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Review Paper

# The Roles of Autophagy in Oxidative Stress

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## ABSTRACT

Autophagy is an evolutionarily conserved, lysosome-dependent, intracellular degradation process that is essential for maintaining cellular homeostasis and adaptation to cellular stresses in eukaryotic cells. Oxidative stress refers to elevated intracellular levels of reactive oxygen species (ROS) that cause damage to lipids, proteins, and DNA. Oxidative stress has been linked to a myriad of pathologies. Autophagy can be involved in various biological processes such as programmed cell death, stress responses, removal of damaged organelles, and growth. The role of autophagy has been identified as a critical mediator in the pathological response to redox signaling. Autophagy is considered a main sensor of redox signaling. ROS are highly reactive molecules produced as byproducts of cellular metabolism, mainly by mitochondria. Mitochondrial ROS (mROS) can be beneficial or harmful to cells depending on their concentration and location. mROS at low physiological concentrations act as redox messengers in intracellular signaling, while overproduction of mROS causes oxidative damage to cellular components and ultimately leads to cell death. Hence, the balance of stress adaptation associated with autophagy and cell death is important for understanding pathogenesis related to redox signaling. Autophagy is an integral biological process critical for cellular and organismal homeostasis. It allows spatial reorganization and energy supply to cells through the regular destruction machinery of unnecessary or inefficient components. In this review, we focus on the basic mechanisms and functions of autophagy in response to oxidative stress and redox signaling in pathology.

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## 1. Context

Autophagy was first introduced by Christian de Duve in 1963 as a lysosome-dependent degradation process [1]. Autophagy is a catabolic process which is necessary to maintain cellular homeostasis by removing cellular molecules, such as protein aggregates and damaged organelles, through lysosomal digestion. Also, fasting induces a notable decrease in Rubicon, a negative regulator of autophagy, in adipose tissue, which is accompanied by an increased level of autophagy. Adipose-specific Rubicon-knockout mice exhibit systemic fat loss [2, 3, 4]. Rubicon regulates the balance between organelle biogenesis, protein synthesis, and cell clearance [5], and also participates in cell rearrangement during development and differentiation [1]. Autophagy occurs in conditions of glucose or amino acid deficiency, oxidative stress, hypoxia, and exposure to xenobiotics [1]. Autophagy has emerged as a critical mediator of pathological responses associated with reactive oxygen species (ROS) in cell signaling as well as cell damage [6]. Furthermore, autophagy in MSCs is regulated by ROS. Thus, in MSCs, the intracellular hypoxic microenvironment acts as a trigger for autophagy. Autophagy functions to maintain low levels of intracellular ROS. The intricate interplay between autophagy and ROS levels determines the fate of stem cell differentiation into preadipocytes. Conversely, the interplay between autophagy and ROS influences the transcriptional regulation of adipose regulatory factors, ultimately affecting the differentiation of preadipocytes. Recently, a research group established a leptin-deletion pig obesity model. Autophagy also plays a role in the development of diabetes, cancer, cardiovascular diseases, neurodegeneration, immune system diseases, and aging [7-10].

Mitochondria are the main source of ROS in cells [1, 11], and mitochondrial ROS (mROS) are generally produced as byproducts of bioenergetics during oxidative phosphorylation (OXPHOS) [1]. ROS are highly reactive metabolites of molecular oxygen ($O_2$), including superoxide anion ($O^{2-}$), and hydrogen peroxide ($H_2O_2$), which are formed by the reduction of oxygen electrons [1]. In the presence of transition metal ions, a more reactive hydroxyl radical (OH) is produced [12].

ROS can act as signaling molecules at the physiological level, which affect various cellular processes including proliferation, differentiation, programmed cell death, innate immunity, autophagy, redox signaling, calcium homeostasis, hypoxic stress responses, and reprogramming of stem cells [1]. On the contrary, excessive oxidative stress causes damage to proteins and cellular components, contributing to various pathologies [13].

Physiological ROS induces autophagy to maintain cellular homeostasis in various cell types, while redox signal regulation disorder can weaken autophagy activity, which is observed in various diseases [1, 14]. However, the underlying mechanism between autophagy and redox signaling needs to be further investigated.

## 2. Data acquisition

In the present study, we reviewed the recent studies on redox signaling in the regulation of autophagy. In addition, we discussed the impact of autophagy on mitochondrial function and its relevance to the pathology of chronic diseases.

## 3. Results

### 3.1. Molecular mechanism of autophagy

#### 3.1.1. Autophagy machine

There are three major types of autophagy: (1) macroautophagy, (2) microautophagy, and (3) chaperone-mediated autophagy (CMA) (Figure 1).

Macroautophagy is the best-known form of autophagy. All types of autophagy cause the destruction of damaged or non-functioning (obsolete) proteins and organelles in the cell. It is considered a non-selective cellular process; however, this type of autophagy controls the quality of cellular contents through selective processing (e.g. long-lived proteins, aggregated proteins, damaged organelles, and intracellular pathogens) [1]. The autophagy pathway begins with the nucleation of a double-membrane structure, the phagophore (also known as isolation or separation membranes), which elongates to sequester material and form a vesicle called an autophagosome. The autophagosome then fuses with the lysosome to break down the contents in the acidic environment. The broken down molecules are recycled into materials to regenerate new cell components [1].

Microautophagy is a process in which cytoplasmic materials are directly absorbed into lysosomes to be destroyed through involution, protrusion, or separation of the lysosomal or endosomal membrane [1, 15]. Endosomal membrane invagination, formed by the endosomal sorting complexes required for transport machinery (ESCRT), integrates sequestered material inside the lysosome [1].

