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Review

Unveiling the Intricacies of Autophagy in Asthma: Unraveling Novel Therapeutic Avenues

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Abstract

Understanding the pathogenesis of different phenotypes of asthma, including glucocorticoid-dependent and glucocorticoid-resistant asthma, is crucial for the development of effective treatments. Autophagy, a fundamental cellular process involved in cell homeostasis, has been implicated in asthma, although the exact mechanisms remain unclear. Recent studies have identified autophagy activation in eosinophilic, neutrophilic, and paucigranulocytic asthma, providing novel insights into the disease. This comprehensive review examines the role of autophagy in the pathogenesis and treatment of asthma, with a focus on various cell types. The goal is to uncover potential therapeutic targets and innovative treatment modalities to improve patient outcomes in clinical settings.

Keywords: neutrophil; eosinophil; paucigranulocytic; phenotypes; treatment

1. Introduction

According to the Global Burden of Diseases, Injuries and Risk Factors study, approximately 262 million individuals were affected by asthma in 2019, with 461,000 deaths attributed to the condition [1]. Asthma is a prevalent chronic inflammatory airway disease that has been linked to both genetic and environmental factors. The pathological manifestations of asthma include the infiltration of mast cells, eosinophils, macrophages, lymphocytes, and neutrophils beneath the airway epithelium. Additionally, functional abnormalities have been observed in the airway mucosa, blood vessels, and smooth muscle. Current clinical treatment strategies for asthma predominantly focus on eosinophil-dependent, corticosteroid-responsive asthma. Such strategies have limited clinical efficacy in the management of neutrophilic, corticosteroid-resistant asthma.

Autophagy is a catabolic process that relies on the lysosomes for the degradation of cytoplasmic components. This is regulated by autophagy-related genes (Fig. 1). Autophagy is implicated in various diseases, including cancer, infection, and neurodegeneration, as it participates in the immune response, inflammatory reactions, and antiviral mechanisms [2]. Studies have shown an association between asthma and single nucleotide polymorphisms (SNPs) in the autophagy-related gene 5 (*ATG5*) gene, specifically rs12201458, rs510432, and rs12212740. Additionally, the SNP rs12212740 has been linked to forced expiratory volume in 1 second *(FEV1)* prior to bronchodilator use, implying a potential connection between autophagy and reduced lung function among individuals with asthma [3,4].

In asthma, eosinophil-driven inflammation is frequently correlated with elevated levels of autophagy, whereas neutrophil-driven inflammation is often linked to impaired autophagic flux [5]. Autophagy has a protective or harmful effect on asthma, partly depending on the cell types involved [6]. On the one hand, autophagy plays a critical role in eliminating dysfunctional intracellular organelles and clearing cytoplasmic components. Autophagy impairment not only leads to the accumulation of these substances but also results in the release of reactive oxygen species (ROS), thereby impacting apoptosis and activating the immune system. Furthermore, autophagy dysregulation can contribute to the onset of airway inflammation and airway hyperresponsiveness (AHR) in asthma [7–9]. Meanwhile, in the context of persistent chronic infection, prolonged autophagy activation can lead to excessive autophagosome accumulation, which is potentially harmful to lung epithelial cells. This can contribute to lung damage and worsen asthma symptoms [10].

Basal levels of autophagy are observed in nearly all cells and the normal level of autophagic activity of autophagy varies between cell types (Fig. 2, Table 1). In asthmatics, the increased expression of LC3-II, IL-8 and eosinophil cationic protein have been observed in sputum granulocytes, neutrophils, peripheral blood eosinophils, and peripheral blood cells, in comparison to healthy controls [11]. Additionally, bronchial biopsies have found increased levels of double-membrane autophagosomes in fibroblasts and epithelial cells [4]. Increased autophagy is also implicated in asthma pathogenesis, contributing to processes such as extracellular matrix deposition, airway re-

