellular redox sensors, they are activated under oxidative stress conditions through various post-translational modifications such as phosphorylation, acetylation, and ubiquitination. These activated sensors then regulate the expression of a series of target genes involved in autophagy, antioxidant defense, cell cycle arrest, and apoptosis [121]. Current research indicates that under oxidative stress, the regulatory mechanisms of the FOXO family on autophagy are primarily manifested in the FOXO1 and FOXO3 subtypes.

Research on the mechanism by which FOXO1 regulates autophagy under oxidative stress is relatively scarce. Lu et al. [122] reported that in porcine endometrial epithelial cells, mild oxidative stress prompts

FOXO1 to export from the nucleus to the cytoplasm, where it undergoes acetylation to form Ac-FOXO1. This acetylated form then binds to the core autophagy protein ATG7, promoting autophagosome formation and enhancing autophagic flux, thereby exerting a cytoprotective effect [122]. Conversely, under severe oxidative stress conditions, FOXO1 is retained in the nucleus and activates the expression of pro-apoptotic target genes, inducing apoptosis [122].

Unlike FOXO1, FOXO3 primarily promotes autophagy through transcriptional activation of autophagy-related genes within the nucleus. Under oxidative stress, dephosphorylated FOXO3 translocates into the nucleus and binds to the forkhead response element in the promoter regions of target genes. This binding transcriptionally activates a series of autophagy-related genes, including LC3 and Bcl-2 interacting protein 3 (BNIP3), which in turn promotes autophagy [123,124]. Furthermore, Lv et al. [125] reported that sodium selenite can activate FOXO3a through the ROS-induced AMPK/mTORC1 pathway and promote autophagy in cervical cancer cells. Ding et al. [126] also reported that an inhibitor of apoptosis proteins (IAPs) antagonist can induce ROS generation and activate FOXO3, ultimately triggering autophagy in tumor cells. Previous studies have also reported that elevated ROS levels induced by dexamethasone in human chondrocytes can induce autophagy through the Akt/FOXO3 pathway [127]. Meanwhile, Zeng et al. [128] discovered in echinoderm research that ROS can promote FOXO dephosphorylation via Akt phosphorylation. Subsequently, FOXO can promote the transcription of LC3 and ATG4 to facilitate autophagy [128].

2.4 Selective Autophagy

Mitochondria are one of the primary sources of ROS; thus, mitophagy plays a crucial role in responding to oxidative stress. This process is regulated by multiple pathways.

2.4.1 Mitophagy

When mitochondrial membrane potential is lost or oxidative damage occurs, PTEN-induced putative kinase 1 (PINK1) undergoes autophosphorylation and stabilizes on the mitochondrial outer membrane [129]. Subsequently, PINK1 recruits the E3 ubiquitin ligase Parkin, which ubiquitinates mitochondrial outer membrane proteins, generating an “eat-me” signal [130,131]. This forms ubiquitin chain signals that recruit adaptor proteins such as p62 and Tax1-binding protein 1 (TAX1BP1), targeting the damaged mitochondria for autophagic degradation [132]. In recent years, numerous therapeutic studies have confirmed that related drugs can alleviate disease progression through PINK1/Parkin-dependent mitophagy [133–135]. Building on this, research by Jin et al. [136] suggests that ROS may activate PINK1 through AMPK activation, thereby exerting a protective effect on chondrocytes. Meanwhile, a study by Zhuang et al. [137] indicates that hydroxycarboxylic acid receptor 2 (HCAR2) may function further upstream of AMPK. Ma et al. [138] also proposed that Peroxiredoxin 6 (PRDX6) accumulates and is consumed under oxidative stress conditions, which promotes the stabilization of PINK1. Furthermore, related research has revealed a series of sensing mechanisms. A study by Zeb et al. [139] found that moderate levels of mitochondrial ROS can oxidize Keap1, thereby disrupting the Keap1 and Phosphoglycerate Mutase 5 (PGAM5) complex. This leads to the accumulation of full-length PGAM5 in the cytoplasm, which subsequently interferes with mitochondrial processing of PINK1, promoting PINK1 stabilization and accumulation on the outer membrane [139]. Ultimately, this accumulation of PINK1 facilitates the recruitment of Parkin. This enhances the sensitivity of mitophagy even before the loss of mitochondrial membrane potential, forming a negative feedback loop that maintains ROS homeostasis [139]. A recent study discovered that mitochondrial ROS (mtROS) generated by mitochondrial stress can activate the ATM-CHK2 pathway [140]. Activated CHK2 can phosphorylate the mitochondrial membrane protein ATPase family AAA domain-containing protein 3A

(ATAD3A) at Ser371, inhibiting the translocation of PINK1 to the inner mitochondrial membrane and causing its accumulation on the outer membrane [140]. Concurrently, CHK2 can target the autophagy adaptor optineurin (OPTN) at Ser177 and Ser473, enhancing the efficiency of targeting ubiquitinated mitochondria to autophagosomes [140]. Finally, CHK2 can also phosphorylate Beclin-1 at Ser90/93 to promote autophagic membrane formation [140]. These mechanisms collectively achieve coordinated regulation from ROS sensing to mitochondrial tagging and clearance.

