Oxidative Stress and Autophagy Postprint

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Abstract

Autophagy is a process whereby cells degrade proteins and organelles through lysosomes, which helps cells adapt to various adverse stimuli and plays a crucial role in maintaining intracellular homeostasis and self-renewal. Oxidative stress is a pathological state resulting from the disruption of homeostasis between oxidant and antioxidant systems. Numerous studies have demonstrated that reactive oxygen species generated during oxidative stress can induce autophagy, which in turn alleviates oxidative stress-induced damage, thereby protecting cell survival. This review primarily summarizes the formation process of autophagy, the mechanisms by which oxidative stress induces autophagy, and the pathways through which autophagy mitigates oxidative stress, aiming to provide a theoretical foundation for alleviating oxidative stress through autophagy regulation in livestock production.

Full Text

Oxidative Stress and Autophagy

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Abstract

Autophagy is a lysosome-dependent process through which cells degrade proteins and organelles, enabling them to adapt to various adverse stimuli and playing a crucial role in maintaining intracellular homeostasis and self-renewal. Oxidative stress is a pathological state arising from disruption of the balance between oxidant and antioxidant systems. Numerous studies have demonstrated that reactive oxygen species (ROS) generated during oxidative stress can induce autophagy, which in turn alleviates oxidative damage and protects cell survival.

This review summarizes the autophagic process, the mechanisms by which oxidative stress induces autophagy, and the pathways through which autophagy mitigates oxidative stress, aiming to provide a theoretical basis for alleviating oxidative stress in livestock production through autophagy regulation.

Keywords: oxidative stress; autophagy; Atg; reactive oxygen species; oxidative damage

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Reactive oxygen species (ROS) are the primary free radicals in organisms, including hydroxyl radicals (· OH), superoxide anions (O ·), hydrogen peroxide (H O), and derived organic peroxide radicals such as alkoxy (RO ·) and peroxy (ROO ·) radicals. As products of normal redox reactions, ROS participate in bactericidal activity, detoxification, and regulation of various metabolic pathways [1]. Under normal physiological conditions, the antioxidant system promptly scavenges ROS to maintain redox balance. However, when organisms encounter stressors or pathogenic infections, ROS production exceeds cellular antioxidant defense capacity, leading to redox imbalance. Excessive ROS in tissues or cells triggers oxidative stress, causing oxidative damage such as DNA hydroxylation, protein denaturation, and tissue injury. To prevent further damage, organisms activate defensive responses, including enhanced antioxidant enzyme activity and initiation of lysosomal degradation pathways. Moreover, recent studies have shown that ROS produced during oxidative stress can induce autophagy [2]. Autophagy is a "self-eating" phenomenon widely present in eukaryotic cells that degrades long-lived proteins and damaged organelles, representing a critical cellular repair pathway for nutrient recycling and survival under stress conditions [3]. Research indicates that autophagy can remove mitochondria, endoplasmic reticulum, peroxisomes, and proteins damaged by oxidative stress, thereby retarding cell death. Conversely, blocking autophagy leads to accumulation of toxic protein aggregates and mitochondrial dysfunction, exacerbating oxidative stress [4-6]. Thus, a close relationship exists between oxidative stress and autophagy.

1.1 Classification of Autophagy

Based on differences in substrate type, transport mechanism, and regulatory pathways, autophagy is classified into macroautophagy, microautophagy, and chaperone-mediated autophagy [3]. Macroautophagy involves the formation of a double membrane derived from the endoplasmic reticulum that engulfs cargo to form an autophagosome, which then fuses with lysosomes for content degradation—this is commonly referred to as autophagy. Microautophagy involves direct invagination of the lysosomal membrane to engulf and degrade materials. Chaperone-mediated autophagy refers to the process where cytosolic soluble proteins bind to chaperones before being translocated into the lysosomal lumen for degradation. While autophagy was long considered non-selective, deeper investigations have revealed that under specific conditions, autophagy can selectively

degrade particular macromolecules and organelles. This selective autophagy includes the Cvt pathway (cytoplasm-to-vacuole transport), pexophagy (peroxisome autophagy), mitophagy (mitochondrial autophagy), and reticulophagy (endoplasmic reticulum autophagy) [7].