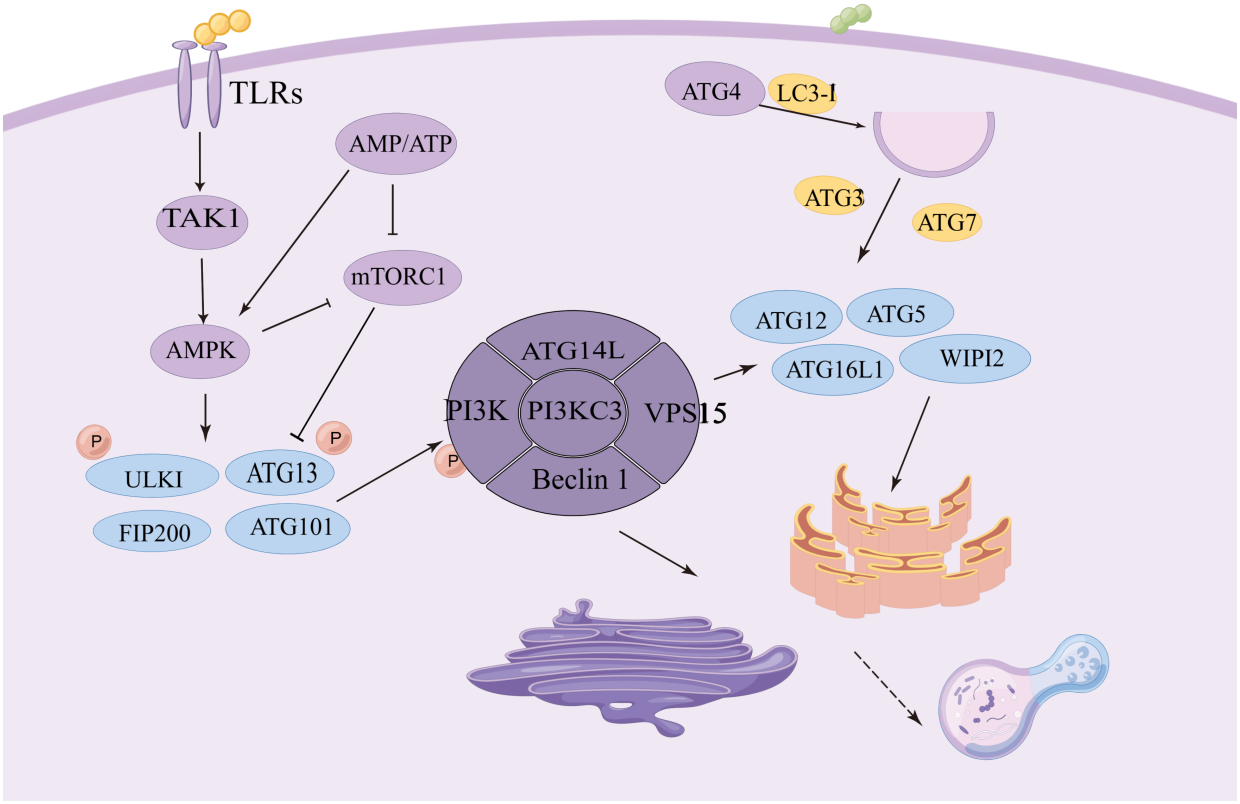

Fig. 1. Autophagy process. Under starvation conditions, MTORC1 activity is inhibited, AMPK is activated, and they promote activation ULK1 complex (ULK1-ATG13-FIP200-ATG101) formation, which mediates the initiation of autophagy. The activation of the ULK1 complex phosphoinositide PI3KC3 complex (Beclin1-PI3K-VPS15-ATG14L) mediates the formation of pre autophagosomal structure in membranous organelles such as endoplasmic reticulum and Golgi apparatus; The PI3KC3 complex further recruits the ATG16L1 complex (ATG16L1-ATG12-ATG5); LC3-I formed by ATG4 cleavage of LC3 precursor is recruited to the autophagic vesicles, under the influence of ATG7 and ATG3. When exposed to phosphatidylethanolamine (PE) is modified to fat-soluble LC3 (i.e., LC3-II). Then LC3-II can further bind to the newly formed autophagy membrane to promote autophagosome fusion and expansion. MTORC1, mammalian target of rapamycin C1; AMPK, adenosine monophosphate-activated protein kinase; ULK1, (Human) recombinant protein; PI3KC3, recombinant phosphoinositide-3-kinase class 3; LC3, microtubule-associated protein light chain 3.

modeling, and immune dysregulation [3,12–15]. This article aims to review the involvement of autophagy in the various cellular processes known to contribute to asthma to offer insights that will facilitate the development of novel biological agents and effective treatment strategies.