In parallel with ubiquitin-dependent mechanisms, this process is also mediated by various ubiquitin-independent pathways. Under oxidative stress conditions, ROS can inhibit the ubiquitin-mediated degradation of hypoxia-inducible factor-1 α (HIF-1 α) [141]. Stabilized HIF-1 α then enhances the transcriptional expression of the mitophagy receptors BNIP3 and Bcl-2 interacting protein 3 like (BNIP3L) [142]. BNIP3 and BNIP3L can directly bind to LC3 via their LC3-interacting region (LIR) motifs, while their Bcl-2 homology domain 3 (BH3) domains can competitively disrupt the Beclin-1-Bcl-2 complex, releasing Beclin-1 to activate autophagosome nucleation [143]. FUN14 domain containing 1 (FUND1) is another receptor located on the mitochondrial outer membrane; it is dephosphorylated and activated upon ROS induction, enhancing its interaction with LC3 to promote mitophagy [144,145]. Additionally, Jia et al. [146] reported that under oxidative stress conditions, miR-6513-5p in human saphenous vein endothelial cells undergoes o8G modification. This modification abolishes its targeted inhibitory effect on the autophagy receptor BCL2L13 (Bcl-2 like 13), which in turn enhances the BCL2L13-LC3 interaction to mediate protective mitophagy [146]. A study by Xu et al. [147] indicates that high glucose-induced oxidative stress can reduce the expression of prohibitin 2 (PHB2) through the Keap1-Nrf2 pathway, thereby inhibiting mitophagy in mouse hippocampal neurons. Gao et al. [148] suggests that hydrogen peroxide-induced oxidative stress may regulate the level of mitophagy by activating the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway.

2.4.2 Pexophagy

Pexophagy refers to the selective autophagic degradation of peroxisomes. Peroxisomes represent another significant intracellular source of ROS, thus rendering pexophagy equally important in the cellular response to oxidative stress.

It is currently widely accepted that oxidative stress-induced pexophagy is primarily achieved through the phosphorylation and ubiquitination of the peroxisomal biogenesis factor 5 (PEX5) protein [149]. PEX5 is the key receptor for importing matrix proteins into peroxisomes and plays a central role in peroxisome biogenesis. Research indicates that when ROS levels increase within the peroxisomal lumen, ATM is activated and recruited to the peroxisomal membrane, where it phosphorylates PEX5 at Ser141 [150]. This phosphorylation event promotes the monoubiquitination of PEX5 at Lys209 by the PEX2-PEX10-PEX12 E3 ubiquitin ligase complex [150,151]. The modified PEX5 then serves as an “eat-me” signal, recognized by adaptor proteins such as p62, which subsequently target the ubiquitinated peroxisome to LC3, ultimately delivering the damaged peroxisome to lysosomes for degradation [152]. Furthermore, Demers et al. [153] reported that the absence of PEX13, a protein involved in peroxisomal matrix import, can promote the accumulation of ubiquitinated PEX5 and increase peroxisomal ROS levels, thereby inducing pexophagy. It is noteworthy that a recent study by Kim et al. [154] proposed a novel regulatory mechanism involving phosphorylation and ubiquitination. The study found that in PEX1-deficient HeLa cells, the accumulation of ROS leads to the phosphorylation and activation of TANK-binding kinase 1 (TBK1) at serine 172. This, in turn, phosphorylates the E3 ubiquitin ligase membrane-associated RING-CH protein 7 (MARCHF7). Phosphorylated MARCHF7 binds to peroxisomal membrane protein 4 (POMP4) and promotes

its ubiquitination at lysine 20. Subsequently, this recruits next to the BRCA1 gene 1 (NBR1) to the peroxisome, which facilitates pexophagy [154].

Similar to mitophagy, pexophagy also possesses ubiquitin-independent backup mechanisms. PEX14, a docking protein on the peroxisomal membrane, participates in PEX5-mediated matrix protein import under normal conditions [155]. However, under oxidative stress, it can act as a direct docking site for LC3 [156]. Studies have shown that PEX14 can bind directly to LC3-II independently of ubiquitin signals, targeting damaged peroxisomes to autophagosomes [156]. This mechanism may play a compensatory role in specific cell types or under particular stress conditions. Additionally, Kim et al. [157] reported that in HeLa cell models, the small molecule compound ZLDI-8 activates ATM by selectively increasing peroxisome-derived ROS and promotes the dephosphorylation and nuclear translocation of TFEB. This subsequently upregulates the expression of autophagy-related genes and induces pexophagy, representing a potentially more upstream regulatory pathway [157,158]. Research by Manandhar et al. [159] found that calcium deficiency leads to increased ROS accumulation in peroxisomes, resulting in TFEB activation and the induction of pexophagy, further validating this conclusion. Chen et al. [160] also reported that elevated ROS levels within the peroxisomal lumen can activate autophagy mediated by the E3 ubiquitin ligase STIP1 homology and U-box containing protein 1 (Stub1), although the more specific mechanisms remain unclear.

2.4.3 Chaperone-Mediated Autophagy (CMA)

CMA is a process that selectively degrades damaged proteins in the cytoplasm [161]. It can clear oxidatively damaged substances and can also be activated by oxidative stress [162]. The classical theory posits that during the CMA process, substrate proteins are recognized by a chaperone-co-chaperone complex and bind to lysosome-associated membrane protein type 2A (LAMP2A), subsequently being degraded [163]. Recent studies have also highlighted the important role of HSC70. ROS induce o8G modification of circPLCE1 and promote HSC70 ubiquitination. This inhibits lung cancer progression through CMA [164]. Research by Ye et al. [165] also indicates that the ROS-FOXO1 signaling axis can drive the expression of the E3 ubiquitin ligase NEDD4. This NEDD4 prevents the degradation of the transcriptional regulator YAP1 through a CMA pathway involving HSC70, which promotes astrocyte proliferation.