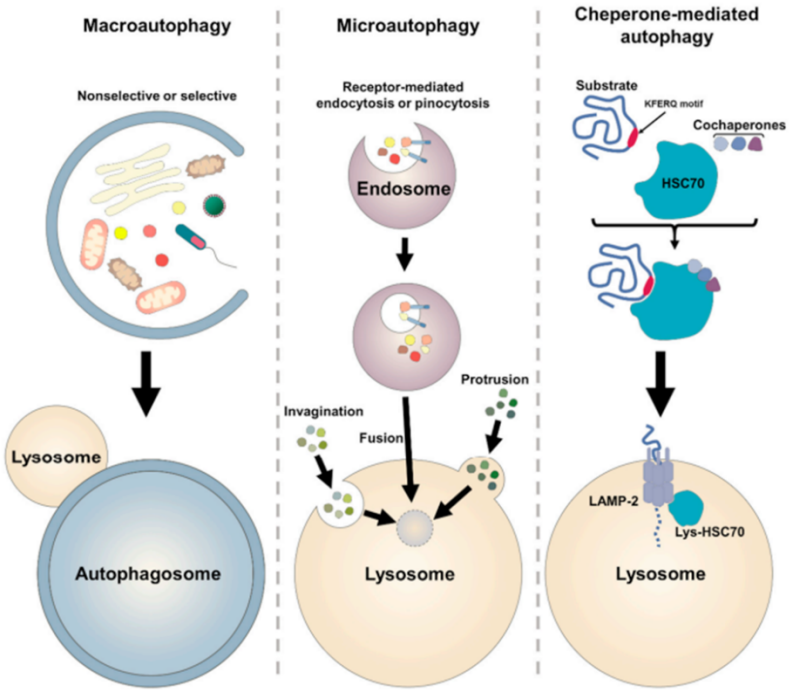


**Figure 1.** Overview of mammalian autophagy pathway

CMA is a type of autophagy that exists in various types of eukaryotic cells and tissues, but is not present in yeast [1]. A cytosolic chaperone, heat shock-associated protein 70 kDa (HSC70), recognizes CMA-targeted proteins that contain a pentapeptide motif that is biochemically related to KFERQ. The HSC70-target protein complex binds lysosome-associated membrane protein 2A (LAMP-2A) on the lysosome membrane, and then the target protein is transported into lysosomes for degradation [1]. The present study focused on the molecular and cellular mechanisms, regulation, and selectivity of mammalian macroautophagy (hereafter referred to as autophagy).

### 3.1.2. Molecular biology of autophagy

Induction of autophagy is stimulated by various cellular events such as nutrient deficiency, hypoxia, oxidative stress, pathogen infection, and endoplasmic reticulum (ER) stress [16]. Multi-protein autophagy complexes are required to induce autophagy, which is hierarchically assembled and acts at autophagosome formation sites called the pre-autophagosome structure or phagophore assembly site (PAS) [1]. In mammalian cells, the autophagy process is initiated by inactivation of the mechanistic/mammalian target of rapamycin (mTOR), which then requires the coordination of several multiprotein complexes [17, 18]. mTOR is a serine/threonine kinase that participates in a wide range of biological processes [1]. Functionally, it forms two different complexes: Mammalian target of rapamycin complex 1 (mTORC1) and mammalian target of mTORC2, which are structurally controlled by their modulators, such as the mTOR regulator-related protein Raptor. Rapamycin-insensitive mTOR companion molecule (Rictor) and SEC13 lethal protein 8 (LST8) are regulated through inter-complex and intra-complex loops [1]. However, mTORC2 is not responsible for controlling autophagy. Under normal conditions, mTORC1 directly phosphorylates autophagy-activating kinase UNC51-like 1 (ULK1), ULK2, and autophagy-related protein 13 (Atg13), which form an autophagy initiation complex through interaction with the interacting protein family. The 200 kDa focal adhesion kinases (FIP200) and Atg101 [1]. ULK1 interacts with Atg13 and FIP200 in its C-terminal region [19] and binds to Atg101 through the N-terminal of Atg13 [1]. In response to starvation or stress conditions, mTORC1 is dissociated from the ULKs complex through the phosphorylation of rheb and raptor by AMP-activated protein kinase (AMPK) [1]. Subsequently, ULk1/2 are rapidly dephosphorylated, and autophosphorylated, and Atg13 and FIP200 are phosphorylated [1]. Autophagic activation of the ULKs complex helps phagophore nucleation [20]. The phagophore is a small cup-like membrane structure that elongates (extends) to form a complete autophagosomal structure, although its origin is still debated [1, 21]. In advanced eukaryotic cells, it is accepted that under nutrient-deprived conditions,

phagophore nucleation occurs in the omegasome, which is morphologically similar to the Greek capital letter omega (Ω), a region of the ER enriched in phosphatidylinositol 3-phosphate [1].

Formation of an omegasome requires phosphatidylinositol 3-kinase class 3 (PI3KC3), which forms a complex with Beclin1, autophagy-regulated protein 1-Beclin1 (AMBRA1), general vesicular transporter factor (p115), p147, and ATG14L [1]. The ULKs complex leads to the activation of the PI3KC3 complex through the phosphorylation of Beclin1 and AMBRA1 [1, 22]. Activated PI3KC3 generates PI3P via phosphorylation of PI on the surface of the phagophore, which recruits dual FYVE domain-containing protein 1 (DFCP1) [1] and WIPI2 to mediate nucleation of phagophore growth [1]. The activity of the PI3KC3 complex is also controlled through interaction with cofactors such as UV resistance-related gene (UVRAG), Bax-interacting factor 1 (Bif1), and Beclin-1-interacting protein containing a cysteine-rich domain and RUN domain (Rubicon) [1].

The phagophore is elongated to become the autophagosome, which is regulated by two ubiquitin-like conjugation systems: Atg5-Atg12 conjugation and microtubule-associated protein light chain 3 processing [1]. Atg12 is activated by Atg7 (E1-like activating enzyme) and then conjugated to Atg5 by Atg10 (E2-like conjugating enzyme) [1]. The Atg5-Atg12 complex non-covalently interacts with Atg16L1 (E3-like ligase enzyme), which leads to the formation of Atg5-Atg12-Atg16L1 multiprotein complex [1]. Atg16L1 is recruited to the phagophore by physically binding to WIPI2 [1]. The Atg5-Atg12-Atg16L1 complex is associated with the induction of curvature in the elongated part of the phagophore through asymmetric insertion of processed LC3B [1]. The Atg5-Atg12-Atg16L1 complex is recruited to the outer membrane of the phagophore, essentially preventing premature fusion with the lysosome [1]. The C-terminal flanking region of nascent LC3B (proLC3B) is converted to LC3B-I through cleavage by Atg4, a cysteine protease. The exposed C-terminal glycine residue of LC3B-I is then activated by Atg7, and LC3B-I is converted to LC3B-II through phosphatidylethanolamine (PE) conjugation by Atg3 [1]. LC3B-II helps to close the autophagosomes [1], and the Atg5-Atg12-Atg16L1 complex is dissociated from the completed autophagosomes [1]. LC3B-II binds to the autophagosomal membrane until it fuses with the lysosome. Then, LC3B-II is cleaved and recycled on the outer surface of the membrane by Atg4 [1], while on the inner surface, it remains attached to the membrane to degrade substrates in the cargo [1]. An LC3-related protein, gamma-aminobutyric acid receptor-associated protein (GABARAP), has similar roles in the process of autophagosome expansion: autophagosome formation and substrate sequestration into double-membrane vesicles [1]. Phagophore development is also supported by the transmembrane protein ATG9, which helps deliver lipid bilayers to the nascent phagophore, further elongating the autophagosome before its closure [21, 23].

