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REVIEW ARTICLE

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Exploring the interplay between oxidative stress and autophagy in asthma: Pathophysiology and therapeutic potential

Ying Liu[a], Tongtong Wang[b], Yu-ang Dong[b], Jun Zhang[a,*]

[a]*School of Chinese Medicine, Anhui University of Chinese Medicine, Hefei City, Anhui Province, 230012, China*
[b]*The First Clinical Medical College, Anhui University of Chinese Medicine, Hefei City, Anhui Province, 230012, China*

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Abstract
Asthma is a chronic respiratory disease, characterized by airway inflammation, hyperresponsiveness, and remodeling. Oxidative stress and autophagy play pivotal roles in asthma pathogenesis. Excessive production of reactive oxygen species (ROS) worsens airway damage and inflammation, and impaired antioxidant defenses in patients with asthma further increase ROS production, leading to tissue damage. Environmental factors, such as allergens and air pollution, and inflammatory cells, such as macrophages and eosinophils, contribute to elevated ROS levels, thereby intensifying the disease. Autophagy, a key mechanism for eliminating damaged organelles and maintaining cellular homeostasis, plays a dual role in asthma. While autophagy activation mitigates oxidative stress, dysregulated or excessive autophagy worsens airway remodeling and inflammation. This review examines the interplay between oxidative stress and autophagy in asthma and discusses emerging therapeutic approaches targeting autophagy to improve disease outcomes.

Introduction

Bronchial asthma is a chronic inflammatory disease of the airways. It has gradually become one of the most common chronic diseases worldwide. Globally, nearly 300 million people are affected by asthma, impacting 1%–29% of the populations in different countries.[1] The main symptoms of asthma include wheezing, shortness of breath, chest tightness, coughing, and expiratory flow limitation.[2] Asthma is clinically characterized by persistent airway inflammation, remodeling, and hyperresponsiveness.[3] Studies have demonstrated that asthma is caused by the combined effects of environmental and genetic factors. Many external environmental stimuli, such as air pollutants and allergens,

***Corresponding author**: Jun Zhang, School of Chinese Medicine, Anhui University of Chinese Medicine, Hefei City, Anhui Province, 230012, China. *Email address*: junzhang80122@sina.com

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can trigger asthma.[4] Numerous studies have reported that patients with asthma exhibit increased oxidative stress under external environmental stimuli.[5] This is reflected not only in the imbalance of the internal antioxidant system, such as decreased activities of antioxidant enzymes (e.g., superoxide dismutase [SOD] and catalase [CAT])[6] but also in the excessive production of reactive oxygen species (ROS) by inflammatory and bronchial epithelial cells.[7,8] Such an imbalance further promotes the development of airway inflammation and aggravates the symptoms of asthma.[9]

Autophagy, one of the mechanisms for organelle recycling and degradation within cells, is a crucial pathway for maintaining cellular homeostasis in eukaryotic cells.[10] Based on the specific degradation targets, autophagy can be classified into proteaphagy, mitophagy, nucleophagy, ribophagy, pexophagy, reticulophagy, lipophagy, and mycophagy.[11] Although these pathways exhibit differences, they all act as regulators of cellular homeostasis by delivering proteins, lipids, nucleic acids, and other components damaged by increased oxidative stress to lysosomes for degradation, thereby maintaining cellular balance.[12] In most cases, autophagy serves as a stress response mechanism within cells that helps preserve cellular homeostasis. However, excessive autophagy activation can lead to cell death.[13] Although the regulatory role of oxidative stress in autophagy is not completely understood, existing research indicates that oxidative stress can promote autophagy.[14] Numerous studies have reported that oxidative stress and autophagy contribute to the development of asthma.[15,16] However, the association between oxidative stress, autophagy, and asthma remains unclear. This review summarizes the sources of oxidative stress and the mechanisms of autophagy in patients with asthma. In addition, it highlights the association between oxidative stress and autophagy and discusses the application of autophagy regulation in the treatment of asthma. This review is expected to advance research on the roles of oxidative stress and autophagy in the treatment of asthma.

Oxidative Stress Mechanisms in Asthma Pathogenesis

At low concentrations, ROS can act as signaling molecules regulating cellular signaling pathways. However, excessive ROS production or damage to the antioxidant system disrupts the redox balance, thereby leading to oxidative stress. As shown in Figure 1, patients with asthma exhibit