2.4.4 Lipophagy

Lipophagy is also a type of selective autophagy that specifically degrades lipid droplets via the lysosomal pathway [166]. It is mainly categorized into macrolipophagy, chaperone-mediated lipophagy, and microlipophagy [167]. Current research indicates that lipophagy plays a significant role in the progression of various diseases such as fatty liver disease and atherosclerosis [168,169]. However, whether lipophagy is regulated by ROS remains inconclusive, and the underlying mechanisms are not yet clear.

2.4.5 Ferritinophagy

Ferritinophagy is a specific type of selective autophagy that selectively degrades ferritin to release free iron, leading to lipid peroxidation and ferroptosis [170,171]. It is currently widely accepted that ferritinophagy is primarily mediated by nuclear receptor coactivator 4 (NCOA4) [172,173]. However, the regulatory role of oxidative stress in this process remains unclear. Yang et al. [174] proposed that ferritinophagy might serve as an intermediate link connecting oxidative stress, mitochondrial damage, and ferroptosis. Qin et al. [175] discovered that mitochondria-derived ROS may trigger ferritinophagy by activating the AMPK-ULK1 pathway.

2.4.6 Endoplasmic Reticulum-Selective Autophagy (ER-Phagy)

Under stress conditions such as oxidative stress, unfolded or misfolded proteins can accumulate within the endoplasmic reticulum (ER) lumen, a state known as ER stress (ERS) [176]. The unfolded protein response (UPR) can partially alleviate this stress, but its sustained activation leads to ER damage, necessitating the restoration of homeostasis through ER-phagy [177,178]. Currently, the mechanisms by which oxidative stress regulates ER-phagy remain unclear. Research by Liang et al. [179] suggests that ER-phagy may be associated with mitochondrial oxidative dysfunction. Relative studies indicate that family with sequence similarity 134, member B (FAM134B) could be an intermediary molecule in the regulation of ER-phagy by oxidative stress, with its expression level positively correlating with the level of ER-phagy [180,181]. Additionally, research by Wei et al. [182] points out that nanoparticle-induced ROS accumulation and ERS promote ER-phagy, although this process is not mediated by autophagy machinery genes.

2.4.7 Others

In addition to the pathways mentioned above, there are other mechanisms through which oxidative stress regulates autophagy. For example, oxidative stress can inhibit the pro-autophagic function of Beclin-1 by promoting its deSUMOylation via the deSUMOylating enzyme sentrin/SUMO-specific protease 3 (SEN3) [183,184]. ROS can activate p38 and its effector kinase, MAP kinase-activated protein kinase 2 (MK2), mediating the MK2-dependent phosphorylation of HSP27, thereby promoting p62-mediated lysophagy to clear damaged lysosomes [185]. Furthermore, ROS-induced ERS can transduce stress signals into autophagic regulatory signals through the UPR [186]. This process is mediated by the three classical UPR pathways involving protein kinase RNA-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1 α (IRE1 α), and activating transcription factor 6 (ATF6) [187]. The activation of PERK can activate activating transcription factor 4 (ATF4) and C/EBP homologous protein (CHOP) by phosphorylating eukaryotic initiation factor 2 α (eIF2 α), subsequently promoting the transcription of autophagy-related genes such as ATG5 and p62 [188,189]. PERK can also promote autophagy through the Nrf2-P62 axis [190]. The activation of IRE1 α , on the other hand, can upregulate Beclin-1 expression by splicing X-box binding protein 1 (XBP1) mRNA to produce the transcription factor X-box binding protein 1-spliced (XBP1-S) [191]. After being cleaved and activated, ATF6 indirectly participates in autophagy induction by upregulating DAPK1, CHOP, and XBP1 [192,193].

3 Regulatory Mechanisms of Autophagy on Oxidative Stress

Autophagy and oxidative stress have a bidirectional regulatory relationship. Unlike oxidative stress-induced autophagy, it is now widely accepted that autophagy serves as a protective mechanism against oxidative stress. The antioxidant mechanisms of autophagy can be broadly categorized into selective autophagy, maintenance of metabolic homeostasis, and regulation of antioxidant signaling pathways (Fig. 2).

3.1 Selective Autophagy Eliminates Damaged Organelles and Harmful Substances

The regulatory role of oxidative stress on selective autophagy has been detailed in the preceding sections. Correspondingly, selective autophagy is also a primary mechanism for eliminating the main sources of ROS and counteracting oxidative stress.