Binding of cellular contents intended for degradation to an engulfing autophagosome by autophagy adapter proteins such as sequestosome1 (SQSTM1/p62), nuclear dot protein 48 kDa (NDP48), neighboring gene (*NBR1*), BRCA1, and the autophagy-related FYVE protein (ALFY) is accelerated [1, 24, 25]. The completed autophagosome fuses with a lysosome to form the autophagolysosome through multiple proteins around the centrosome [26].

## 3.2. Redox signaling in autophagy

### 3.2.1. mROS and redox signaling

ROS are small, short-lived and highly reactive molecules that are usually formed as byproducts of oxygen metabolism in the mitochondrial electron transport chain (mETC) [1]. During OXPHOS, electron leakage from complexes I and III of mETC leads to the formation of partially reduced and highly reactive metabolites of molecular oxygen ($O_2$), including superoxide ($O^{2-}$) and $H_2O_2$, which are among the most important molecules in cellular signaling [1]. Mitochondrial superoxide ($O_2^{\cdot}$) is catalyzed to $H_2O_2$ by two dismutases, including Cu/Zn superoxide dismutase (Cu/ZnSOD) in the mitochondrial intermembrane space (IMS) and cytosol, and manganese-dependent superoxide dismutase (MnSOD) in the mitochondrial matrix [1]. $H_2O_2$ can be converted into OH by Fenton's reaction [1]. $O^{2-}$ in mitochondria also binds with hydrogen protons to form uncharged hydroperoxyl radical (.HOO), which reacts with unsaturated fatty acids of mitochondrial membrane lipids to produce lipid radicals [1]. Mitochondrial NO interacts with $O^{2-}$ to form RNS such as ONOO-, which causes cell dysfunction by nitrosylating S proteins [1]. Mammalian cells have numerous enzymes for $H_2O_2$ degradation, including peroxiredoxins (Prxs), glutathione peroxidases (Gpxs), thioredoxins (Trxs), and catalase (CAT). Mitochondrial $H_2O_2$ is primarily eliminated by the action of the Gpx1, Gpx2, and Gpx4; Prx3 and Prx5; and Trx2 systems, in which glutathione (GSH) is essential [1]. Oxidized GSH (GSSG) is reduced (regenerated) to GSH by glutathione reductase (GR) [1]. Oxidized Trx2 is also recycled by thioredoxin reductase (TrxR). $H_2O_2$ scavenging systems

depend on nicotinamide adenine dinucleotide phosphate (NADPH), which is regenerated by three mitochondrial matrix enzymes: NADP+-dependent isocitrate dehydrogenase (IDH), malate dehydrogenase (MDH), and nicotinamide nucleotide transhydrogenase (NNT) [1]. CAT catalyzes the decomposition of hydrogen peroxide into water and oxygen [1]. So far, it has been reported that ROS is associated with the induction of autophagy during the deprivation of nutrients such as glucose, amino acids, or serum [1]. Autophagy is activated in response to oxidative stress to protect cells from apoptosis [1], while the impairment of autophagy leads to the accumulation of oxidative stress [1]. In addition, antioxidant molecules moderately or completely suppress the initiation of autophagy [1]. Therefore, mROS not only activates but also inhibits autophagic signaling. In turn, mROS and autophagy are mutually affected. The relationship between mROS production and autophagic activation is summarized in Figure 2.

The autophagic process is divided into five distinct steps: Initiation, phagophore nucleation, autophagosome formation (elongation), autophagosome-lysosome fusion (autophagolysosome), and cargo degradation. Autophagy is stimulated by various cellular stress conditions such as nutritional starvation (nutrient deprivation) and oxidative stress. Under stress conditions, mTORC1 is inhibited, activating the ULKs complex, which includes ULK1/2, FIP200, ATG101, and ATG13. Subsequently, phagophore nucleation is induced by the activated ULKs complex, which is then mediated by the PI3KC3 complex. This complex consists of several proteins including Beclin1, AMBRA1, p115, p147, and ATG14L. The ULKs complex promotes the activation of the PI3KC3 complex through the phosphorylation of Beclin1 and AMBRA1. Activated PI3KC3 generates PI3P through phosphorylation of PI at the phagophore surface, which in turn recruits DFCP1 and WIPI2 for phagophore nucleation and extension. The phagophore is elongated to form the autophagosome, which is regulated by two ubiquitination-like conjugation systems: Atg5-Atg12 conjugation and LC3B-II conjugation. Atg12 is activated by Atg7, and then conjugated to Atg5 by Atg10. The Atg5-Atg12 complex interacts with Atg16L1. Atg16L1 is recruited to the phagophore through association with WIPI2. The Atg5-Atg12-Atg16L1 complex is involved in the curvature of the elongating phagophore through the asymmetric import of processed LC3B. The Atg5-Atg12-Atg16L1 complex is recruited to the outer membrane of the phagophore to prevent premature autophagosome-lysosome fusion. Nascent LC3B (proLC3B) is converted to LC3B-I via cleavage by Atg4. The exposed C-terminal glycine residue of LC3B-I is then activated by Atg7, and LC3B-I is converted to LC3B via PE conjugation by Atg3. LC3B-II binds to the autophagosomal membrane until autophagolysosome formation. Finally, the contents of the autophagolysosome are degraded by lysosomal enzymes.