1.2 Autophagy Formation and Signal Transduction

The autophagic process comprises six stages: induction, vesicle nucleation and elongation, cargo recognition, autophagosome formation, autophagosome-lysosome fusion, and cargo degradation [3]. Various factors can induce autophagy, including nutrient deprivation, microbial infection, cellular damage, protein misfolding or aggregation, and oxidative stress [8-9]. Upon autophagic signaling, a "lipid-like" membrane structure called a phagophore forms in the cytoplasm. The phagophore elongates to engulf cargo, forming a sealed double-membrane autophagosome that fuses with lysosomes to form an autolysosome, where the engulfed materials are degraded. The resulting fatty acids and amino acids are transported back to the cytoplasm for recycling. Over 30 autophagy-related genes (Atg) participate in this process, primarily mediated by four protein complexes [10].

1.2.1 ULK1 Complex (ULK1–Atg101–FIP200–Atg13) The ULK1 complex (ULK1 being a homolog of Atg1) participates in the induction phase and is mainly regulated by mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK) signaling. mTOR acts as a sensor for intracellular amino acids, ATP, and hormones. Under nutrient-rich conditions, mTOR phosphorylates Atg13, reducing its affinity for ULK1 and decreasing ULK1 kinase activity. During starvation or stress, mTOR activity is suppressed, Atg13 becomes dephosphorylated, and the ULK1 complex is activated and translocates from the cytoplasm to the endoplasmic reticulum to induce phagophore formation [11]. AMPK is a crucial positive regulator of autophagy that can directly inhibit mTOR activity to induce autophagy. Additionally, phosphorylated AMPK can activate the TSC1-TSC2 complex to indirectly suppress mTOR activity, thereby inducing autophagy [12]. AMPK can also bind directly to the ULK1 complex and phosphorylate ULK1 to promote autophagic membrane formation [13].

1.2.2 Class III Phosphatidylinositol 3-Kinase (PI3K) Complex (Beclin1-VPS34-Atg14) The class III PI3K complex participates in autophagosome nucleation. The catalytic subunit VPS34 of class III PI3K forms a complex with Beclin1 (a homolog of Atg6) and Atg14. Activated by the ULK1 complex, this complex localizes to the endoplasmic reticulum and generates PI3P, which recruits effector molecules containing PI3P-binding domains such as DFCP1 (double FYVE-containing protein 1) and WIPI family proteins (WD-repeat domain proteins interacting with phosphoinositides) to mediate phagophore formation [14]. Beclin1 is considered a key factor in autophagy formation. Besides regulating the lipid kinase activity of VPS34

(vacuolar protein-sorting 34), Beclin1 is a multifunctional protein containing a BH3 domain that can bind anti-apoptotic proteins such as Bcl-2 and Bcl-xL, thereby exerting dual regulatory roles in autophagy and apoptosis. Funderburk et al. [15] found that the anti-apoptotic protein Bcl-2 inhibits autophagy by binding to Beclin1 and disrupting its interaction with VPS34.

1.2.3 Atg12-Atg5-Atg16 Ubiquitin-Like Conjugation System The Atg12-Atg5-Atg16 complex participates in phagophore elongation. Atg12 and Atg5 are conjugated via covalent bonds through the E1-like enzyme Atg7 and E2-like enzyme Atg10. This conjugate non-covalently binds to Atg16 to form the Atg12-Atg5-Atg16 complex, which translocates to the phagophore to mediate membrane elongation.

1.2.4 LC3-II-PE Ubiquitin-Like Conjugation System The LC3-II-PE complex participates in phagophore elongation and autophagosome formation. Mammalian microtubule-associated protein 1 light chain 3 (LC3, a homolog of Atg8) is cleaved by Atg4 into soluble LC3-I. In a reaction mediated by Atg7 and the E2-like enzyme Atg3, LC3-I conjugates with phosphatidylethanolamine (PE) to form LC3-II-PE, which participates in phagophore membrane elongation and is symmetrically distributed on both the inner and outer membranes of autophagosomes. When autophagosomes fuse with lysosomes, intralysosomal LC3-II is degraded by hydrolases. Therefore, LC3-II levels or the LC3-II/LC3-I ratio reflect autophagic activity and serve as a classic autophagy marker [16]. In selective autophagy, LC3-II-PE can deliver cargo to the autophagosome lumen via p62 (also called SQSTM1, a multifunctional ubiquitin-binding protein). p62 acts as an adaptor protein that links LC3 to ubiquitinated cargo through its LIR domain (LC3-interacting region) and UBA domain (ubiquitin-associated domain), respectively. This ternary complex targets cargo into autophagosomes for lysosomal degradation [17]. p62 degradation is an important indicator of autophagic flux [16].