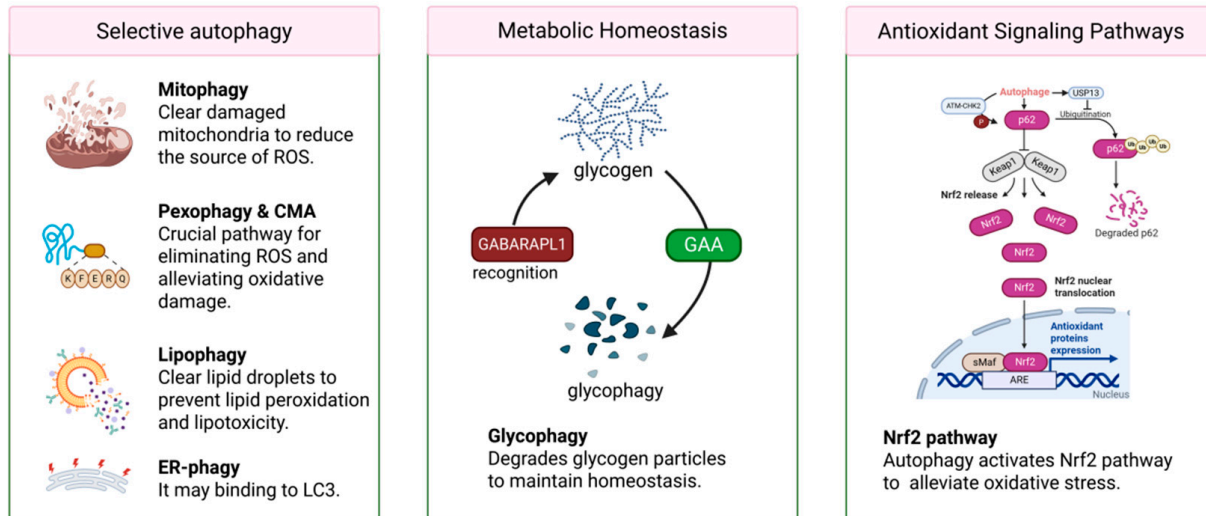


Figure 2: Regulatory Mechanism of Autophagy on Oxidative Stress. Autophagy alleviates oxidative stress via selective autophagy, maintenance of metabolic homeostasis supports cellular balance, and regulation of antioxidant signaling pathways (Created in BioRender. Zhang, D. (2026) <https://BioRender.com/homr85t>). Abbreviations: ROS, reactive oxygen species; CMA, chaperone-mediated autophagy; ER, endoplasmic reticulum; Nrf2, nuclear factor erythroid 2-related factor 2; Keap1, Kelch-like ECH-associated protein 1; GABARAPL1, GABA type A receptor-associated protein-like 1; GAA, acid alpha-glucosidase.

3.1.1 Mitophagy, Pexophagy, and CMA

Currently, the view that mitophagy can alleviate oxidative stress and mitochondrial damage by clearing damaged mitochondria is widely accepted, and numerous therapeutic studies have substantiated this [194–196]. Regarding the specific mechanisms of this process, many signaling pathways closely related to oxidative stress have been discussed earlier. Beyond these, mitophagy may also be regulated by other mechanisms. A recent study indicated that activating the nuclear translocation of TFEB can promote BNIP3-mediated mitophagy, thereby alleviating oxidative stress in acute pancreatitis [197]. Research by Feng et al. [50] similarly highlighted the important role of TFEB in this process and found that TFEB activation may be associated with calcium signaling triggered by TRPML1. Zhang et al. [198] discovered in hepatocellular carcinoma cells that thioredoxin-related transmembrane protein 2 (TMX2) can promote both macroautophagy and mitophagy by concurrently facilitating TFEB nuclear translocation and Parkin recruitment. It is noteworthy that these findings were primarily established under conditions of oxidative stress, thus their occurrence may still be regulated by the level of oxidative stress. Additionally, mitochondrial DNA damage is also a significant factor leading to mitochondrial dysfunction and exacerbating oxidative stress. If damaged mitochondrial DNA is not promptly cleared by mitophagy, the cGAS-STING pathway can become activated, resulting in cellular damage [199]. Research by Shu et al. [200] has found that ATAD3B acts as a mitophagy receptor, mediating the clearance of oxidative stress-induced damaged mitochondrial DNA. Furthermore, the DNA damage response regulator ataxia telangiectasia and Rad3-related protein (ATR) may be essential for PINK1-mediated mitophagy [201].

Similar to mitophagy, pexophagy, and CMA are also crucial pathways for eliminating ROS and alleviating oxidative damage. Current research on the regulatory mechanisms of pexophagy and CMA is largely associated with oxidative stress, so it will not be reiterated here.

3.1.2 Lipophagy and ER-Phagy

Although the regulatory role of ROS in lipophagy remains unclear, current research suggests that lipophagy can prevent lipid droplets from serving as substrates for peroxidation and being attacked by ROS by clearing excess lipid droplets, thereby averting lipotoxicity and the accumulation of peroxidation products [202,203]. Dysfunction of lipophagy, conversely, leads to lipid accumulation and oxidative damage [204,205]. The signaling pathways regulating this process basically overlap with those of macroautophagy and involve PI3K, mTORC1, Nrf2, and ULK1, among others [206,207]. As for ER-phagy, besides the previously mentioned FAM134B, other proteins such as testis-expressed protein 264 (TEX264), calcium-binding and coiled-coil domain-containing protein 1 (CALCOCO1), cell cycle progression gene 1 (CCPG1), and translocation protein SEC62 (Sec62) are considered important receptors in this selective autophagy process [208–210]. These receptors may be involved in binding to LC3, but the specific mechanisms require further investigation.