### 3.2.2 Regulation of autophagy by redox signaling

Mitochondria are producers and targets of ROS and are inseparable from oxidative stress [1]. The accumulation of oxidative stress causes oxidation and damage to cellular components, including proteins, DNA, and lipids, which activates the autophagy process [1]. Mitochondrial $H_2O_2$ plays an important role in cell signaling, as it

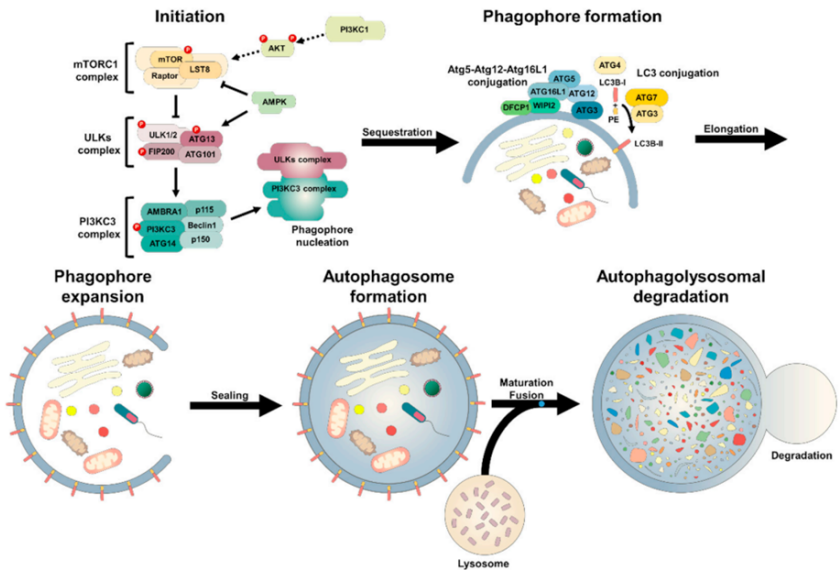


**Figure 2.** General process of autophagy.

is more stable than other ROS molecules and can easily diffuse into the cytosol [1, 27]. In response to nutrient deficiency, energetic stress probably increases the demand for ATP production from mitochondria, which subsequently increases electron leakage, and thus excess ROS are produced [1]. Indeed, mitochondrial $H_2O_2$ has long been involved in the pathway of autophagic signaling is involved. In response to food starvation, $H_2O_2$ enables the reduced form of Atg4 to convert LC3B-I to LC3B-II via thiol modification of cysteine 81 of Atg4, thus leading to increased autophagosome formation. However, the reduced form of Atg4 protease cleaves LC3 and inhibits autophagosomal membrane elongation, resulting in the suppression of autophagy [1]. Exogenous $H_2O_2$ also leads to oxidative stress and mitochondrial dysfunction, thereby inducing autophagy [1]. Treatment with $H_2O_2$ stimulates both autophagy and apoptosis in malignant glioma cells [1]. Treatment with TNFα increases the level of ROS and thus induces autophagy and cell death in Ewing sarcoma, which is also stimulated by treatment with exogenous hydrogen peroxide. These effects are reversed by chemical lipid radical scavengers or NF-κB pathway activation [1]. Similarly, lipopolysaccharides (LPS) induce autophagy through $H_2O_2$ generation [1]. $O^{2-}$ also plays a role in the induction of autophagy under conditions of starvation deficiency) of glucose and amino acids [1]. Endogenous cellular $O^{2-}$ levels are reduced in an mETC-deficient cervical cancer cell line even under starvation conditions, despite the absence of endogenous $H_2O_2$. Autophagy induced by starvation is significantly attenuated in these cells [1]. Nutrient starvation also activates AMP-activated protein kinase (AMPK), which inhibits mTORC1 activity and directly phosphorylates ULK1 at serine 317 (S317) and serine 777 (S777), resulting in the enhancement of autophagosome formation and autophagic flow [1, 28]. AMPK also phosphorylates ATG13 at Ser224 to regulate autophagy, which increases the intensity and duration of autophagy [29]. AMPK activation induced by starvation is reduced in cells with increased expression of MnSOD [1]. Treatment with compound C, an AMPK inhibitor, or inhibition of AMPK catalytic subunit α1 expression also prevented starvation-induced autophagy [1]. AMPK-activated autophagy is modulated by ROS [1], with involvement of AMPK upstream kinases, leading to the induction of autophagy [1]. $H_2O_2$ directly activates AMPK by oxidizing the cysteine residues of the alpha and beta subunits [1], or by oxidation of ataxia-telangiectasia mutant (ATM) protein kinase [1]. Oxidative stress-activated ATM initiates its downstream signaling, AMPK-tuberous sclerosis complex 2 (TSC2), to repress mTORC1, thereby inducing autophagy [1]. Additionally, in response to $H_2O_2$, AMPK is activated through phosphorylation at threonine 172 (T172) by liver kinase B1 (LKB1), which represses mTORC1 and thereby induces autophagy [1].

Nitric oxide (NO) is produced enzymatically from L-arginine by NO-synthase (NOS) during the oxidation process [1]. In autophagy signaling, NO has different effects depending on the cell type. NO inhibits autophagosome formation by weakening the activity of S-nitrosylated substrates such as c-Jun N-terminal kinase 1 (JNK1) and inhibitor of nuclear factor kappa B (IκB) subunit β kinase (IKKβ). Starvation-induced autophagy is activated by JNK1 in an mTOR-independent manner. JNK1 can phosphorylate Bcl-2 (B cell lymphoma) to disrupt its interaction with Beclin1, thereby inducing autophagy [1]. IKKβ also induces autophagy by increasing inhibition of mTOR, dependent on AMPK phosphorylation and Bcl-2 phosphorylation by JNK1 [1]. However, in glioma cells, inhibitory effects on the autophagy process were induced by treatment with NO donors, such as sodium nitroprusside (SNP) and S-nitrosoglutathione (GSNO), following LC3B-II accumulation [1].

It has been increasingly reported that the interplay between mROS and $Ca^{2+}$ signaling plays important roles in the regulation of autophagy. In response to hypoxia, mROS help translocate stromal interacting molecule 1 (STIM1) to the plasma membrane, which activates $Ca^{2+}$ release-activated $Ca^{2+}$ channels (CRAC), thereby inducing increased $Ca^{2+}$ influx and activation of calcium/calmodulin-dependent protein kinase 2 (CAMKK2). As a result, AMPK and autophagy are activated [1]. In addition, mROS activates the lysosomal $Ca^{2+}$ channel mucolipin 1 (MCOLN1), which leads to $Ca^{2+}$ release and calcineurin-dependent nuclear translocation of transcription factor EB (TFEB), which induces ATGs and lysosomal proteins [30]. Nuclear factor erythroid-related factor 2 (NRF2) is a prominent transcription factor that regulates gene expression of several genes encoding antioxidant and detoxification enzymes that maintain cellular redox homeostasis [1]. Kelch-like ECH-associated protein 1 (KEAP1) is a substrate adapted protein in a larger E3 ubiquitin ligase complex containing cullin 3 (CUL3) and Ring-box protein 1 (RBX1). It enables ubiquitination and proteasomal degradation of substrates, including NRF2 [1]. In response to oxidative stress, NRF2 dissociates from KEAP1 and binds to an antioxidant response element (ARE) in the nucleus to activate its target genes. In autophagic signaling, NRF2 induces *p62* gene expression, which triggers a response to oxidative stress, further activating the NRF2 protein and forming a positive feedback loop [1]. Similarly, Sestrin2 leads to further activation of NRF2 [1].