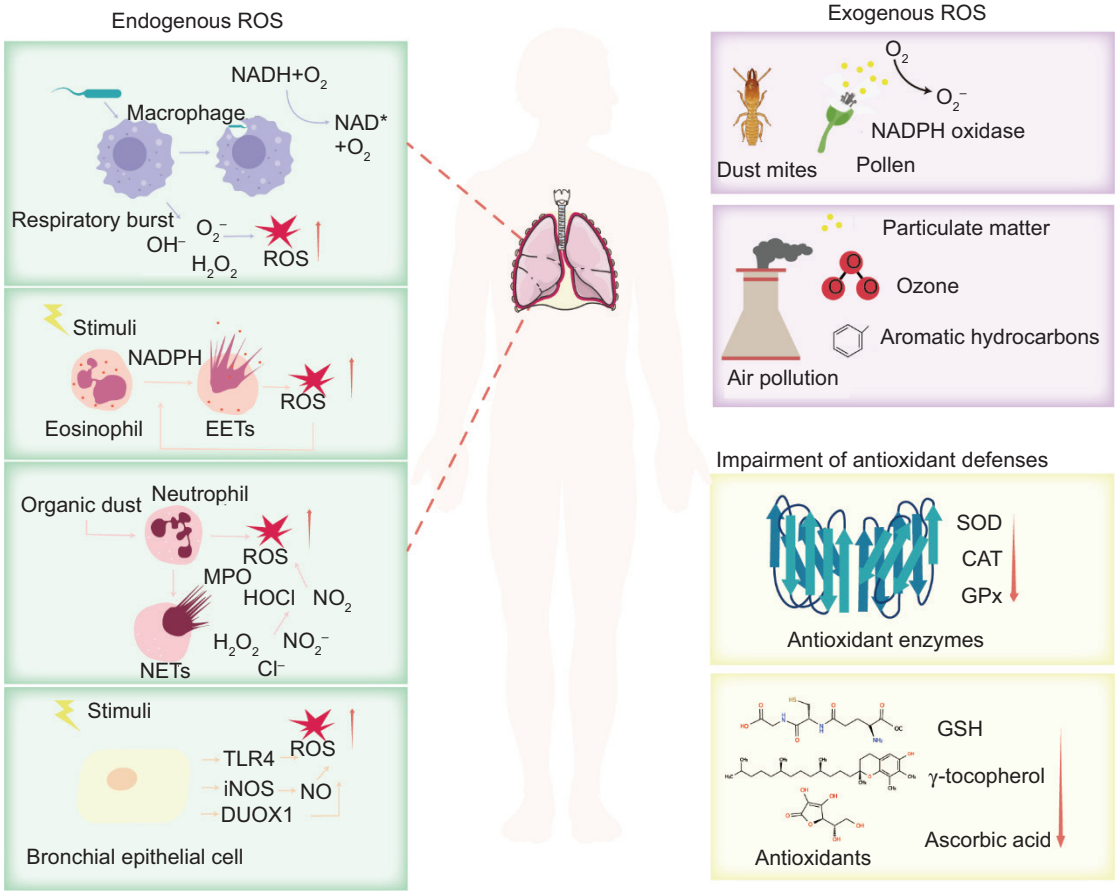

Figure 1 Sources of reactive oxygen species (ROS) in patients with asthma. These patients have impaired endogenous antioxidant systems, including decreased levels of antioxidant enzymes and antioxidants. In addition, external environmental allergens and air pollutants stimulate ROS production in these patients. At the cellular level, macrophages, neutrophils, eosinophils, and bronchial epithelial cells produce excessive ROS during immune responses or upon stimulation.

impaired antioxidant systems and increased oxidative stress, promoting tissue damage and modulating cellular signaling, thereby aggravating asthma symptoms.[17]

Impairment of Antioxidant Defenses Dysregulation of Antioxidant Enzyme Function

ROS within cells are scavenged by antioxidant enzymes. For example, superoxide anions are converted into hydrogen peroxide and water by superoxide dismutase (SOD). Then, CAT breaks down hydrogen peroxide into water and oxygen. In addition to CAT, glutathione peroxidase (GPx) plays a role in the elimination of hydrogen peroxide. GPx catalyzes the reduction of hydrogen peroxide using glutathione, converting reduced glutathione (GSH) into oxidized glutathione (GSSG). Subsequently, GSSG is reduced back to GSH by glutathione reductase utilizing NADPH, thereby continuing the antioxidant cycle.[18] A study by Ahmad et al. reported that the antioxidant enzyme system of patients with asthma is significantly impaired compared with that of healthy individuals, demonstrating a marked decrease in the activities of SOD, CAT, and GPx in red blood cells.[6] Such a reduction in these activities indicates the diminished ability to scavenge ROS in patients with asthma, making them more susceptible to tissue damage induced by oxidative stress. However, it is noteworthy that studies on changes in the activity of antioxidant enzyme in patients with asthma have yielded inconsistent results. For example, Mak et al. examined antioxidant enzyme levels in 106 patients with asthma and 135 healthy individuals and found that the SOD and CAT activities in red blood cells substantially increased rather than decreased in the former compared with the latter group.[19] Similarly, a study by Anes demonstrated no significant differences in the SOD and CAT activities between the groups.[20] Nonetheless, both studies supported the finding that the GPx activity was reduced in patients with asthma.[6,19,20] Therefore, the reduced GPx activity may be the primary impairment in the antioxidant enzyme system of patients with asthma, and the resulting oxidative stress may further enhance cellular response to ROS, leading to increased SOD and CAT activities.

Perturbations in Antioxidant Levels and Oxidative Biomarkers

In addition to impaired antioxidant enzyme systems, patients with asthma exhibit reduced antioxidant levels. Ascorbic acid, an antioxidant, can scavenge free radicals, preventing the increase in oxidative stress and reducing lipid peroxidation and inflammation levels.[21] The level of ascorbic acid is positively correlated with the percentage of forced expiratory volume in 1 second (FEV1%) and the percentage of forced vital capacity (FVC%).[22] Patients with asthma have been found to have significantly decreased ascorbic acid levels[20,23] and GSH levels.[24] GSH reacts with peroxides, such as lipid peroxides, converting them into hydroxyl derivatives, during which GSH is oxidized to GSSG. Low GSH levels are associated with worsening symptoms of asthma.[25] Research suggests that reduced GSH/GSSG ratio and the resulting redox imbalance can exacerbate type 2 (T2) inflammation in asthma.[26] In addition, vitamin E is reduced in patients with asthma.[24] Vitamin E is present in different isomers, and studies have demonstrated that different isomers exert varying effects on lung function. Increased serum concentrations of α-tocopherol are typically associated with improved lung function (higher FEV1 and FVC), whereas γ-tocopherol is associated with poorer lung function (lower FEV1 and FVC).[27] Antioxidants are generally associated with oxidative markers in the body. Studies have demonstrated that the plasma levels of malondialdehyde (MDA) and total protein carbonyl compounds are elevated in patients with asthma compared with healthy individuals and further increase as the symptoms of asthma worsen.[6] MDA is a lipid peroxidation product, whereas total protein carbonyl compounds are markers of protein oxidative damage. The increase in these levels indicates heightened oxidative stress. This finding is consistent with the study by Ammar et al., which showed that the levels of advanced oxidation protein products are elevated in patients with asthma.[28]