2. Autophagy and Eosinophil Asthma

2.1 Definition and Characteristics of Eosinophilic Asthma

Eosinophils differentiate from the eosinophil lineage-committed progenitor (EoP) cells which are a type of human common myeloid progenitor (hCMP) cell found in the bone marrow [16]. Eosinophils are stimulated to migrate to the lungs and airways by cytokines and chemokines. They play a crucial role in the immune responses to bacteria and parasites, as well as allergic responses. The effector function of eosinophils is attributed to the release of stored particles from their cytoplasm, such as eosinophil cationic proteins. Eosinophils can also form extracellular traps that capture and neutralize harmful substances [17].

Eosinophilic asthma is a unique asthma phenotype that is pathologically associated with thickening of the basement membrane zone and pharmacologically associated with the physical response to corticosteroids [18]. Eosinophilic asthma can be classed, primarily, as an allergen-dependent type 2 T helper (Th2) pulmonary immune response. This response is mediated by dendritic cells and T lymphocytes [19]. The most prevalent and distinctive form of this condition is allergic asthma, which is characterized by eosinophilic airway inflammation. Allergic asthma is associated with heightened production of type 2 cytokines, including IL-4, IL-5, and IL-13, which are secreted by group 2 innate lymphoid cells (ILC2s). Individuals with allergic asthma exhibit elevated levels of allergen-specific immunoglobulin E (IgE) antibodies [3]. Eosinophilic inflammation results in varying degrees of airflow obstruction and airway hyperresponsiveness (AHR) [20].