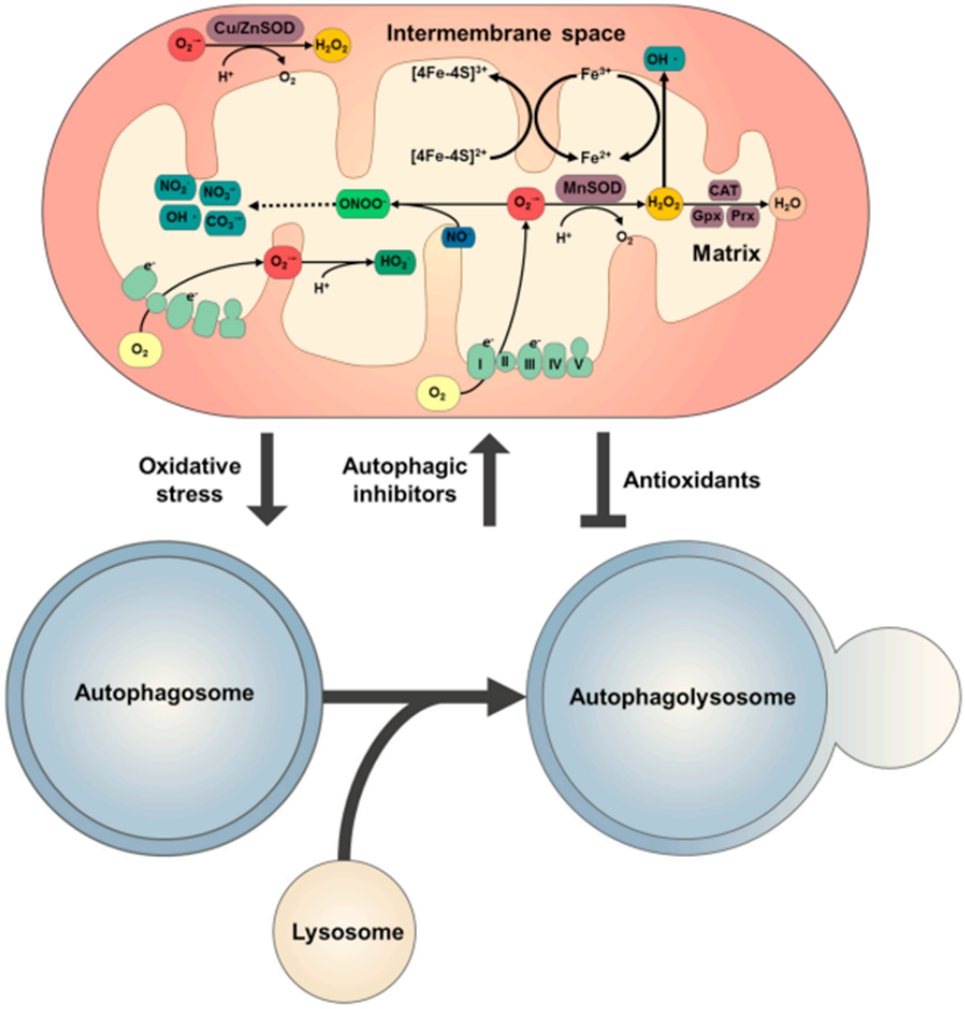


**Figure 3**. Interaction between mROS production and autophagy activation

Ubiquitinated p62 is phosphorylated, which increases its affinity for KEAP1 to facilitate autophagic degradation of KEAP1, thereby stabilizing NFR2 [1].

Tumor protein 49 (TP49 or P49)-induced glycolysis and apoptosis regulator (TIGAR), a target of TP49, interacts with hexokinase 2, which modulates the glycolytic pathway, thereby increasing NADPH production and decreasing the levels of ROS [1]. Inhibition of TIGAR causes the production of ROS and autophagy, while overexpression of TIGAR reduces autophagy induced by nutrient deprivation or hypoxia in a p49-independent manner [1]. TIGAR inhibition also induces mitophagy during ischemic injury, which is reversed by antioxidant treatment [1]. Damage-regulated autophagy modulator (DRAM), a p49-regulated gene, also induces autophagy [1]. In addition, Sestrin1 and Sestrin2-induced p49 induce autophagy through AMPK activation and thus inhibit mTORC1 [1].

### 3.3. Mitophagy

mROS are spontaneously generated during mitochondrial ATP production by OXPHOS, which leads to a certain degree of mitochondrial damage. Damaged mitochondria lead to a decrease in ATP and the release of cytoplasmic cytochrome c (Cytc) which ultimately causes caspase activation and triggers apoptosis [1].

To prevent cell death, dysfunctional mitochondria are consequently removed from the mitochondrial network through selective autophagy, known as mitophagy [2]. Mitophagy can limit the overproduction of mROS, supporting mitochondrial recycling and preventing the accumulation of dysfunctional mitochondria. Mitophagy is mainly regulated by the PTEN-induced parkin kinase 1 (PINK1) pathway, which is stimulated by mitochondrial membrane potential (MMP) depolarization. PINK1 is a Ser/Thr kinase that translocates to the outer mitochondrial membrane (OMM), where it is stabilized under

conditions of low MMP, thereby indicating mitochondrial depolarization [1]. PINK1 then recruits Parkin, which ubiquitylates proteins located in the OMM, such as VDAC1, leading to the recruitment of the autophagic machinery and the selective sequestration of ubiquitylated mitochondria into autophagosomes [2]. In addition, mitochondrial proteins BNIP3 and NIX contribute to mitophagy [1]. In response to oxidative stress after ischemia/reperfusion (I/R), BNIP3 is activated through homodimerization, which causes mitophagy [1]. NIX, an atypical BH3-onlyprotein, is required for mitophagy in developing erythrocytes. It directly recognizes GABARAP located in the autophagosome and subsequently initiates mitophagy [1]. ULK1 also regulates mitophagy by translocating to mitochondria to phosphorylate the FUN14 domain-containing 1 protein (FUNDC1), an OMM protein, that serves as a receptor for hypoxia-induced mitophagy [1]. The relationship between mROS and autophagy is shown schematically in Figure 3.