Exogenous Drivers of ROS Production

Oxidative responses induced by allergen

Both indoor and outdoor environments have a variety of allergens, which can activate immune cells and promote ROS production.[29] House dust mites (HDM) are the most common allergens affecting approximately 85% of patients with asthma. HDM proteases are recognized by protease-activated receptors and trigger innate immunity.[30] Studies have demonstrated that in an asthma mouse model induced by HM, a significant increase in oxidative damage markers of proteins, lipids, and nucleic acids and increased apoptosis were observed. DNA repair inhibitors further exacerbate DNA damage and apoptosis in bronchial epithelial cells, indicating that the mechanism by which HDM promotes asthma may involve DNA damage and apoptosis induced by ROS.[31] In addition, pollen exposure has been shown to cause allergic airway inflammation. Boldogh et al.[32] reported that pollen extracts contain high levels of NADPH oxidases, which rapidly increase the ROS levels in lung epithelial cells and elevate oxidative stress markers, such as GSSG and 4-hydroxynonenal, in the airway lining fluid. These oxidative stress markers recruit neutrophils to the airways and induce airway inflammation. Further studies have demonstrated that heat-inactivated birch pollen extract retains its ability to induce allergic asthma and that this effect can be alleviated by antioxidants, such as N-acetyl-L-cysteine or dimethylthiourea, indicating that allergic airway diseases induced by pollen allergen may not solely depend on NADPH oxidase.[33]

Airborne pollutants and ROS generation

Ozone is a major component of air pollutants that can disrupt the epithelial cell barrier, increase mitochondrial damage, and promote the release of inflammatory cytokines, such as IL-1β, IL-18, and IL-17A, leading to increased ROS and airway hyperresponsiveness (AHR).[34,35] It also impairs the sensitivity of patients with asthma to glucocorticoids.[36]

In addition to ozone, air pollutants contain various contaminants, including sulfurdioxide, particulate matter (PM), and nitrogen dioxide. A case–control study by Zmirou et al. that involved 217 pairs of volunteers reported that traffic-related air pollution could contribute to childhood asthma.[37] However, some studies suggested a decline in these pollutants during increased incidence of asthma.[38] The worsening traffic-related air pollution has led to a continuous increase in the amount of PM. Studies have demonstrated that particulates of different sizes can stimulate epithelial cells to produce oxidative stress, with ultrafine particles (<0.1 μm) significantly depleting intracellular glutathione and promoting the expression of oxidative stress markers, such as heme oxygenase-1, in epithelial cells, suggesting that ultrafine particles are more potent in generating ROS.[39] Further studies reported that the small size of ultrafine particles enables them to more effectively penetrate tissues and localize to the mitochondria, causing mitochondrial damage.[39] In addition, traffic-related particulate pollutants contain high levels of polycyclic aromatic hydrocarbons and persistent organic pollutants, which bind to aryl hydrocarbon receptors, thereby inducing the expression of cytochrome P450 enzymes and leading to excessive ROS production and oxidative stress.[40] Particulate pollutants also contain transition metals such as ferrous ions. Through the Fenton reaction, the ferrous ions in diesel exhaust particulates generate hydroxyl radicals, which cause lung damage.[41]

Endogenous Generation of ROS

In the lungs, the primary ROS-producing cells are inflammatory cells, such as macrophages, neutrophils, and eosinophils. Macrophages act as the first line of defense for airway epithelial cells and can activate immune responses to combat pathogens.[42] However, studies have demonstrated that macrophages can produce superoxide anions through the NADH-dependent phagocyte oxidase. Superoxide anions dismutate into hydrogen peroxide, which enters bacteria to exert bactericidal effects.[43] On the one hand, macrophages generate ROS to eliminate pathogens; on the other hand, they produce large amounts of superoxide and ROS, a process known as respiratory burst, in response to pathogen stimulation.[44] Lohmann-Matthes et al.[45] reported that stimulating macrophages with phorbol myristate acetate produces large quantities of superoxide anions, hydrogen peroxide, and hydroxyl radicals, which, while effective in killing bacteria, cause lung damage. Furthermore, studies have shown that patients with severe asthma exhibit decreased lipoxin A4 levels, attributed to impaired lipoxin A4 synthesis in macrophages.[7] This impaired synthesis has been positively correlated with elevated oxidative stress, indicating that macrophage-generated ROS kill bacteria and impair lipoxin A4 synthesis, thereby contributing to the progression of asthma.[8]

Many exogenous stimuli, such as pathogens, can activate eosinophils, which release extracellular traps composed of DNA and granular proteins to mediate eosinophil extracellular trap cell death (ETosis), enhancing immune defense. This process promotes the release of ROS and is NADPH-dependent.[46] A study by Ueki et al. has shown that eosinophil lysis depends on extracellular ROS, which can be inhibited by CAT and the NADPH oxidase inhibitor DPI.[46] Furthermore, eosinophils produce superoxide in response to stimuli,[47,48] leading to increased oxidative stress, airway inflammation, and AHR. These superoxide radicals further promote ETosis.[46]

A study by McGovern reported that mice treated with organic dust (OD) exhibited dose-dependent AHR and neutrophilic lung inflammation. The depletion of neutrophils reduced AHR induced by OD, suggesting that neutrophils contribute to asthma symptoms induced by OD.[49] Further research showed that mice treated with OD exhibited increased antioxidant levels and upregulated NRF-2 pathway genes, suggesting that OD exposure increases oxidative stress, an effect mitigated by the antioxidant dimethylthiourea or neutrophil depletion antibodies. This suggests that asthma symptoms induced by OD depend on neutrophil-mediated oxidative stress.[49] Similar studies have reported increased neutrophil counts and enhanced neutrophil extracellular trap (NET) formation in patients with severe asthma.[50] NETs consist of various antimicrobial proteins and enzymes, including myeloperoxidase (MPO), a member of the heme peroxidase superfamily. MPO catalyzes the conversion of hydrogen peroxide to hypochlorous acid, inducing oxidative stress and inflammation.[51] Moreover, it catalyzes the nitration of tyrosine residues on proteins via NO^{2-}, a posttranslational modification that promotes epithelial cell damage and inflammation.[52] This indicates that neutrophils may promote asthma by releasing MPO-containing NETs, which increase ROS production. This finding is consistent with Pham et al.'s study, which indicated that NETs and MPO antibodies ameliorated airway epithelial damage induced by NET.[53]