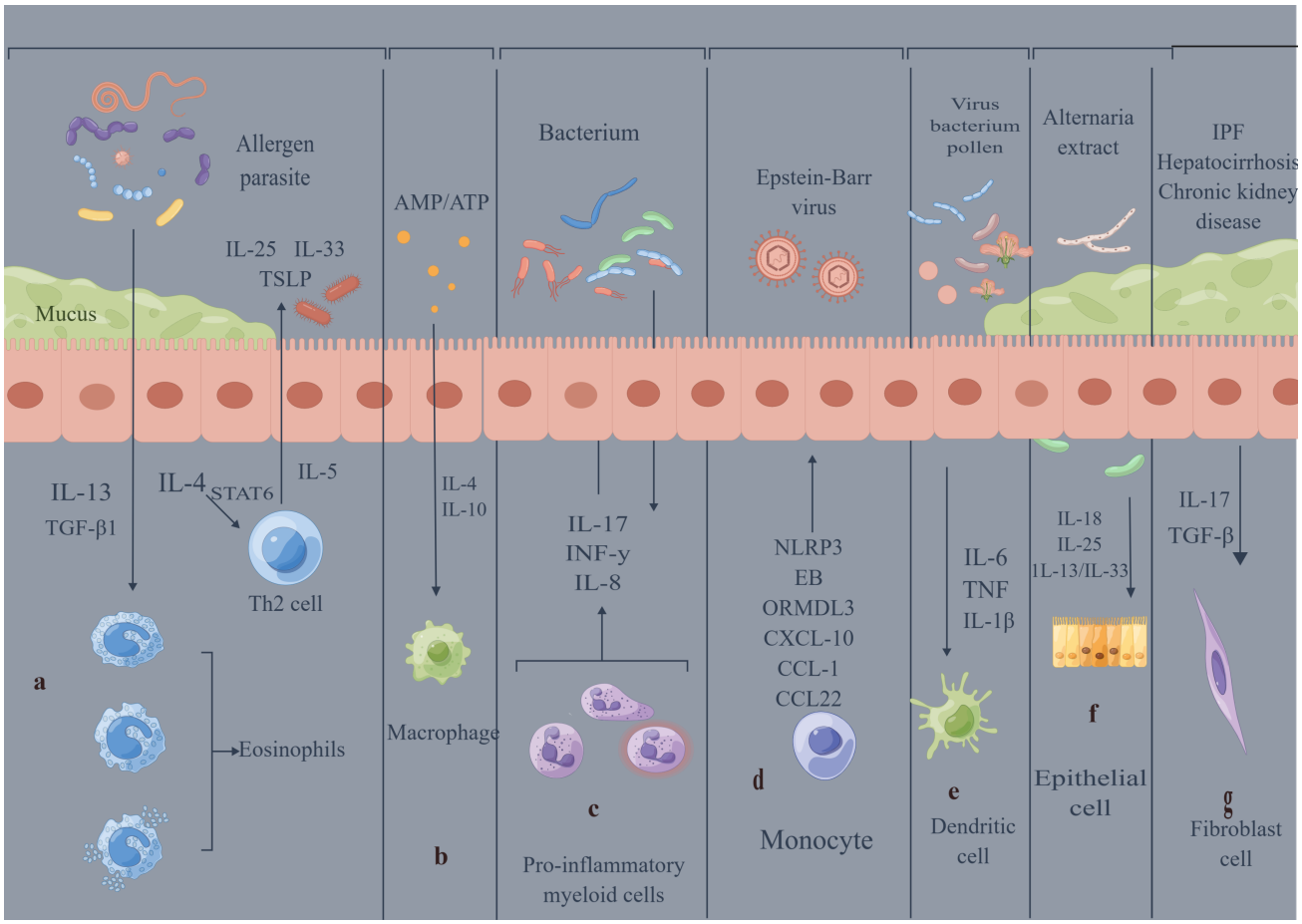

Fig. 2. Autophagy in different cells of asthma. STAT6, signal transducer and activator of transcription 6; TSLP, thymic stromal lymphopoietin; IFN-y, interferon-gamma; NLRP3, recombinant NLR family, pyrin domain containing protein 3; EB, transcription factor; ORMDL3, orosomucoid-like 3; CXCL-10, M1-associated cytokine; CCL-1 and CCL-22, M2-associated cytokines; TNF, tumor necrosis factor; TGF-β, transforming growth factor β; IL, Interleukin; IPF, idiopathic pulmonary fibrosis.

2.2 Role of Autophagy in Eosinophilic Asthma

Th2 cytokines such as IL-4, IL-5, and IL-13 are heavily involved in eosinophilic airway inflammation. Additionally, IL-4-induced signal transducer and activator of transcription 6 (STAT6) signals are transmitted to Th2 cells during T-cell polarization [21]. IL-5 contributes significantly to the proliferation, activation, and recruitment of eosinophils to specific tissues. Its primary sources are Th2 cells and ILC2s. Along with dendritic cells, Th2 cells mediate eosinophil involvement in allergic pulmonary inflammation. ILC2s are the main cellular source of IL-5 in tissue. They interact with epithelial cells, stimulating the production of IL-25, IL-33, and thymic stromal lymphopoietin, which further enhance eosinophilia [17]. In asthma, IL-5 induces autophagy in the airways of individuals with asthma and upregulates the expression of the eosinophil cationic proteins (ECPs) [11,15]. The upregulation of tumor necrosis factor-alpha (TNF-α) during allergen sensitization is associated with the induction of Th2 cell responses [21]. IL-13 is involved in the regulation of epithelial cell differentiation into goblet cells, as well as the promotion of intracellular oxidative stress and secretion of the mucin MUC5AC. These processes are associated with increased autophagic activity. Knockdown of autophagy-related protein 5 (Atg5) or depletion of autophagy inhibits goblet cell secretion [22] and intracellular ROS production, which is mediated by the activation of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase dual oxidase 1 (DUOX1) [23].

Galle-Treger *et al.* [20] have demonstrated that activated ILC2s rely on autophagy for their effector function and homeostasis. The absence of autophagy in ILC2s inhibits the effector function and their ability to mediate AHR. A lack of autophagy in activated ILC2s can inhibit the nuclear factor kappa B (NF-κB) pathway and induce cell apoptosis. It also hinders lipolysis, the induction of glycolytic metabolism, and the tricarboxylic acid cycle [20].

Transforming growth factor-beta 1 (TGF-β1) is a mediator of Th2-induced eosinophilic inflammation and the progression of airway remodeling [21]. Recent investigations have revealed that aryl hydrocarbon receptors (AhRs) in alveolar epithelial type II (AT2) cells are involved in

Table 1. Autophagy in different cells of asthma.