CU/ZnSOD and MnSOD (copper/zinc and manganese superoxidases) catalyze the conversion of the superoxide radical ($O^{2-}$) to $H_2O_2$ in the mitochondrial IMS and matrix, respectively. $H_2O_2$ is converted to water by CAT, as well as by a group of Gpxs and Prxs. $H_2O_2$ reacts with redox-active ferrous iron ions ($Fe^{2+}$) to produce hydroxy radical (.OH) through the Fenton reaction. Hydrogen peroxide can easily diffuse to other parts of the mitochondria or cytosol. The reaction between superoxide ($O^{2-}$) and nitric oxide (NO.) produces peroxynitrite (ONOO-), which decomposes into some highly oxidizing intermediates, including nitrogen dioxide ($NO_2$), OH, and carbonate radical ($CO_{3-}$), and finally forms $NO^{3-}$, a stable end product. Superoxide can also reduce ferric ion ($Fe^{3+}$) to ferrous ion ($Fe^{2+}$) in the iron-sulfur centers of proteins, leading to enzyme inactivation and simultaneous loss of $Fe^{2+}$ from enzymes. In addition, ($O^{2-}$) can form the more reactive hydroproxyl radical ($HO_2$) through protonation. Oxidative stress induced by mROS stimulates autophagy, and autophagy inhibitors such as chloroquine (CQ) and bafilomycin A1 (BafA1) can further increase mROS production. In contrast, antioxidants suppress autophagic activation.

## 4.3 Clinical applications

### 4.3.1. Cancer

Cancer cells show continuous proliferation as a common feature, avoiding growth suppression and resisting cell death, during which metabolic activity is increased through anaerobic metabolism, known as the Warburg effect [1]. This effect leads to the generation of ROS through incomplete OXPHOS. In addition, cancer cells are exposed to a microenvironment characterized by relatively low levels of nutrients, oxygen (hypoxia), and pH, which further promotes ROS production [1]. Therefore, the level of mROS is often increased in cancer cells compared to normal cells [1]. In addition, treatment with chemotherapy agents or radiation therapy induces the production of mROS in cancer cells [1]. Undoubtedly, autophagy is one of the defense mechanisms against oxidative stress. mROS-regulated autophagy exerts both beneficial and detrimental effects in cancer biology [1]. First, it is considered to have a tumor-suppressive effect during tumor initiation and malignancy progression, helping to remove damaged organelles and cells, thereby preventing uncontrolled cell proliferation and genomic instability [31]. Mutant p49 blocks the autophagy process by inhibiting the transcription of Sestrin1 and Sestrin2, which are AMPK activators [1].

Similarly, mTOR, a nutrient sensor, plays a role in suppressing autophagy and promoting proliferation in cancer cells. It is activated by glucose, amino acids, nucleotides, fatty acids, lipids, growth factors, and hypoxia [32]. One of these factors, phosphatidic acid (PA) —produced by the catalytic hydrolysis of phosphatidylcholine through phospholipase D (PLD) —can stimulate the activation of mTOR complex 1 (mTORC1) and thereby inhibit AMPK in cancer cells [1]. Therefore, the control of PLD can be important for the efficacy of chemotherapeutic agents by facilitating autophagic pathways. Reduced expression of Beclin1 is often observed in various human cancers, including breast, prostate, and ovarian cancer [1]. Loss of Beclin1 impairs autophagy induction and increases cancer cell proliferation. Similarly, attenuation of UVRAG or Bif-1 also promotes cancer cell proliferation by disrupting autophagosome formation [1]. Epidermal growth factor receptor (EGFR) inhibits autophagy by interacting with Beclin1, while administration of cetuximab suppresses EGFR by downregulating microRNA 216b (miR-216b), which in turn prevents the translation of Beclin1 [33].

On the other hand, autophagy plays a role in tumor progression, supporting the survival of cancer cells and the expression of oncogenes [1]. Although autophagy is inactivated during the initiation of tumorigenesis, it tends to promote tumor progression by allowing cancer cells to acquire chemotherapy resistance [1]. In addition, autophagy enables cellular components to be recycled to supply metabolic substrates and removes damaged mitochondria in cancer cells [1]. In particular, the NRF2 transcription factor is the main regulator of antioxidant response in cancer cells [34]. NRF2 activation is asso-

ciated with a poor prognosis in chemotherapy-resistant cancer patients due to reduced oxidative stress [34, 35]. In cancer metabolism, NRF2 facilitates the breakdown of glutamine to glutamate, which provides a nitrogen source for cancer cells to synthesize non-essential nucleotides and amino acids [1, 35]. In addition, in response to oxidative stress, NRF2 induces autophagy through its non-canonical signaling pathway involving *p62* gene activation, by which cancer cells avoid apoptosis [1]. NRF2 activation impairs the efficacy of cancer therapy by promoting autophagy. Therefore, a combination therapy to simultaneously target autophagy and NRF2 could be a promising strategy in cancer treatment. Cancer stem cells (CSCc) are a subset of cancer cells that have the ability to self-renew and are directly associated with tumor initiation, chemoresistance, and metastasis [1]. Autophagy (specifically mitophagy) also plays a role in the survival of cancer stem cells through redox balance [36]. Autophagy is required for the CD44+/CD24- phenotype in breast CSCs, which is reduced by LC3 or ATG12 deletion, or chloroquine treatment [1].

Autophagy plays an important role in the transformation of pancreatic cancer cells into CD132+ CSC-like cells (CD132+ cancer stem cells) under hypoxic conditions [1]. Similarly, autophagy-related proteins, such as Beclin 1, ATG5, and ATG7, are increased in CD132+ liver cancer stem cells under hypoxic conditions [1].