Bronchial epithelial cells also contribute to oxidative stress. Dickinson et al. reported increased iNOS expression in BEAS-2B cells challenged with HDM.[54] iNOS produces NO, which reacts with superoxide to form reactive nitrogen species.[55] Activation of TLR4 pathway in bronchial epithelial cells has been shown to result in excessive ROS production, thereby promoting proinflammatory cytokine production and tissue damage.[56] HDM has been found to activate TLR4 expression in airway epithelial cells, suggesting that the TLR4 pathway is involved in ROS production in epithelial cells upon HDM stimulation.[54] TLR4 activation also drives IL-33 activation, promoting Th2-type immune responses that lead to asthma inflammation.[57] The activation of Th2 responses releases a cascade of downstream cytokines, including IL-4, IL-5, IL-10, and IL-13.[58] Studies have reported significant increases in ROS and NADPH oxidase DUOX1 levels in the airway epithelial cells of asthmatic mice induced by ovalbumin (OVA). This is because of IL-13 upregulating DUOX1 expression and increasing autophagosome formation. Under the action of the autophagy regulatory protein ATG5, DUOX1 is targeted to the apical membrane of epithelial cells, where it produces superoxide.[59]

Nexus Between Oxidative Stress and Autophagy in Asthma

The mechanism of autophagy is illustrated in Figure 2. Excessive ROS production leads to increased oxidative stress, which in turn causes damage to proteins, lipids, nucleic acids, and other cellular components.[60]

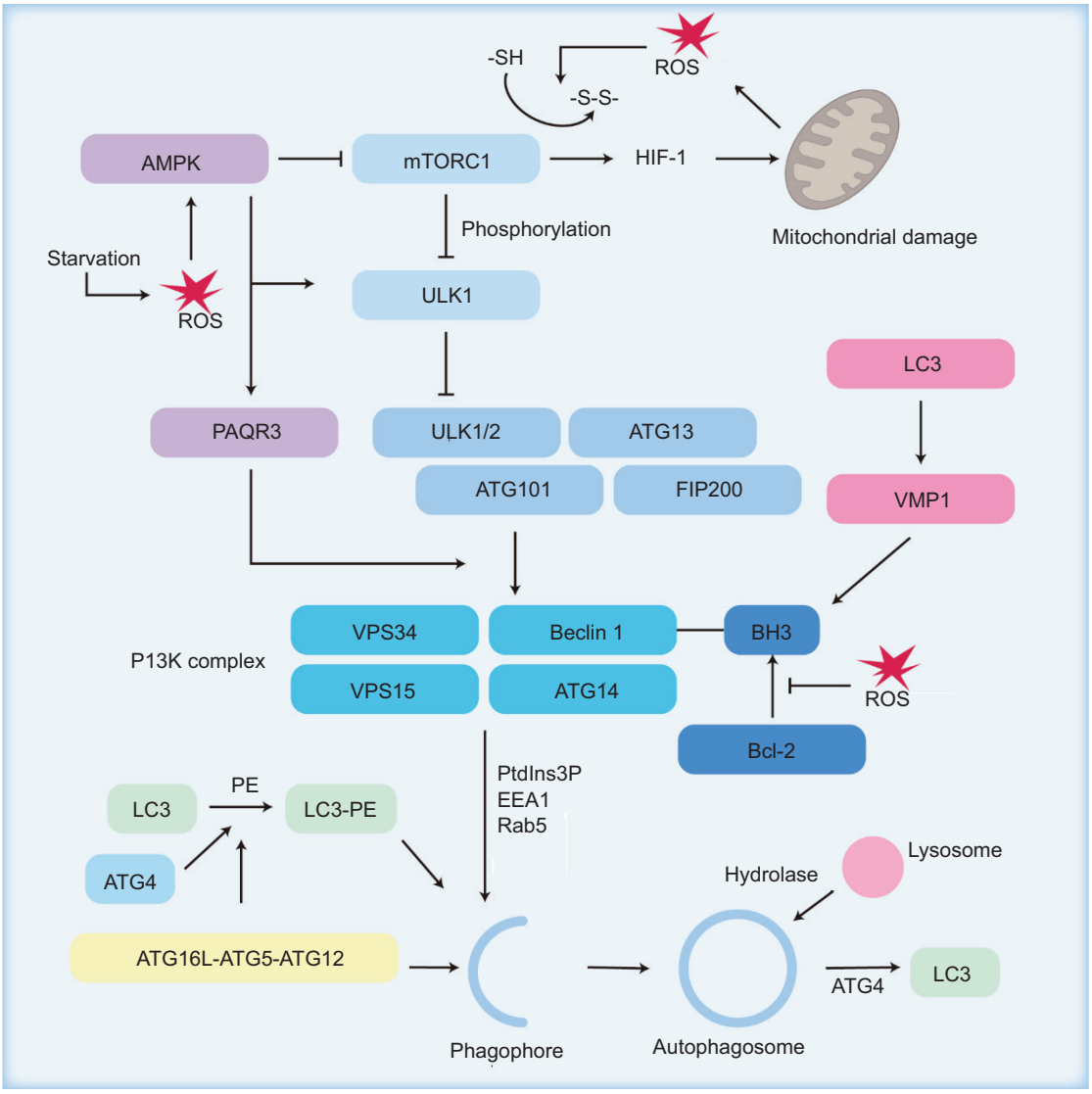

Figure 2 Autophagic pathway and its association with reactive oxygen species (ROS). When mTORC1 is activated, autophagy is inhibited. Under starvation conditions, ROS production activates autophagy by activating the AMPK pathway. AMPK inhibits mTORC1, on the one hand, and directly activates ULK1, on the other hand, promoting the formation of the ULK complex. The formation of the ULK complex leads to the formation of the PI3K complex. With the involvement of LC3-PE, ATG16L-ATG5-ATG12, and PtdIns3P, autophagosomes are formed, which fuse with lysosomes to degrade their cargo while simultaneously releasing LC3 back into the cytoplasm. In this process, mTORC1 and ATG4 are regulated by ROS.