Level	Cells involved	Effects
a	Eosinophils	Th2 cytokines (such as IL-4, IL-5, and IL-13) promote eosinophilic inflammation in the airways, IL-4-induced STAT6 signaling to Th2 cells during T cell polarization, IL-5 acts on epithelial cells, promotes IL-25, IL-33, and TSLP, and further promotes eosinophilia.
b	Macrophages	IL-10 inhibits starvation-induced macrophage activation in mice by increasing PI3K signaling and mTORC1 activation, and IL-10 significantly inhibits rapamycin-induced autophagy and autophagy flux by increasing PI3K signaling and mTORC1 activation, and IL-10 significantly inhibits rapamycin-induced autophagy and autophagy flux to a similar degree to 3-MA when inducing M2-like phenotypes in M-CSF and monocytes-derived macrophages cultured in IL-4.
c	Neutrophils	IL-8 is an important neutrophil chemoattractor that stimulates neutrophils and increases mucus secretion in severe asthma, IL-17 produced by the CD4T effector cell lineage (Th17) targets various cell types to promote neutrophil stimulation and attraction to the site of inflammation, IFN-y upregulates IL-12 expression in antigen-presenting cells, and then induces Th1 cell polarization through the STAT4 signaling pathway.
d	Monocytes	NLRP3 induces monocytes activation, ARG transcription factor EB-mediated reprogramming of monocytes inflammatory response, asthma susceptibility risk alleles increase the expression of ORMDL3 in lung tissue, epithelial-derived TSLP reduces the production of the CXCL-10 and increases the production of CCL-1 and CCL-22.
e	Dendritic cells	Dendritic cell-specific knockout of ATG5 reduces the expression of cytokines such as IL-6, TNF, and IL-1β, while IL-17A expression is increased.
f	Airway epithelial cells	Allergen-induced inflammation promotes IL25 production, IL-18 secretion increases, and exposure of airway epithelial cells to IL-13 or IL-33 in asthmatic patients activates autophagy by inhibiting mTORC1.
g	Fibroblasts	Autophagy dysregulation is associated with increased release of TGF-β, IL-17 induces autophagy and mitochondrial autophagy in bronchial fibroblasts in patients with asthma.

3-MA, 3-Methyladenine; M-CSF, macrophage colony-stimulating factor; ARG, autophagy-related gene.

the prevention of allergic airway inflammation. This is achieved through the regulation of TGF-β1 release and the control of autophagy adapters calcium binding and coiled-coil domain 2 (CALCOCO2) and S100 calcium-binding protein A9 (S100A9), which, in turn, regulate the autophagy process [24].

In a mechanistic study, Zhang *et al*. [12] provided evidence for an allergen-ROS-oxidized Ca^{2+}/calmodulin-dependent protein kinase II (ox-CAMKII)-mitophagic axis in the development of allergic airway inflammation and asthma. The axis was observed in both allergen-treated human bronchial epithelial cells and a mouse model. Furthermore, it was discovered that CAMKII can regulate autophagy/mitophagy by directly phosphorylating Beclin 1, which is a core player in autophagosome formation and maturation [12].

Eosinophils have been shown to rapidly release mitochondrial DNA and granulin rapidly in a ROS-dependent manner when exposed to IL-5 or interferon-gamma (INF-γ). This leads to the formation of eosinophil extracellular traps (EETs), which possess bactericidal properties [25,26]. EET generation relies on autophagy rather than cell death. Notably, inhibiting autophagy hinders the release of EETs, leading to a decrease in mucus and lung inflammation [27].

3 Autophagy and Neutrophil Asthma

3.1 Definition and Characteristics of Neutrophilic Asthma

Neutrophilic asthma is characterized by elevated levels of neutrophils in the sputum. Individuals with neutrophilic asthma often have inherent immune system abnormalities, increased bacterial colonization of the airways, and elevated levels of airway endotoxins [21]. Th17 cells, a T lymphocyte subset, have been identified as significant contributors to the pathobiology of neutrophilic asthma. These cells produce IL-17A and IL-17F [28], which stimulate the recruitment of neutrophils by binding to the IL-17R on epithelial cells [29]. Consequently, the epithelial cells produce chemokines, including IL-8, which promote further neutrophil recruitment [30]. IL-8 concentrations have been found to correlate with the number of neutrophils present in the airways. This continuous recruitment and expansion of the neutrophil population contributes to the characteristic features of neutrophilic asthma, which include elevated levels of pro-inflammatory cytokines and neutrophilic inflammation of the airways. Various circulatory mediators of inflammation are also activated within the neutrophil-infiltrated airways [31,32]. Activated neutrophils adhere to the airway epithelium and stimulate the inflammatory response [28,33,34]. Neutrophil autophagy and the formation of neutrophil extracellular traps (NETs)

[35] exacerbate asthmatic severity. These processes can disrupt the integrity of the airway epithelium and trigger an inflammatory response in human airway epithelial cells and peripheral blood eosinophils [15]. Damage to the airway epithelium can consequently lead to ongoing airway obstruction and remodeling [36,37].