3.2 Maintenance of Metabolic Homeostasis

By clearing damaged mitochondria, proteins, lipids, or ROS, autophagy normally supports the maintenance of cellular metabolic homeostasis. In addition to the various forms described above, glycophagy also contributes to maintaining cellular homeostasis by degrading intracellular glycogen particles [211]. Currently, there is limited research on glycophagy. Its fundamental process relies on the recognition function of GABA type A receptor-associated protein-like 1 (GABARAPL1) and the degradation function of acid alpha-glucosidase (GAA) [212,213]. The PI3K-Akt pathway may negatively regulate it upstream [212,213]. Another noteworthy point is that, unlike the positive-promoting role of ROS in other forms of autophagy, a study by Fan et al. [214] reported that ROS may have an inhibitory effect on glycophagy.

3.3 Regulation of Antioxidant Signaling Pathways

In addition to the role of autophagy itself, autophagy can also activate antioxidant systems, and the two work synergistically to counteract oxidative stress. The primary antioxidant pathway in this process is mediated by Nrf2. As mentioned earlier, the Keap1-Nrf2-p62 pathway possesses a positive feedback amplification mechanism [110]. Specifically, when autophagy is activated, p62 accumulates and competitively inhibits Keap1, leading to further stabilization of Nrf2 levels, thereby activating this pathway [111]. At the post-translational modification level, besides the phosphorylation of p62 by ATM-CHK2 [108], ubiquitin-specific protease 13 (USP13) can also enhance the stability of p62 through deubiquitination, further activating the Nrf2-mediated antioxidant pathway [215]. Interestingly, beyond the core role of Nrf2, recent studies have found that the mitochondrial protein chromosome 15 open reading frame 48 (C15ORF48) can activate AMPK-mediated autophagy by reducing mitochondrial membrane potential and ATP levels [216]. Mechanistically, this autophagic induction upregulates intracellular glutathione levels in an ATG5/ATG7-dependent manner, as knockdown of either ATG5 or ATG7 abrogates the glutathione increase. The elevated glutathione levels subsequently reduce oxidative stress and promote cell survival [216]. This suggests a potentially broader connection between autophagy and redox regulation.

4 Cell Fate Decisions

As discussed earlier, oxidative stress and autophagy synergistically play a decisive role in determining cell fate. Specifically, oxidative stress and autophagy can regulate cellular adaptation and survival, mediate various modes of cell death, including apoptosis, pyroptosis, ferroptosis, and autosis, and also induce cellular senescence (Fig. 3).