This damage activates the autophagy pathway to degrade the damaged proteins and maintain cellular homeostasis.[12] The association between autophagy and oxidative stress is mutually regulatory—oxidative stress can activate autophagy, and autophagy can maintain cellular homeostasis by regulating the redox balance.[61] Through autophagy, damaged proteins and organelles are transported to lysosomes for degradation and recycling.[9]

Autophagy: Cellular Mechanisms and Regulatory Pathways

The mechanism of autophagy was first reported in the 1950s. Autophagy involves autophagy-related genes (ATG), with 32 ATGs identified in yeast thus far.[9] The entire process of autophagy requires the involvement of 16 ATGs, each of which plays a role in different stages, including initiation, nucleation, elongation, fusion, and degradation.[16] Autophagy is activated by external stimuli, such as starvation or oxidative stress.[62] This activation is mainly regulated by the mammalian target of rapamycin (mTOR), a protein kinase comprising two complexes: mTORC1 and mTORC2. mTORC1 is mainly responsible for regulating autophagy.[63] Under normal conditions, mTORC1 is active and inhibits autophagy by phosphorylating ULK1, thereby disrupting the ULK1–AMPK interaction, which prevents ULK1 activation. This inhibition blocks the formation of the ULK1/2 complex (consisting of ULK1/2, ATG13, ATG101, and FIP200), suppressing autophagy. Under nutrient deprivation

or high energy consumption, AMPK is activated and inhibits mTORC1 activity, promoting the activation of the ULK1/2 complex. In addition, activated AMPK has been reported to directly activate ULK1.[64] ULK1/2 complex activation is a key step in the initiation of autophagy. The activated ULK1/2 complex interacts with the endoplasmic reticulum membrane and promotes the formation of the class III phosphatidylinositol-3-kinase complex (PI3K), which includes Beclin 1, VPS34, VPS15, and ATG14.[65] In this process, AMPK plays a pivotal role by phosphorylating the T32 site of PAQR3, a Golgi-resident protein, thereby activating it. The activated PAQR3 promotes the formation of the ATG14-bound PI3K complex.[66] Beclin 1 plays a crucial role within the PI3K complex. It is an important positive regulator of autophagy and contains a BH3 domain that can bind to the antiapoptotic proteins Bcl-2 and Bcl-xL, thereby regulating the activation of the Beclin 1-VPS34 complex.[67] Studies have demonstrated that ROS can induce the dissociation of Beclin 1 from Bcl-2, forming the Beclin 1-VPS34-ATG14 complex, which facilitates membrane separation and autophagosome nucleation, initiating autophagy.[68] Furthermore, Beclin 1 can directly bind to the C-terminal ATG domain of VMP1 through its BH3 domain.[69] VMP1 is an autophagy protein localized to the endoplasmic reticulum. It promotes membrane curvature and autophagosome formation. Moreover, it is involved in the recruitment of microtubule-associated protein 1 light chain 3 (LC3) and the integration of LC3 into the autophagosome membrane to promote autophagosome elongation and maturation.[69,70] Beclin 1 can also phosphorylate and activate VPS34, a phosphatidylinositol-3-kinase that catalyzes PtdIns3P production, thereby promoting the formation of autophagic vesicles and providing a structural foundation for subsequent autophagosome formation.[71] PtdIns3P specifically binds to FYVE domains through the interaction between the conserved amino acid residues in the FYVE domain and the polar head groups of PtdIns3P.[72] This specific binding recruits proteins containing FYVE domain to the PtdIns3P-enriched membranes, participating in endosome formation.[73] For example, early endosomal antigen 1 (EEA1), a 170-kDa polypeptide, is crucial for endosome fusion. Lawe et al. found that under the influence of Rab5, EEA1 binds to PtdIns3P and is recruited to endosomal membranes, thereby facilitating endosome formation.[74]

After forming the PI3K complex, the phagophore elongates to form a double-membrane autophagosome, a process involving ATG16L and microtubule-associated light chain protein 3 (LC3-I)[75,76] ATG16L is a key protein in autophagy, and studies have reported that ATG16L interacts with WD-repeat protein interacting with phosphoinositide (containing an FYVE domain), recruiting it to the preautophagosomal structure.[77] It is also associated with the ATG5–ATG12 complex, facilitating autophagosome membrane formation and elongation.[76] ATG16L is involved in LC3 lipidation, forming the ATG16L–ATG5–ATG12 complex, which acts as an E3 ligase to promote the conjugation of LC3 to phosphatidylethanolamine (PE), a process referred to as LC3–PE.[78] LC3–PE promotes the formation and closure of the autophagosome membrane. It specifically localizes to the extended autophagosome until it fuses with the lysosome. Once fusion occurs, LC3–PE is delipidated by ATG4 and lysosomal acidic hydrolases, releasing LC3 back into the cytoplasm for recycling.[79,80]

Oxidative Stress as a Catalyst for Autophagy

Autophagy activation induced by ROS

Autophagy plays a pivotal role in degrading and recycling damaged proteins and organelles resulting from increased oxidative stress, maintaining cellular homeostasis, and promoting cell survival.[81] When autophagy is impaired, mitochondrial dysfunction occurs, leading to excessive ROS production.[65] Conversely, autophagy itself is regulated by oxidative stress.