3.2 Role of Autophagy in Neutrophil Asthma

Neutrophils migrate via the bloodstream to the site of an infection or injury by traversing damaged endothelial cells (EC) that line the blood vessels. Recent studies have revealed that acutely inflamed microvascular venules induce autophagy induction at the junctions between EC. *In vivo* experiments have further established that endothelial cell autophagy negatively regulates the physiological transendothelial migration of neutrophils. This suggests that the exploitation of EC autophagy has therapeutic potential as an anti-inflammatory strategy that would protect the host from excessive tissue damage caused by neutrophils [38].

Neutrophil airway inflammation in asthma has been linked to polymorphisms of the autophagy-related genes *ATG5* and *ATG7* [39]. A recent study by Suzuki *et al*. [8] demonstrated that depleted Atg5 levels in CD11c cells result in airway inflammation induced by steroid-resistant neutrophils. The authors of the study propose that enhancing pulmonary autophagy could ameliorate refractory severe asthma [8]. Bhattacharya *et al*. [40] investigated neutrophil biology using Atg7/Atg5-deficient mice and observed that the absence of autophagy can decrease neutrophil degranulation and inflammatory potential due to secretion defects. They identified reduced production of NADPH-induced ROS as a mechanism that contributes to autophagy-deficient neutrophils as this reduction diminishes the degranulation of neutrophils. These findings highlight the role of autophagy in regulating neutrophil functions and suggest that autophagy may serve as a potential target for modulating neutrophil-mediated inflammation [40].

An increase in the presence of NETs and NET components in the airways of asthmatic patients and, sometimes, the accumulation of excessive NETs, has been associated with the activation of the innate immune response. This implicates NETs in the pathogenesis of asthma [25,41]. NETs are composed of mitochondrial DNA and antimicrobial proteins released by viable neutrophils [42]. NETs ensnare and degrade microorganisms [43] and can induce inflammation by disrupting airway epithelial cells (AECs), stimulating AECs to produce IL-8, and activating eosinophils to release their granules. NETs can also exacerbate asthma by causing small airway obstruction through increased formation of cellular aggregates [44]. Pham *et al*. [15] found that patients with severe asthma (SA) exhibit higher levels of autophagy and NET production than those with non-severe asthma (NSA). Autophagy plays a crucial role in the regulation of neutrophil survival and the formation of NETs. Inhibition of autophagy led to activation of caspases and to the appearance of morphological features of apoptosis, such as membrane blebbing [45]. Inhibition of autophagy prevents the decondensation of intracellular chromatin and this attenuates NET production. In turn, this results in apoptotic cell death. Thus, the dysregulation of autophagy and NET formation may contribute to the pathogenesis of SA [45].

The polarization of Th1 and Th17 cells is predominantly regulated by IL-12 and IL-6, both of which contribute to neutrophil-mediated inflammation. Notably, the Th1 cytokine IFN-γ is upregulated in the induced sputum of patients with SA and is positively correlated with high sputum neutrophil levels. This suggests a potential link between Th1 polarization, neutrophilic inflammation, and the severity of asthma in these patients [46]. Transgenic mouse experiments have shown that IFN-γ promotes the polarization of Th1 cells by upregulating the transcription factor T-bet. This, in turn, inhibits the polarization of Th2 cells. IFN-γ also suppresses the recruitment of eosinophils into lung tissue following antigen stimulation by inhibiting the infiltration of CD4+ T cells [47]. However, elevated levels of IFN-γ can induce neutrophilic airway inflammation, emphysema [48], and AHR [49].