2 Mechanism of ROS-Induced Autophagy Formation

ROS are direct initiators of oxidative stress, with approximately 90% of ROS originating from the mitochondrial inner membrane respiratory chain. Electron leakage from the mitochondrial respiratory chain generates superoxide radicals, which subsequently produce ROS. Numerous studies have shown that mitochondria-derived ROS are the primary inducers of autophagy under oxidative stress [2,4,18]. ROS can induce autophagy by mediating various signaling pathways involved in autophagy formation.

During the induction phase, ROS can trigger autophagy by regulating mTOR, a key negative regulator of autophagy whose activity is controlled by multiple signaling pathways including PI3K-Akt and AMPK. Excessive ROS can inhibit the PI3K-Akt-mTOR pathway to activate autophagy [19]. In isolated guinea pig hearts perfused with sevoflurane, ROS induced autophagy by activating

AMPK and inhibiting the mTOR signaling pathway [20]. During autophagosome formation, ROS primarily regulate autophagy by inhibiting Atg4 activity. ROS-mediated inactivation of Atg4 causes LC3-II accumulation and increased autophagosome formation. Under starvation conditions, cells generate large amounts of ROS, particularly H O , which oxidizes and inhibits Atg4, thereby preventing LC3-II delipidation and ensuring phagophore elongation [21]. Additionally, ROS can promote cargo ubiquitination, enabling ubiquitinated cargo to bind with p62 and LC3-II for autophagosomal degradation [22].

Furthermore, ROS can regulate autophagy through the mitogen-activated protein kinase (MAPK) signaling pathway. MAPKs, consisting of sequentially activated kinases, play crucial roles in cell proliferation, differentiation, stress adaptation, and apoptosis. The major MAPK subfamilies include c-Jun N-terminal kinase (JNK), p38 kinase, and extracellular signal-regulated kinase (ERK). MAPKs can regulate autophagy-related gene expression by modulating transcription factors such as activator protein-1 (AP-1), forkhead box transcription factor O (FoxO), and nuclear factor-kappa B (NF- B). Many exogenous substances, including ROS, can activate autophagy via MAPK signaling [23]. Studies have demonstrated that ROS induce autophagy in cultured mouse mesenchymal stem cells (MSCs) through the JNK pathway [24]. The p38 pathway participates in ROS-activated autophagy by regulating Atg7 expression during autophagosome-lysosome fusion and E3 ligase expression during protein ubiquitination, processes that depend on FoxO transcriptional activation [25]. Additionally, arsenite can induce autophagy through ROS-mediated activation of the ERK1/2 pathway [26].

3 Pathways of Autophagy Alleviating Oxidative Stress

3.1 Clearance of Damaged Proteins and Organelles and Regulation of Mitochondrial Function During oxidative stress, mitochondrial ROS homeostasis is disrupted, and excessive ROS accumulation causes lipid peroxidation of membranes, leading to structural damage of cellular, mitochondrial, and endoplasmic reticulum membranes. Studies have shown that protein and organelle damage caused by oxidative stress can induce dissociation of Beclin1 from the anti-apoptotic protein Bcl-2, allowing formation of the Beclin1-VPS34-Atg14 complex that initiates membrane nucleation and autophagosome formation to clear damaged components [27].

Persistent severe oxidative stress causes mitochondrial damage, and mitophagy serves as the primary pathway for removing damaged mitochondria. Damaged mitochondria undergo depolarization and fragmentation, followed by clearance via mitophagy. This process is mainly regulated by PTEN-induced putative kinase 1 (PINK1) and the Parkin gene. PINK1 is a kinase localized to the mitochondrial outer membrane that remains stable when mitochondrial membrane potential is low. Upon mitochondrial depolarization, PINK1 rapidly senses the change and recruits the E3 ubiquitin ligase Parkin to ubiquitinate damaged mitochondrial membranes [28]. Ubiquitinated mitochondrial membranes are

recognized by p62 and targeted to autophagosomes via LC3 for degradation. Mitophagy also regulates mitochondrial function and ROS levels. Lipopolysaccharide (LPS)-induced oxidative stress in cardiomyocytes generates numerous damaged mitochondria and sharply increases ROS production; timely removal of damaged mitochondria through mitophagy maintains ROS at low levels [29]. Dysfunctional autophagy leads to impaired mitochondrial function, and deletion of autophagy-related genes in yeast under starvation conditions exacerbates ROS accumulation [30].