#### 4.3.2. Diabetes

Diabetes mellitus, especially type 2 diabetes (T2DM), is one of the most common metabolic diseases, which is primarily associated with hyperglycemia-induced mitochondrial dysfunction, insulin resistance, fat accumulation, and abnormal regulation of autophagy [1, 37]. ROS and oxidative stress are closely related to the onset of diabetes and its complications [1]. Hyperglycemia stimulates the diacylglycerol (DAG)-protein kinase C (PKC)-NADPH oxidase (NOXs) axis, leading to ROS accumulation, as has been suggested. It contributes to the development of diabetes [1]. However, mitochondria are also considered as the main source of ROS in diabetes, because glucose is the primary energy source for the ETC during OXPHOS [1]. In addition, altered levels of antioxidant enzymes have been observed in diabetic patients with increased oxidative stress [1]. Autophagy (specifically mitophagy) has cellular protective roles against insulin resistance and obesity by reducing oxidative stress caused by mROS [1]. Autophagy is suppressed by chronic hyperglycemia and subsequent insulin resistance. The β-pancreatic cell line, INS-1 cells, show apoptotic cell death due to autophagy disruption following cathepsin inhibitor treatment under high-glucose conditions [1]. Autophagy is involved in cell structure and function: Genetic ablation of Atg7 in pancreatic β-cells causes islet degeneration and impaired insulin secretion, and Atg7 mutant mice show impaired glucose tolerance and hypoinsulinemia [1]. In addition, autophagy is inhibited in streptozotocin-induced diabetic mice under high-glucose conditions [1]. In diabetic hearts, autophagy is reduced through inactivation of AMPK and subsequently the JNK1-Bcl2 pathway, which fails to inhibit mTORC1 [1]. A decrease in autophagic proteins has been observed in the skeletal muscle of insulin-resistant T2DM patients [40]. In adipose tissue, autophagy is increased due to weak mTORC1 activity [1]. In the liver, autophagy is inhibited in the presence of insulin resistance and hyperinsulinemia [1]. Although autophagy clearly has a beneficial role in insulin resistance and T2DM, the exact underlying mechanism in T2DM remains to be investigated and elucidated in detail. Autophagy is also involved in lipotoxicity. Cholesterol-induced ER stress increases autophagic flux in pancreatic β-cells and facilitates the conversion of LC3B-I to LC3B-II. Cholesterol-induced autophagy was reduced by treatment with the chemical chaperone 4-phenylbutyrate (4-PBA) [38]. Autophagy induced by ER stress can be regulated independently of mTORC1. In addition, glucolipotoxicity induces autophagy through TFEB in primary pancreatic β-cells [39].

#### 4.3.3. Neurodegeneration

Neurodegenerative diseases are closely related to specific protein accumulations and abnormal autophagy processes. Therefore, autophagy plays important roles in neurodegenerative pathology and treatment [1]. Autophagy is related to the maintenance and integrity of nerve cells due to the post-mitotic nature of neurons [1]. It also reduces oxidative stress by removing unnecessary or damaged organelles and abnormal protein accumulations in damaged neurons, which is beneficial for cell survival [1]. Emerging roles of autophagy, including antioxidant defense mechanisms for neural homeostasis, have been suggested [40]. It has been proven that autophagy dysfunction caused by excessive oxidative stress is involved in the development and progression of neurological diseases [1]. Alzheimer's disease (AD) is one of the most common types of dementia, characterized by extracellular amyloid beta (Aβ) plaques and intracellular tau (τ) protein aggregates. Aβ is produced by the enzymatic cleavage of amyloid precursor protein (APP) [1]. Oxidative stress is important in the pathogenesis of AD and is related to the formation of Aβ plaques, the phosphorylation of τ protein, and the formation of

neurofibrillary tangles [41]. Autophagy participates in Aβ degradation [42]. The accumulation of Aβ leads to disruption of the fusion between autophagosomes and lysosomes [1]. Autophagy is involved in the release of Aβ into the extracellular space, where it forms plaques. Deletion of ATG7 in APP transgenic mice leads to a decrease in Aβ secretion and plaque formation [1]. A mutation in Presenilin1 (PSEN1), which is involved in APP cleavage, shows one of the main features of AD [1] and leads to impaired lysosomal function and AB accumulation [1]. PSEN1 also acts as an ER chaperone for the V0a1 subunit of the lysosomal V-ATPase, the mutation of which disrupts the maturation of the lysosomal v-ATPase, thereby increasing lysosomal pH [1]. Accumulation of τ protein in intracellular neurons is also one of the prominent pathologies of AD. Hyperphosphorylated τ protein colocalizes with LC3B-II and p62 in patients with AD as well as other neurodegenerative disorders such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) [42]. In addition, aberrant τ proteins impair axonal vesicle transport through complex inhibition, thereby increasing the number of autophagosomes in AD [1]. Recently, it has been reported that the flow of autophagy and stress granule dynamics can be regulated by RNA-binding proteins (RBPs) such as T cell intracellular antigen 1 (TIA-1), poly(A)-binding protein (PABP), Ras GTPase-activating protein–binding protein 1 (G3BP1), fused in sarcoma (FUS), and DEAD-box helicase 5 (DDX5) [7]. The level of these proteins increase in response to chronic stress and glucocorticoid exposure. Furthermore, these RBPs appear to be associated with oxidative stress responses and may serve as therapeutic targets to prevent stress granule formation in AD and other tau-related pathologies.

As a movement disorder, Parkinson's disease (PD) is characterized by the loss of dopaminergic neurons in the substantia nigra [43], which is pathologically associated with mitochondrial oxidative stress, dysfunction, and protein accumulation [1]. In PD, the autophagy pathway is disrupted, leading to the accumulation of abnormal proteins [1]. Several genes are associated with the early pathology of PD, including *PINK1*, *Parkin*, *α-synuclein*, and glucocerebrosidase (*GBA*) [1]. Autosomal recessive PD is associated with mutations in PINK1 and Parkin, which impair the degradation of damaged mitochondria through mitophagy activation [44]. Genetic ablation of Pink1 leads to disruption of striatal mitochondrial respiration and increased vulnerability to oxidative stress in nerve cells [1]. Similarly, Parkin deletion impairs striatal mitochondrial function and synaptic plasticity [1]. PD is also characterized by intracytoplasmic inclusions (Lewy bodies) present in the neuronal nucleus, which consist of an insoluble protein aggregate of α-synuclein that are normally degraded by CMA. However, mutant α-synuclein has a high affinity for lysosome-associated membrane protein 2A (LAMP-2A), which prevents lysosomal uptake of substrates, thereby inhibiting CMA-dependent degradation [1]. Independent of the protein's mutation status, elevated levels of α-syncline disrupt autophagy by causing mislocalization of ATG9 [1]. In addition, GBA is one of the genetic risk factors for PD, and its homozygous mutations cause lysosomal storage disorders, including Gaucher disease. Loss of GBA function leads to the accumulation of its substrate, glucosylceramide, in the lysosome, whichdisrupts autophagy through lysosomal dysfunction [42].

Huntington's disease (HD) is a neurological disorder caused by mutated proteins with expanded polyglutamine (polyQ) repeats [1]. The pathogenesis of HD is strongly influenced by neuronal autophagy dysfunction. Huntingtin (HTT) is the most studied polyQ protein, and its mutation in HD impairs cargo recognition by autophagosomes [1]. Wild-type HTT acts as a scaffolding protein involved in the recruitment of several autophagy-related proteins to the autophagosome during selective autophagy [1]. Loss of huntingtin reduces autophagosomal transport, thereby impairing the degradation of substrates [1]. Mutant huntingtin also inhibits a striatal-specific protein, Rhes, which interacts with Beclin1 to regulate autophagy [1].