IL-17, produced by the CD4+ T effector cell lineage known as Th17, plays a significant role in regulating airway remodeling in asthma. It can target various cell types and trigger the production of cytokines [50]. Moreover, IL-17 acts as a stimulator, attracting neutrophils to the site of inflammation. IL-17 also induces the production of matrix metalloproteinases (MMPs) which contribute to the degradation of inflammatory tissues [51,52]. In individuals with SA, IL-17-induced autophagy has been shown to regulate mitochondrial dysfunction and fibrosis in bronchial fibroblasts [53]. Deficiency in the Th17-associated cytokine IL-23 has been associated with corticosteroid resistance [52]. Suzuki *et al*. [8] demonstrated that neutrophilic asthmatic mice with a deficiency in the autophagy-related gene Atg5 exhibit glucocorticoid resistance and dependence on IL-17A. IL-17A is a glycoprotein [54] secreted by IL-17-producing cells that is implicated in chronic inflammatory and autoimmune diseases. Mi *et al*. [55] revealed that particulate matter 2.5 (PM2.5) activates the TGF-β signaling pathway by promoting the secretion of IL-17A in $\gamma\delta$T/Th17 cells, thereby inhibiting autophagy in bronchial epithelial cells. This activation causes epithelial-mesenchymal transition and ultimately exacerbates lung inflammation and fibrosis [55]. Targeting IL-17A creates a shift in the immune response in fibrotic lung tissue from an inhibitory state to a Th1 type, induces effective autophagy, facilitates autophagy-related cell death, and alleviates both acute and chronic pulmonary fibrosis. Moreover, IL-17A has been found to impede collagen degradation and inhibit autophagy in a TGF-β1-independent manner [55].

Kawaguchi *et al*. [56] have shown that IL-17, either alone or in combination with other cytokines (IL-4, IL-13, and IFN-γ), can induce IL-8 production. IL-8 is a neutrophil chemoattractant that stimulates neutrophils, increases mucus secretion, promotes the transient adhesion of eosinophils, prolongs the contact time between eosinophils and EC, and enhances the immune response in those with SA. In migration experiments, it was observed that pretreatment with LY294002(a PI3K inhibitor) and HCQ significantly decreases the migration of neutrophils toward IL-8 [11,15]. This suggests that the suppression of autophagy could be considered an effective therapeutic approach for the management of corticosteroid-resistant neutrophilic asthma.

4. Autophagy and Paucigranulocytic Asthma

4.1 Definition and Characteristics of Paucigranulocytic Asthma

In comparison to other forms of asthma, paucigranulocytic asthma (PGA) is characterized by reduced levels of eosinophils and neutrophils in the airways, improved lung function, relatively low expression of inflammatory biomarkers in exhaled and induced sputum, and favorable responses to treatment [57,58]. The remaining inflammatory cells, such as epithelial cells, macrophages, monocytes, dendritic cells, fibroblasts, mast cells, etc., are known to be involved in the initiation and propagation of this form of asthma.

4.2 Role of Autophagy in other Cell Types Involved in Asthma

4.2.1 Epithelial Cells

AECs are the initial targets in the allergic inflammation associated with asthma. Allergen-induced inflammation leads to reduced rapamycin (mTOR) activity and increased autophagy in AECs. This increases the release of proallergic cytokines such as IL-25, leading to type 2 immune reactions, exacerbating airway inflammation, and perpetuating the inflammatory cascade [59]. The exposure of human bronchial epithelial cells to particulate matter initiates endocytosis and autophagy, resulting in the upregulated expression of inflammatory cytokines and mucin MUC5AC within epithelial cells. However, the inhibition of autophagy through the knockdown of Beclin-1 and microtubule-associated protein 1A/1B-light chain 3 B (LC3B) has been shown to effectively reduce airway inflammation and inhibit excessive mucus production [60]. Within human AECs, prolonged exposure to Alternaria extract (ALT-E) enhances the formation of autophagosomes, the conversion of LC3-I to LC3-II, and the degradation of p62. This triggers the release of IL-18 from these cells, initiating a Th2-type immune response. However, the secretion of IL-18 can be prevented by the use of autophagy inhibitors, such as 3-methyladenine and bafilomycin [61]. A significant correlation has been found between the expression of the asthma-risk gene orosomucoid-like 3 (*ORMDL3*) and autophagy-related genes in bronchial epithelial cells. Overexpression of *ORMDL3* results in an increased number of autophagosomes and elevated levels of Beclin-1 and autophagy-related proteins, including LC3B, *ATG3, ATG5, ATG7*, and *ATG16L1*. Furthermore, in asthma, *ORMDL3* interacts with the sarco-/endoplasmic reticulum (SERCA2), leading to impaired bronchial epithelial function and promoting epithelial autophagy [62].