As aforementioned, mTOR plays a pivotal role in the initiation of autophagy, and its activation and expression are regulated by oxidative stress. mTOR contains a highly conserved FATC domain with a redox-sensitive disulfide bond. The oxidation and reduction of this disulfide bond can considerably affect the flexibility of the FATC domain and alter its ability to bind substrates.[82] Moreover, mTOR has been shown to be involved in the activation of hypoxia-inducible factor 1 (HIF-1)[83], and cell proliferation induced by hypoxia can be inhibited by mTOR overexpression.[84] Studies have shown that under hypoxic conditions, the activity of complex III in the mitochondrial electron transport chain increases, resulting in increased ROS production.[85] This indicates that redox imbalance induced by hypoxia and oxidative stress contribute to mTOR inhibition. In addition, a study by Desai showed that mTOR not only exists in the cytoplasm but is also associated with the outer mitochondrial membrane, enabling it to respond to changes in the redox environment caused by mitochondrial dysfunction.[86] Zhang et al. further demonstrated that cells treated by hydrogen peroxide exhibit changes in the transcriptional levels of mitochondrial fission and fusion genes, alterations in mitochondrial membrane permeability, and increased mTOR expression, supporting the association between mTOR inhibition, mitochondrial damage, and elevated ROS.[87] While existing evidence suggests that ROS participates in mTOR inhibition, contradictory findings do exist. For example, Leslie et al. reported that hydrogen peroxide and intracellular oxidants can activate the PI3K/Akt signaling pathway by inhibiting PTEN, upregulating the mTORC1 expression downstream of PI3K/Akt.[88] Further research demonstrated that oxidants deactivate PTEN by oxidizing its thiol groups, forming disulfide bonds[88] Huang reported that ROS generated by UV light can activate p70 S6 kinase by phosphorylating Thr389, Thr421, and Ser424. However, this activation can be inhibited by rapamycin and N-acetyl-L-cysteine,[89] suggesting that ROS activates p70 S6 kinase through mTOR.

ATG4 is a key protein in autophagy and plays roles in LC3 processing and activation and LC3-PE recycling.[90] Studies have reported that ATG4 activity is regulated by the redox environment.[91] ATG4 contains a cysteine residue, and under conditions of excessive ROS, the Cys78 residue close to the catalytic site (Cys74) is oxidized, resulting in the inactivation of ATG4.[92] Furthermore, excessive ROS can cause ATG4 aggregation and further inactivation.[91] ATG4 regulation by ROS is essential for autophagy because after ATG4 initially processes LC3 (ATG8), it must lose its activity to allow LC3 to be lipidated and to participate in autophagosome formation. Once the autophagosome fuses with the lysosome, the redox environment shifts to low oxidative

stress, allowing ATG4 to reactivate, release, and recycle LC3.[92] In addition, angiotensin II has been demonstrated to promote autophagy by increasing ROS production.[93] Further research showed that angiotensin II enhances the expression levels of autophagy-related proteins, such as Beclin-1, Vps34, ATG5-ATG12, ATG4, and ATG7, indicating that angiotensin II promotes ROS generation to upregulate ATG4 expression.[94] Another study reported that N-benzoyl-O-(N'-(1-benzyloxycarbonyl-4-piperidiylcarbonyl)-D-phenylalanyl)-D-phenylalaninol (BBP) promotes apoptosis in MCF-7 cells through autophagy. BBP activates the JNK pathway and induces ROS production, which subsequently upregulates ATG4 expression, thereby promoting LC3 cleavage and autophagy. This further highlights the role of ROS in regulating ATG4 to facilitate autophagy.[95]

Mitophagy: A critical process for redox homeostasis

Mitophagy removes damaged mitochondria via autophagy to maintain cellular energy and redox homeostasis.[96] Through autophagy, cells can selectively eliminate damaged mitochondria, preserving the mitochondrial quality and preventing excessive ROS production from the mitochondria.[97] Mitophagy is mainly mediated by the PINK1/Parkin pathway, BNIP3 and NIX pathways, and FUNDC1 pathway.[98,99]

The PINK1/Parkin-dependent pathway involves two key proteins, namely, PINK1 and Parkin. PINK1 is a mitochondrial kinase that regulates mitochondrial function and the occurrence of mitophagy.[100] Under normal physiological conditions, PINK1 is transported from the outer to the inner mitochondrial membrane, where it is degraded.[101] However, the loss of membrane potential in damaged mitochondria prevents PINK1 from entering the inner membrane, leading to its accumulation on the outer mitochondrial membrane. The accumulated PINK1 phosphorylates the E3 ubiquitin ligase Parkin, thereby activating it.[102] The activated Parkin ubiquitinates proteins on the outer mitochondrial membrane, marking the damaged mitochondria for autophagic recognition and facilitating their clearance by autophagosomes.[103]

The BNIP3, NIX, and FUNDC1 pathways mediate mitophagy independently of Parkin's ubiquitination.[98] BNIP3, NIX, and FUNDC1 are receptor proteins that are located on the outer mitochondrial membrane. Under hypoxic conditions, HIF-1α promotes BNIP3 and NIX expressions and FUNDC1 dephosphorylation and activation.[104,105] BNIP3, NIX, and FUNDC1 contain LC3-interacting regions, enabling them to directly bind to LC3, thereby promoting mitophagy.[99]

Mitophagy is regulated by the cellular redox environment. The use of the mitophagy activator carbonyl cyanide m-chlorophenylhydrazone has been shown to substantially enhance ROS production and mitochondrial membrane depolarization, thereby activating mitophagy. However, this effect can be mitigated by antioxidants, suggesting that ROS production plays a role in promoting mitophagy.[106] In the PINK1/Parkin pathway, ROS can facilitate the recruitment of Parkin to mitochondria, promoting PINK1/Parkin-mediated mitophagy.[106] The expressions of BNIP3 and NIX are significantly upregulated by HIF-1α, which has been associated with increased oxidative stress.[85,104] The BNIP3 and NIX pathways are also associated with ROS regulation. In cells lacking BNIP3, the accumulation of damaged mitochondria and significantly increased ROS levels were observed, suggesting that mitophagy mediated by the BNIP3 and NIX pathways is a crucial mechanism for ROS clearance.[107]

The Role of Autophagy in the Pathophysiology of Asthma

Asthma is a complex respiratory disease, characterized by airway inflammation, hyperresponsiveness, and remodeling. Many studies have reported that oxidative stress plays a pivotal role in asthma by causing damage to airway epithelial cells,[108] exacerbating airway inflammation,[109] and promoting disease progression.[110] Autophagy also plays an important role in asthma by contributing to eosinophil extracellular trap formation and airway inflammation,[111] remodeling,[112] and hyperresponsiveness.[113]