3.2 Participation in DNA Damage Repair DNA is a major target of ROS attack. Massive ROS production causes base modifications, single/double-strand breaks, and point mutations in DNA molecules, resulting in DNA damage [31]. DNA damage activates a series of cellular responses, including DNA damage repair. Various proteins mediate this process: sensor proteins rapidly recognize damage, while transducer and effector proteins transmit signals from the nucleus to the cytoplasm to initiate responses such as cell cycle arrest. However, cells undergo death when DNA damage is severe or irreparable [32].

Autophagy is both a cell survival mechanism and a form of programmed cell death, making it critical for cell fate determination during DNA damage. Experimental evidence demonstrates that autophagy participates in DNA damage repair. Knockdown of autophagy-related genes such as Beclin1, UVRAG (UV radiation resistance-associated gene), Atg5, and Atg7 leads to accumulation of DNA damage [33-35]. Additionally, inhibition of the ULK1 complex component FIP200 (FAK-family interacting protein of 200 kDa) under radiation-induced oxidative stress impairs DNA damage repair and accelerates cell death [36]. Autophagy can participate in ROS-mediated DNA damage repair through direct or indirect pathways, though the initiation mechanisms remain to be fully elucidated. In yeast, the selective autophagy Cvt pathway plays a direct role in DNA damage repair by activating the G2/M cell cycle phase and promoting deoxyribonucleotide triphosphate (dNTP) and DNA synthesis [37-38]. In higher eukaryotes, direct evidence for the Cvt pathway is lacking, and autophagy primarily contributes to damage repair by clearing mitochondria and toxic aggregates, thereby reducing ROS levels and DNA damage accumulation at the source [39]. Key molecules mediating autophagy in DNA damage repair include PARP1 (poly ADP-ribose polymerase-1) and ATM (ataxia-telangiectasia mutated gene), which induce autophagy by activating AMPK and inhibiting mTOR signaling [40-41]. Additionally, p53, a master regulator of DNA damage repair, is rapidly activated upon DNA damage and can regulate expression of genes involved in autophagy induction (PTEN, TSC2, AMPK subunits) and autophagosome formation (ULK1, UVRAG, Atg2, Atg4, Atg7, Atg10, etc.) [42], thereby mediating autophagy activation.

3.3 Antioxidant Function Through the p62-Kelch-like ECH-associated protein 1 (Keap1)-Nuclear Factor Erythroid 2-related Factor 2 (Nrf2) Pathway The Keap1-Nrf2 signaling pathway is a crucial antioxidant pathway

in cells. Under normal physiological conditions, Keap1 binds to Nrf2, promoting its continuous ubiquitination and proteasomal degradation. Upon cellular stimulation, increased ROS oxidizes cysteine residues on Keap1, facilitating Nrf2 dissociation from Keap1 and nuclear translocation. Nuclear Nrf2 binds to antioxidant response elements (ARE) to promote transcription of antioxidant proteins and phase II detoxifying enzymes, thereby enhancing cellular resistance to oxidative stress [43]. Studies have shown that ubiquitinated p62 can directly interact with Keap1, mediating Keap1 degradation through autophagy and enabling Nrf2 to dissociate from Keap1 and accumulate stably in the nucleus [44]. Moreover, since the p62 enhancer contains ARE sequences, p62 expression is also regulated by Nrf2 [45]. These two pathways form a positive feedback loop for antioxidant responses. Experiments have demonstrated that oral administration or intraperitoneal injection of 10% H O in piglets significantly increased jejunal autophagy levels after 7 days, likely associated with activation of the Nrf2-Keap1 signaling pathway [46].

Since both antioxidant responses and autophagy are protective mechanisms activated by oxidative stress to reduce ROS levels and clear oxidative damage, and autophagy is closely related to DNA damage repair—particularly ROS-induced DNA damage [2]—elucidating the underlying molecular regulatory mechanisms will clarify the antioxidant functions mediated by autophagy.