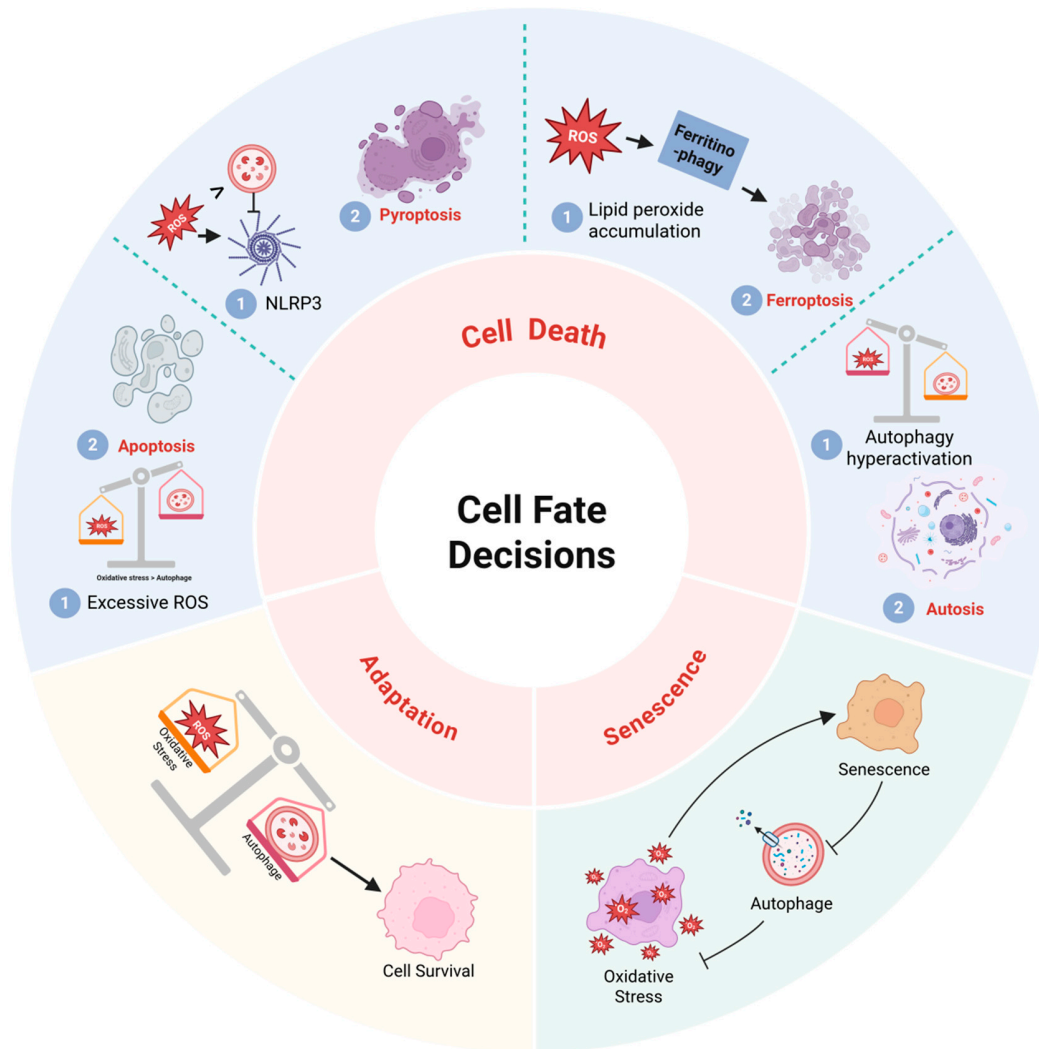


Figure 3: Cell Fate Decisions (created with BioRender). The balance between autophagy and oxidative stress dictates cell fate. A balanced state supports survival. Excessive autophagy relative to oxidative stress leads to autosis. Overwhelming oxidative stress drives apoptosis, pyroptosis, or ferroptosis. Oxidative stress-induced senescence inhibits autophagy, creating a vicious cycle that accelerates aging (Created in BioRender. Zhang D. (2026) <https://BioRender.com/hrw751e>). Abbreviations: ROS, reactive oxygen species; NLRP3, NOD-like receptor family, pyrin domain-containing protein 3.

4.1 Adaptation and Survival

Firstly, under normal conditions, autophagy constitutes a core defense network for cellular adaptation to oxidative stress and promotes survival by selectively clearing ROS-producing organelles and degrading oxidatively damaged proteins [7,217,218]. Relevant details have been thoroughly described in the preceding sections.

However, it is important to note that from a systemic perspective, ROS-mediated cell death and autophagy-promoted cell survival do not play absolutely positive or negative roles. This is particularly evident during tumor initiation and progression. In the early stages of carcinogenesis, elevated ROS levels may increase cancer risk, whereas autophagy exerts tumor-suppressive effects by clearing damaged organelles and maintaining genomic stability [219]. Relevant studies have demonstrated that a deficiency in

autophagy-related genes may increase cancer incidence [220,221]. During the solid tumor stage, however, cancer cells often exploit autophagy to cope with internal oxidative stress and external therapeutic pressures. As a result, tumor survival, therapeutic resistance, and metabolic adaptation are promoted [222,223]. For example, a study by Lock et al. [224] found that autophagy can promote RAS-driven cancer cell invasion by coordinating the production of multiple secretory factors, including interleukin-6 (IL-6), which may represent an important mechanism for tumor metastasis. Research by Chen et al. [225] demonstrated that autophagy mediated by ATG5 and Beclin-1 can resist the cytotoxicity caused by chemotherapeutic drugs, thereby promoting drug resistance in tumor cells. A recent study by Shao et al. [226] also points out from a therapeutic perspective that inhibiting protective autophagy in tumor cells can effectively treat tumors. Conversely, since the accumulation of ROS can induce cell death, promoting oxidative stress in tumor cells may represent an effective therapeutic strategy [226–228]. Notably, numerous studies have also indicated that inducing autophagy can eliminate drug-resistant tumor cells, potentially through excessive activation of autophagy to achieve cellular damage [228,229].

4.2 Apoptosis

Oxidative stress itself is a significant factor promoting apoptosis, and a large body of research has demonstrated that excessive ROS can induce apoptotic cell death [230,231]. Under normal conditions, autophagy also plays a protective role in this context, and disrupting autophagy can exacerbate ROS-induced apoptosis [232,233]. Regarding the interplay among these three factors, current research suggests that when autophagy fails to maintain cellular homeostasis, cells shift from autophagic signaling to apoptotic signaling, a process that is significantly influenced by ROS [234]. At the mechanistic level, a study by Cao et al. [235] found that mild oxidative stress enables DJ-1 to recruit and inhibit the activity of another MAPK family member, apoptosis signal-regulating kinase 1 (ASK1), consequently activating autophagy and maintaining cellular homeostasis. However, under excessive oxidative stress conditions, hyperoxidized DJ-1 dissociates from and activates ASK1, mediating apoptosis through the activation of p38 [235]. A recent study by Liu et al. [236] also confirmed the role of ASK1 in this process. Research by Tang et al. [237] focused on high-mobility group box 1 protein (HMGB1), revealing that oxidized HMGB1 can mediate apoptosis and enhance the effects of anticancer drugs, whereas reduced HMGB1 induces Beclin-1-dependent autophagy and increases tumor cell resistance. Furthermore, as mentioned earlier, a recent study by Lu et al. [122] suggests that FOXO1 may also serve as a critical switch regulating the conversion between autophagy and apoptotic signaling under oxidative stress conditions.