A hallmark of airway remodeling in asthma includes increased airway smooth muscle (ASM) mass, epithelial fibrosis, increased mucus secretion, and epithelial-mesenchymal transition.[114] Studies have suggested that ASM hypertrophy is a key determinant of severe persistent asthma.[115] Transforming growth factor-β1 (TGF-β1) is a profibrotic factor promoting airway wall fibrosis and structural changes. Redington et al. found that the TGF-β1 levels in bronchoalveolar lavage fluid from patients with asthma were significantly elevated compared with those from healthy individuals. They also discovered that exposure to allergens increased the TGF-β1 concentration in the airways after 24 h. This indicates that TGF-β1 may play a role in asthma-related airway remodeling.[116] Human atrial fibroblasts treated with TGF-β1 exhibited increased synthesis of type I collagen α2 and fibronectin and enhanced autophagic activity. The inhibition of autophagy reduced fibrosis induced by TGF-β1, indicating that TGF-β1 regulates fibrosis via autophagy.[117] Fibrosis is a key feature of tissue remodeling, and studies have demonstrated that airway fibrosis in asthma is associated with collagen deposition.[118] TGF-β1 expression has been positively correlated with type I collagen gene expression, and TGF-β1 promotes the synthesis of the type I collagen α2 chain. However, this effect is inhibited when ATG5 is knocked out. This suggests that autophagy induced by TGF-β1 and airway remodeling involves ATG5.[119] Similar studies have shown that the G allele of the ATG5 gene rs12212740 is more frequent in patients with asthma than in healthy individuals. In both the SLSJ and CAMP study populations, patients carrying the G allele exhibited a negative correlation between prebronchodilator FEV1 and the G allele. Considering the crucial role of ATG5 in autophagy, this indicates that the single nucleotide polymorphism (SNP) affects ATG5 regulation, influencing the autophagy process and leading to airway remodeling and lung function decline in patients with asthma.[120] This finding is consistent with those of Martin et al., who demonstrated increased Atg5 expression in the nasal epithelium of patients with acute asthma and reported that ATG5 SNPs rs12201458 and rs510432 are associated with asthma, with the latter enhancing gene

promoter activity.[121] These findings suggest that ATG5 SNPs enhance autophagy by increasing ATG5 expression, thereby contributing to airway remodeling in asthma.

One of the key features of asthma is chronic airway inflammation, which involves inflammatory responses from various cell types, including eosinophils, lymphocytes, dendritic cells, and mast cells.[122] In asthma, inflammation is often associated with the overactivation of the Th2 immune pathway, which leads to excessive immune responses, triggering airway inflammation, bronchoconstriction, and allergic reactions.[123] In the Th2 pathway, Th2 cells and T2 innate lymphoid cells promote eosinophil production and activation by releasing cytokines, such as IL-4, IL-5, and IL-13, resulting in airway inflammation.[124] Liu et al. found that the eosinophils of OVA-treated mice formed autophagosomes and exhibited increased LC3 expression. The inhibition of autophagy significantly reduced eosinophil infiltration, and treatment with anti-IL-5 antibodies decreased the expression of the autophagy-related protein LC3, indicating a close association between autophagy, eosinophilic inflammation, and asthma severity.[113] For example, Murai et al. reported that exposure to the outdoor allergen *Alternaria alternata* promoted the conversion of LC3-I to LC3-II in bronchial epithelial cells, degradation of p62, and release of the proinflammatory cytokine IL-18. This effect could be suppressed by the autophagy inhibitors 3-methyladenine and bafilomycin, suggesting that the release of IL-18 in response to *A. alternata* stimulation depends on the activation of autophagy.[125] Autophagy may play different roles in inflammation depending on the involved cell type. Overactive autophagy induces T2 immune responses and eosinophilic inflammation, whereas reduced autophagy exacerbates neutrophilic asthma.[80] This finding is consistent with those of Suzuki et al. who reported that ATG5 gene knockout, which impairs autophagy, causes severe lung inflammation and increased levels of the proinflammatory cytokine IL-17A in neutrophilic asthma.[126]

Therapeutic Modulation of Autophagy in Asthma

Autophagy plays a dual role in asthma. While it can promote the development of asthma, some studies have reported that the loss of autophagy has also led to lung inflammation, indicating that autophagy can promote and interfere with the pathogenesis of asthma.[16,125,126] Because of the off-target effects of autophagy-regulating drugs, only a few have reached the clinical treatment stages. For example, while chloroquine shows promise as an autophagy inhibitor in cancer therapy, its combination with chemotherapy drugs has side effects, including damage to the kidneys and other organs.[127] Nonetheless, autophagy regulation is often preferred over direct ROS clearance because while the latter can reduce oxidative damage, it may also interfere with ROS signaling and inhibit autophagy activation. Autophagy, as a natural cellular protective mechanism, helps maintain cell health by eliminating damaged organelles and proteins.[16] Table 1 summarizes the autophagy-modulating drugs and their roles in the treatment of asthma.

Table 1 The application and mechanism of autophagy-modulating drugs in asthma.

Drugs	Types of models	Mechanisms/effects	References
3-Methyladenine	BEAS-2B cells C57BL/6 mice	Reduces the expression of LC3; inflammatory factors IL-1β, IL-6, and TNF-α; and ROS in cells and lung tissues while enhancing the activity of the antioxidant enzyme SOD in cells and lung tissues.	(134)
Agnuside	OVA-LPS-induced Balb/c	Reduces airway inflammation, fibrosis, and remodeling and suppresses autophagy by downregulating the expressions of Beclin-1, p62, and Bcl2/Bax.	(128)
VNLE	OVA-LPS-induced allergic asthma in mice	Reduces the expression of the autophagy-related protein LC3A/B, improving pathological changes, such as inflammatory cell infiltration, congestion, fibrosis, bronchial thickening, and alveolar collapse in mice.	(129)
Leupeptin	Human lung mast cells	Inhibits the infiltration of human lung mast cells and reduces the expressions of Beclin-1 and LC3B in macrophages.	(130, 131)
Oleuropein	BALB/c mice	Inhibits the infiltration of inflammatory cells in the airways and reduces pulmonary fibrosis in OVA-exposed mice.	(132)
Budesonide Simvastatin	Patients with severe asthma	Inhibits autophagy by suppressing the key proteins Beclin-1 and LC3 while promoting the production of anti-inflammatory IL-10 to alleviate asthma inflammation, with simvastatin enhancing this effect.	(136)
	Albumin (OVA)-sensitized and challenged mice	Promotes autophagy by upregulating ATG5, LC3B, and Beclin-1; facilitating autophagosome formation in bronchial smooth muscle cells; and reducing the expressions of IL-4, IL-5, and IL-13.	(137)
Rapamycin	BALB/c mice	Inhibits airway hyperresponsiveness, IgE production, and goblet cell metaplasia.	(139)
Vitexin	OVA-LPS-induced allergic asthma in mice	Upregulates Beclin-1 and p62 to activate autophagy, inhibiting inflammatory cell infiltration, mast cell activation, alveolar collapse, congestion, and lung tissue fibrosis.	(140)