4 Research Prospects on Antioxidants Alleviating Oxidative Stress Through Autophagy

Oxidative stress has emerged as a significant hazard in modern intensive animal production and represents an important predisposing factor for numerous diseases. Studies have found that pregnant sows are susceptible to oxidative stress during gestation and lactation, leading to reduced milk production and reproductive performance [47]. Oxidative stress is also a major cause of "post-weaning stress syndrome"in piglets, where oxidative damage impairs growth performance and feeding efficiency [48]. Additionally, Hodgkinson et al. [49] reported that dairy cows during colostrum secretion exhibit significantly elevated expression of vascular cell adhesion molecule-1 (VCAM-1) in mammary tissue when under oxidative stress, and acute phase cytokine expression induced by oxidative stress increases inflammatory tissue damage. Diseases caused by oxidative stress in animal production mainly include enteritis, sepsis, pneumonia, heart disease, ascites, peripartum disorders, retained placenta, and mastitis [50-51], all of which severely impact livestock production and economic efficiency.

Nutritional regulation to alleviate oxidative stress has become a research hotspot in recent years. Numerous studies have shown that dietary supplementation with antioxidants such as trace elements, vitamins, and plant extracts can effectively mitigate oxidative stress. Recent findings indicate that autophagy plays an important role in how exogenous antioxidants alleviate oxidative stress. For example, the heme oxygenase-1 (HO-1) agonist cobalt protoporphyrin enhances autophagy and reduces LPS-induced oxidative damage in rat liver [52]. In a

mouse model of oxidative stress established by restraint stress, the natural antioxidant resveratrol upregulates mitophagy to alleviate oxidative damage in peritoneal macrophages [53]. In a mouse model of hepatic ischemia-reperfusion-induced oxidative stress, vitamin D supplementation enhances antioxidant capacity and reduces oxidative stress by regulating autophagy [54]. These antioxidants primarily induce autophagy by modulating autophagy signaling pathways (p62-Keap1-Nrf2, PI3K-Akt-mTOR, AMPK, etc.) and autophagy gene expression, thereby alleviating oxidative stress and reducing apoptosis. For instance, DHA not only activates antioxidant enzymes but also increases protein expression of Nrf2, p62, and Atg5 to activate autophagy [55]. Pretreatment of EA.hy926 cells with 5–20 μmol/L curcumin for 4 hours before co-culture with 200 μmol/L H O revealed that curcumin protects cells from H O -induced oxidative damage and reduces apoptosis by inhibiting the PI3K-Akt-mTOR pathway and activating autophagy [56]. Furthermore, apigenin and orientin protect cells by regulating AMPK and Akt-mTOR signaling pathways and Bcl-2 expression to activate autophagy [57-58].

These studies demonstrate that exogenous antioxidants can regulate autophagy, enhance cellular antioxidant function, protect cells from oxidative damage, and delay cell death. Different antioxidants alleviate oxidative stress by activating distinct autophagy signaling pathways and autophagy-related genes. Additionally, autophagy plays a role in maintaining livestock health. In early-weaned piglet models, autophagy levels are significantly elevated in the liver, spleen, and skeletal muscle, contributing to nutrient balance and cellular function [59]. Intravenous injection of different glutamine concentrations in Holstein dairy calves increases autophagy levels in a dose-dependent manner [60]. In DF-1 cells infected with avian leukosis virus subgroup J (ALV-J), autophagy function is impaired and viral replication increases, whereas treatment with the autophagy activator rapamycin reduces viral replication, suggesting that autophagy facilitates viral clearance [61]. Therefore, systematic investigation of how different exogenous antioxidants affect autophagy and related signaling pathways will provide new insights into the molecular mechanisms underlying antioxidant-mediated alleviation of oxidative stress in animals.

Oxidative stress is a major cause of economic losses in animal production. In recent years, researchers have continuously explored nutritional strategies and regulatory mechanisms to mitigate oxidative stress. The development of autophagy theory provides a new direction for oxidative stress research. Oxidative stress can activate autophagy, which in turn clears oxidative damage, delays cell death, and maintains intracellular homeostasis. Understanding how to regulate autophagy to alleviate oxidative stress will offer novel approaches for investigating the mechanisms of antioxidant function.

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Note: Figure translations are in progress. See original paper for figures.