4.3 Pyroptosis

Pyroptosis is another form of programmed cell death, closely associated with the NOD-like receptor family, pyrin domain containing protein 3 (NLRP3) inflammasome [238]. Its core mechanism involves the cleavage of gasdermin D (GSDMD) by different inflammatory caspases to form GSDMD-N, which then pores in the cell membrane, leading to membrane rupture [239]. The activation of the pyroptosis pathway mainly includes the caspase-1-dependent canonical pathway and the caspase-4/5/11-dependent non-canonical pathway [239]. Regarding the canonical pathway, when oxidative stress occurs, excessive ROS can activate the NLRP3 inflammasome, which subsequently activates caspases and cleaves GSDMD to generate GSDMD-N, resulting in pyroptosis [240]. Therefore, autophagy, especially mitophagy, as a protective mechanism that clears ROS, can effectively inhibit the pyroptotic process [241]. Numerous therapeutic studies have shown that drugs promote autophagy to reduce oxidative stress and inhibit pyroptosis. These effects are likely mediated by multiple autophagy regulatory mechanisms, including

TFEB, the TRPML1-calcineurin axis, and the AMPK-mTORC1 axis [242–244]. Correspondingly, inhibiting autophagy can induce pyroptosis by exacerbating oxidative stress and activating the caspase1/GSDMD pathway [245]. Additionally, relevant studies have found that autophagy can directly degrade NLRP3 to inhibit pyroptosis [246]. As for the non-canonical pathway, lipopolysaccharide (LPS) can directly activate and cleave caspase-4/5 in humans or caspase-11 in mice, which in turn cleaves GSDMD to induce pyroptosis. Additionally, when GSDME is highly expressed in response to tumor necrosis factor or drug treatment, caspase-3 can trigger pyroptosis via the GSDME pathway [247]. Moreover, Lee et al. used a hydrophilic and lipophilic photocatalyst localized to the intracellular membrane to demonstrate that membrane-focused oxidative stress triggers non-canonical pyroptosis [248]. In addition, inhibition of NLRP3 can suppress autophagy by reducing levels of Beclin-1 and LC3-II [249]. This suggests that a bidirectional regulatory mechanism may exist between autophagy and pyroptosis.

4.4 Ferroptosis

As mentioned earlier, ROS can trigger ferroptosis through ferritinophagy mediated by NCOA4 or the AMPK-ULK1 pathway [172,173]. In addition to this pathway, research by Hirata et al. [250] has found that conjugated fatty acids (CFA) can activate CMA and selectively degrade glutathione peroxidase 4 (GPX4) through a LAMP2A-dependent pathway. GPX4 is a core enzyme responsible for clearing lipid peroxides, and its degradation leads to the accumulation of lipid peroxides, driving ferroptosis [250,251]. Park et al. [252] also reported that ROS-mediated autophagy can induce iron-dependent ferroptosis by degrading ferritin and inducing the expression of transferrin receptor 1 (TfR1), a process that can be reversed by inhibiting autophagy. Research by Jiang et al. [253] discovered that oxidative stress triggered by viral infection can mediate pexophagy through the ATM-PEX5-p62 axis, promoting the accumulation of labile iron and subsequent ferroptosis. Furthermore, in ischemic stroke models, either inhibition or excessive activation of post-ischemic autophagy can elevate ROS levels, while the interaction between ROS and lipids during ferroptosis further exacerbates ROS accumulation [254]. Elevated ROS can continue to induce autophagy and synergize with labile iron to trigger ferroptosis, forming a positive feedback amplification loop [255]. However, it is noteworthy that, contrary to the aforementioned mechanisms, relevant studies have indicated that inhibiting autophagy may exacerbate drug-induced oxidative stress, ferroptosis, and cellular damage [256]. Conversely, drugs may also alleviate oxidative stress and ferroptosis through autophagy promotion mediated by the Nrf2 signaling pathway [257]. This suggests that autophagy may exert different effects under varying conditions.

4.5 Autosis

Autosis is considered a form of programmed cell death resulting from excessive activation of autophagy [258]. Early studies suggested that autosis is induced by stress conditions such as starvation, ischemia, and hypoxia, and is regulated by Na^+ , K^+ , and ATPase [259]. However, current understanding of this type of cell death remains limited and controversial [37].

4.6 Senescence

Beyond survival and death, senescence represents another cellular fate under the interplay between oxidative stress and autophagy. Oxidative stress caused by ROS accumulation can damage lipids, proteins, nucleic acids, and organelles, ultimately leading to cellular senescence, which is one of the core mechanisms mediating aging [260]. Therefore, autophagy, by clearing ROS, can effectively inhibit the process of cellular senescence [261,262]. However, it is noteworthy that cellular senescence often results in impaired

autophagic function [263]. At the mechanistic level, Hoshino et al. [264] reported that with aging, p53 can inhibit PINK1/Parkin pathway-mediated mitophagy by suppressing the translocation of Parkin. Research by Suzuki et al. [265] found that in an oxidative stress-induced premature aging model, TFEB exhibits transient nuclear translocation followed by functional exhaustion, leading to insufficient autophagic flux and decreased lysosomal biogenesis. Chen et al. [266] also discovered that mTOR activity is increased in hematopoietic stem cells of aged mice, which may contribute to the inhibition of autophagy. Bleomycin activation generates ROS, which impair autophagic flux by preventing autophagosome elimination. This results in autophagolysosome accumulation, a higher percentage of SA-GLB1-positive cells, and cellular senescence [267]. These findings suggest a potential positive feedback amplification mechanism among oxidative stress, autophagy, and aging.

4.7 Autophagy-Oxidative Stress Balance Determines Cell Fate

The dynamic balance between autophagy and oxidative stress serves as a critical determinant of cell fate. Under physiological conditions, a well-maintained equilibrium enables cellular adaptation and survival, as autophagy effectively clears ROS-producing damaged organelles and maintains redox homeostasis. However, when this balance is disrupted, various pathological outcomes emerge. Specifically, when autophagic activity excessively outweighs oxidative stress, it may lead to autosis. Conversely, when oxidative stress overwhelms the protective capacity of autophagy, cells undergo apoptosis, pyroptosis, or ferroptosis, depending on the molecular context. Notably, cellular senescence is another key cell fate. The senescence induced by oxidative stress inhibits autophagy, and the resulting imbalance between oxidative stress and autophagy creates a vicious cycle that accelerates the aging process.