Plant extracts hold great potential for the treatment of asthma. For example, Tirpude et al. reported that the iridoid glycoside agnuside, extracted from *Vitex agnus-castus*, inhibited lung structural damage in allergic asthma mouse models induced by OVA and LPS and reduced inflammation, congestion, fibrosis, airway remodeling, and alveolar collapse. Further studies have demonstrated that agnuside decreases Beclin-1 expression, indicating that its therapeutic effects involve autophagy inhibition.[128] *Vitex negundo* leaf extract has been shown to reverse pathological changes in an allergic pulmonary inflammation Balb/c mouse model induced by OVA-LPS, including inflammation, congestion, fibrosis, bronchial thickening, and alveolar collapse, likely through autophagy inhibition.[129] Leupeptin, a protease inhibitor, has shown potential in the treatment of asthma by reducing inflammation and oxidative stress. It inhibits key inflammatory markers, such as NO, ROS, and TNF-α; regulates cytokine balance; and restores immune homeostasis.[130] In addition, it modulates autophagy by reducing Beclin-1 and LC3B and increasing p62, indicating its role in correcting autophagy imbalance.[131] Oleuropein, a polyphenolic compound extracted from olive oil, reduces oxidative stress induced by smoking and inhibits autophagy,[11] and has been shown to reduce airway inflammation and pulmonary fibrosis in mice exposed to OVA.[132]

In addition to plant extracts, 3-methyladenine, an autophagy inhibitor, suppresses VPS34 activity, thereby inhibiting autophagosome formation.[133] Studies have reported that in asthmatic mice induced by OVA and BEAS-2B cells induced by IL-13, 3-methyladenine substantially reduced LC3 expression, inhibiting autophagosome formation, reducing inflammatory cytokine expression, and alleviating asthma.[134] Budesonide, an inhaled glucocorticoid, has been widely used in the daily treatment of asthma.[135] A recent randomized controlled trial showed that budesonide suppresses macrophage autophagy in patients with asthma by inhibiting Beclin-1 and LC3 expressions, enhancing macrophage anti-inflammatory IL-10 secretion, and reducing asthma-related inflammation. Statins, such as simvastatin, enhance the ability of budesonide to inhibit autophagy, thereby amplifying its anti-inflammatory effects.[136] However, another study reported that simvastatin promotes autophagosome formation by upregulating ATG5, LC3B, and Beclin-1 while reducing the expressions of IL-4, IL-5, and IL-13, suggesting that simvastatin acts as an autophagy activator with anti-inflammatory properties.[137] Therefore, the role of simvastatin in autophagy regulation appears inconsistent, but it indeed modulates autophagy to counteract bronchial inflammation.

Besides simvastatin, other autophagy activators have shown therapeutic potential for the treatment of asthma. For example, rapamycin, an autophagy activator, directly binds and inhibits the mTOR complex 1 activity, thereby promoting autophagosome formation.[138] Mushaben et al. found that rapamycin substantially suppressed AHR, IgE levels, T-cell activation, and increased IL-13 and leukotrienes in mice induced by HDM, suggesting that the activation of mTOR pathway has potential for the treatment of allergic asthma by alleviating symptoms through its effects on key inflammatory factors.[139] Vitexin, a trihydroxyflavone derived from plant extracts, activates autophagy by upregulating Beclin-1 and p62 and inhibits inflammation, mast cell activation, alveolar collapse, congestion, and pulmonary fibrosis in asthmatic mice induced by OVA-LPS.[140]

Conclusion and Perspectives

Oxidative stress and autophagy play pivotal roles in the pathophysiology of asthma. Excessive ROS production exacerbates airway damage and worsens symptoms of asthma by regulating inflammatory signaling pathways. An impaired antioxidant system amplifies oxidative stress, whereas decreased levels of antioxidant enzymes and antioxidants in patients with asthma further weaken the body's ability to clear ROS, leading to increased tissue damage and inflammation. Exogenous factors, such as air pollution and allergens, also significantly increase ROS production, inducing airway inflammation and allergic reactions. Endogenous inflammatory cells, such as macrophages, neutrophils, and eosinophils, also contribute to the development of asthma by releasing ROS, thereby intensifying inflammation and airway remodeling. Simultaneously, autophagy serves as an essential intracellular defense mechanism, maintaining cellular homeostasis by clearing damaged organelles and proteins. In the context of asthma, autophagy plays a dual role: on the one hand, its activation helps mitigate damage induced by oxidative stress; on the other hand, excessive or imbalanced autophagy may worsen asthma symptoms, including airway remodeling and inflammation. Thus, the interplay between autophagy and oxidative stress in asthma is a complex regulatory process.

Although existing research has highlighted the importance of oxidative stress and autophagy in asthma, targeting autophagy regulation to reduce oxidative stress and improve asthma symptoms remains a challenge. Future studies should elucidate the complex association between ROS and autophagy, particularly in the specific mechanisms of different asthma phenotypes. Furthermore, natural compounds such as plant extracts show promise in regulating autophagy and ROS, warranting further investigation.

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Consent to Participate

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Authors Contributions

Ying Liu and Jun Zhang wrote the main manuscript. Tongtong Wang and Yu-ang Dong collected the data. All authors reviewed the manuscript.

Conflicts of Interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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