#### 4.3.4. Cardiovascular diseases

Autophagy at basal levels is necessary to maintain cellular homeostasis in cardiomyocytes [1]. Cardiomyocytes depend on the removal of damaged proteins and dysfunctional organelles for maintenance and survival [1]. In particular, cardiomyocytes are highly enriched in mitochondria. When damaged or exhausted, these organelles are rapidly eliminated by autophagic degradation a process known as mitophagy. Disturbance in the autophagic degradation pathway causes high levels of mROS accumulation, which leads to the buildup of protein aggregates, dysfunctional mitochondria, and pathological remodeling of the heart [1]. Ischemia/reperfusion (I/R) injury is also associated with these processes [45]. Danon disease (also known as glycogen storage disease type IIb) is an X-linked lysosomal and glycogen storage disorder associated with cardiac hypertrophy. In Danon disease, LAMP-2, which is required for autophagosome-lysosome fusion, is genetically deficient [1]. In models of transverse aortic constriction (TAC), deletion of myocardial Atg5 causes cardiac hypertrophy, left ventricular dilation, and contractile dysfunction [1]. In addition,

knockdown of Beclin 1 inhibits autophagosome formation and consequently increases cell death in a mouse model of I/R [1]. In chronic ischemia, autophagy and mitophagy are required for cardiomyocyte survival to avoid tissue damage [1]. Vacuolar assembly of the integral membrane protein VMA21 ATPase, a V-ATPase chaperone, together with V-ATPase, facilitates the proton pump and acidifies the organelles, which causes a lysosomal pH shift and thereby interrupts autophagolysosomal degradation in X-linked myopathy with excessive autophagy. Conversely, autophagy may play a detrimental role in cardiovascular disease. Haploinsufficient Beclin-1 attenuates cardiac pathological remodeling and counteracts TAC-induced overload stress. Conversely, heart-specific Beclin1 overexpression enhances the pathological remodeling response. In addition, inhibition of Beclin1 by the cardiac peptide urocortin causes cardiomyocyte weakening and cell death by inducing excessive autophagy in I/R injury [1].

### 5.3. Immunity

Autophagy plays an important role in immunity, which consequently affects the pathogenesis of inflammation [1]. Autophagy destroys invading pathogens through a selective xenophagy pathway in response to various types of infections [1]. Adapter proteins such as NDP48, optineurin, and p62 play a role in xenophagy by binding to ubiquitinated proteins and directing autophagic proteins forward, which is related to various aspects of adaptive and innate immunity including antigen presentation, cytokine and interferon production, and lymphocyte development. Microbial infection activates the host's immune system, where autophagy can act as part of innate immunity, thereby eliminating invading pathogens [1]. Inflammasomes are cytosolic protein complexes that form in response to invading pathogens and lead to the subsequent processing and release of interleukin-1 alpha, interleukin-1 beta, and interleukin-18. Inflammasomes contain an apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), pro-caspase-1, and proteins for sensing microbial products, including the nucleotide oligomerization domain (NOD)-like receptor family of proteins, which include NLRP1, NLRP3 and NLRC4. MROS and lysosomal damage can cause the activation of inflammation, which is inhibited by clearing the damaged organelles through autophagy. The antimicrobial role of autophagy is also controlled by Th2/Th1 helper T cell polarization. Th1 cytokines induce phagocytosis, while Th2 cytokines prevent it [1]. Autophagy is activated through sensing by Toll-like receptors (TLRs), by which invading pathogens are destroyed. Crohn's disease is a type of inflammatory bowel disease (IBD) that is closely related to autophagy dysregulation [1] which is characterized by a single nucleotide polymorphism (SNP) in ULK1. Therefore, the autophagy process is impaired during disease. Mutations in the leucine-rich domain of nucleotide oligomerization domain-containing protein 2 (NOD2) are also associated with Crohn's disease. NOD2 recruits ATG16L to the plasma membrane during bacterial invasion. Mutations in NOD2 perpetuates inflammation through disruption of autophagy induction and antigen presentation [1]. The SNP in ATG16L also reduces autophagosome formation in the disease. An autophagy-related protein, microtubule-associated protein 1S (MAP1S), interacts with LC3B and is involved in autophagosome formation, which promotes survival of intestinal epithelial cells through Wnt/β-catenin signaling in Crohn's disease [1]

## 4. Conclusion

In the present study, we gave an overview of the functions of mROS in autophagy and other pathological states. mROS are inevitably produced as byproducts of bioenergetics, which in turn are part of cellular nature. In addition, they are directly or indirectly responsible as messengers for various cell signaling pathways. Autophagy is an integral biological process critical for cellular and organismal homeostasis. It allows spatial reorganization and energy supply to cells through the regular destruction machinery of unnecessary or inefficient components. Evidence suggests that mROS are upstream modulators of autophagy. Therefore, mROS and autophagy are very important for maintaining cell homeostasis and viability. Autophagy primarily has beneficial effects on mROS, which sense oxidative stress and thereby eliminate damaged or expired cellular components. In pathology, a number of studies have also demonstrated the interrelationship between redox signaling and autophagy in the progression of various diseases. Excessive production of ROS causes the accumulation of oxidative stress, which is certainly involved in chronic pathologies such as metabolic, neurodegenerative, cardiovascular, and immune diseases, as well as cancers. Disruption of the autophagy process causes mitochondrial dysfunction and thus increases the production of mROS. Certainly, autophagy tends to reduce oxidative stress. However, depending on the cellular or tissue environments, autophagy in response to mROS production can exacerbates diseases. In this aspect, autophagy repair may be a therapeutic strategy for oxidative stress-related diseases. In summary, mROS-induced autophagy can be a cellular protective mechanism that reduces oxidative stress or a destructive process. Therefore, we still need

to elucidate the regulatory mechanisms of autophagy in redox signaling across various cellular physiologies and pathologies. Proper regulation of autophagy is crucial for the development of future therapeutic strategies for chronic pathologies related to the oxidative stress response, based on pharmacological modulation.

## Ethical Considerations

### Compliance with ethical guidelines

This article is a review study with no human or animal sample.

### Data availability

The data that support the findings of this study are available upon request from the corresponding author.

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### Author contributions

Conceptualization, study design, writing, and final approval: All authors; Data acquisition, analysis and interpretation: Mahboobeh Talebi Mehrdar.

### Conflict of interest

The authors declared no conflict of interest.

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