5 Conclusions

Autophagy and oxidative stress constitute a bidirectional, dynamic regulatory network that acts as a central molecular hub governing cell fate decisions. Oxidative stress drives autophagic initiation through multiple interconnected pathways, including direct oxidative modification of core autophagy-related proteins (ATG4, ATG3, ATG7, TFEB), modulation of canonical signaling cascades (mTORC1, AMPK, MAPK, Ca^{2+}), activation of transcription factors (Nrf2, FOXO), and induction of selective autophagy (mitophagy, pexophagy, CMA, ferritinophagy, ER-phagy). In turn, autophagy serves as a pivotal cytoprotective mechanism by eliminating ROS-producing damaged organelles, sustaining metabolic homeostasis, and reinforcing antioxidant signaling, thereby counteracting oxidative damage.

The balance between these two processes determines whether cells adapt and survive, undergo programmed death (apoptosis, pyroptosis, ferroptosis, autosis), or enter senescence. Dysregulation of this crosstalk contributes to the pathogenesis of diverse disorders, including cancer, neurodegeneration, inflammation, metabolic diseases, and aging. In the early stages of tumorigenesis, autophagy acts as a tumor suppressor by maintaining genomic stability; in established tumors, it promotes survival, metastasis, and therapeutic resistance. Impaired lipophagy leads to lipid droplet accumulation and promotes the progression of MASLD [167]. Meanwhile, excessive ROS or insufficient autophagy drives oxidative injury and cell death in degenerative and inflammatory conditions.

Collectively, understanding the molecular mechanisms underlying the interplay between autophagy and oxidative stress provides a theoretical foundation for the development of novel therapeutic strategies. For instance, recent preclinical studies have demonstrated that targeting autophagy in combination with immune checkpoint inhibitors can overcome ICI resistance by converting immune “cold” tumors into “hot” tumors, providing a concrete example of harnessing the autophagy–oxidative stress axis for cancer

therapy [268]. Furthermore, enhancing mitophagy by targeting the USP30 or PINK1 pathway represents a promising therapeutic strategy for neurodegenerative diseases, with related small-molecule agents having entered phase I clinical trials [269]. Targeting this axis offers substantial promise for the clinical intervention and management of a wide spectrum of human diseases. Potential strategies include enhancing protective autophagy, suppressing pathological autophagy, or modulating ROS levels.

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Conflicts of Interest: The authors declare no conflicts of interest.

Nomenclature

ROS	Reactive oxygen species
CMA	Chaperone-mediated autophagy
NADPH	Nicotinamide adenine dinucleotide phosphate
ATG	Autophagy-related proteins
LC3	Light chain 3
TFEB	Transcription factor EB
mTORC1	Mechanistic target of rapamycin complex 1
ERK2	Extracellular signal-regulated kinase 2
C212A	Cys-212 to alanine
TRPML1	Transient receptor potential mucolipin 1
MCOLN1	Mucolipin 1
SRXN1	Sulfiredoxin-1
MITF	Microphthalmia-associated transcription factor
AMPK	AMP-activated protein kinase
KPNA2	Karyopherin $\alpha 2$
ATM	Ataxia-telangiectasia mutated kinase
TSC2	Tuberous sclerosis complex 2
ULK1	Unc-51-like kinase 1
AKT	AKT serine/threonine kinase
PIP2	Phosphatidylinositol-4,5-bisphosphate
PIP3	Phosphatidylinositol-3,4,5-trisphosphate
PTEN	Phosphatase and tensin homolog
SIRT1	Sirtuin 1
MAPK	Mitogen-activated protein kinase
SERCA	Sarco/endoplasmic reticulum calcium ATPase
MCU	Mitochondrial calcium uniporter
mPTP	Mitochondrial permeability transition pore
CaM	Calmodulin

DAPK	Death-associated protein kinase
Nrf2	Nuclear factor erythroid 2-related factor 2
Keap1	Kelch-like ECH-associated protein 1
FOXO	Forkhead box O
IAPs	Inhibitor of apoptosis proteins
PINK1	PTEN-induced putative kinase 1
TAX1BP1	Tax1-binding protein 1
mtROS	Mitochondrial ROS
HIF-1 α	Hypoxia-inducible factor-1 α
BNIP3L	Bcl-2 interacting protein 3-like
LIR	LC3-interacting region
FUNDC1	FUN14 domain-containing 1
cGAS-STING	Cyclic GMP-AMP synthase-stimulator of interferon genes (STING) pathway
PEX	Peroxisomal biogenesis factor
MARCHF	Membrane-associated RING-CH protein
CMA	Chaperone-mediated autophagy
YAP1	Yes-associated protein 1
ER-phagy	Endoplasmic reticulum-selective autophagy
CHOP	C/EBP homologous protein
eIF2 α	Eukaryotic initiation factor 2 α
XBP1	X-box binding protein 1
TMX2	Thioredoxin-related transmembrane protein 2
GPX4	Glutathione peroxidase 4

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