4.2.2 Macrophages

Macrophages also known as histocytes, originate from monocytes in the bloodstream that migrate through the blood vessels and enter the connective tissue. Research has shown that autophagy in key asthma effector cells is associated with augmentation of T2 inflammation and suppression of the anti-inflammatory cytokine IL-10. IL-10 is an anti-inflammatory cytokine that inhibits IL-10 secretion through macrophage autophagy in patients with asthma, resulting in reduced IL-10 levels in the sputum [63–65]. Corticosteroids and statins control asthmatic inflammation by suppressing autophagy and enhancing IL-10 production [66]. Ip *et al*. [67] have demonstrated that IL-10 inhibits the mechanistic target of rapamycin complex 1 (mTORC1) signaling and inflammasome activation in macrophages via STAT3, a vital transcription factor that operates downstream of IL-10R signaling. This signaling pathway promotes mitochondrial autophagy, mitigating the accumulation of dysfunctional mitochondria and the production of mitochondrial ROS [67]. Recent research has discovered that long non-coding RNA (lncRNA) not only plays a critical role in macrophage development but also contributes to macrophage inflammation in asthma. Specifically, lncRNA reduces autophagy and impedes autophagy-induced apoptosis in macrophages, promoting the inflammatory processes associated with asthma [68].

4.2.3 Dendritic Cells

In murine models of bronchial asthma, the knockdown of dendritic *ATG5* leads to decreased expression of cytokines such as IL-1α, IL-1β, and IL-23 [8]. Conversely, the expression of IL-17A is increased in these models, exacerbating lung inflammation. In the context of respiratory syncytial virus (RSV)-induced asthma, the regulation of dendritic cell (DC) autophagy is dependent on the 5′ adenosine monophosphate-activated protein kinase/serine-threonine kinase 1 (AMPK/ULK1) signaling pathway. Elevated expression of AMPK and ULK1 in pulmonary tissue increases autophagy in DCs, resulting in the mitigation of chronic airway inflammation, AHR, and airway remodeling. This mechanism contributes to the amelioration of RSV-induced asthma [69,70].

4.2.4 Fibroblasts

Fibroblasts are fibrosis effector cells. The dysregulation of autophagy is strongly associated with heightened

fibrosis, and the expression of various collagen types is positively correlated with autophagy-related genes [71]. TGF-β serves as a regulatory factor in fibrosis, and the suppression of autophagy-related genes weakens fibrotic processes [72]. Activated fibroblasts from various tissues demonstrate the expression of Atg5 or Atg7. Pharmacological interventions that inhibit autophagy by knocking down Atg5 or silencing Atg7 effectively attenuate fibrotic processes [73]. IL-17 exacerbates mitochondrial dysfunction and upregulates the expression of fibrotic genes in bronchial fibroblasts through the activation of autophagy. Conversely, treatment of IL-17 with bafilomycin-A1 (Baf-A1) has been shown to reverse IL-17-induced mitochondrial damage and associated profibrotic characteristics [53]. Bronchial fibroblasts derived from SA individuals demonstrate upregulation of the mitochondrial autophagy pathway, accompanied by elevated expression of Pink-1/Parkin and LC3-II. These cells also exhibit a profibrotic phenotype and the activation of the AMPKα/sirtuin 1(Sirt1)/peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) signaling axis. This is believed to be a compensatory response to the mitochondrial dysfunction observed in asthma cells [74].

4.2.5 Monocytes

Monocytes originate from hematopoietic stem cells within the bone marrow and develop at the same anatomical site. Developed cells pass from the bone marrow into the bloodstream but maintain an immature phenotype. There is clinical evidence that NLR family pyrin domain containing 3 (NLRP3), a sensor protein associated with inflammasomes, contributes to the initiation of asthma through inflammation in monocytes in both the circulation and the lungs. In an experimental model that inhibited autophagy, NLRP3 was found to activate monocytes. This activation was enhanced by the reduced levels of autophagy in circulating monocytes. Autophagy impairment relies on the transcription factor EB (TFEB)-mediated reprogramming of inflammatory responses in monocytes and is positively correlated with the severity of asthma [75]. Thymic stromal lymphopoietin (TSLP), a Th2-like cytokine derived from epithelial cells, exerts regulatory control over ROS production and mitochondrial autophagy via AMPK signaling pathways and histone modifications. Furthermore, TSLP modulates the expression of M1/M2 chemokines in human monocytes. These effects can lead to pulmonary fibrosis in asthmatics [76]. Research indicates that TSLP can reduce the production of C-X-C motif chemokine ligand 10 (CXCL-10), an M1-associated cytokine, and enhance the production of chemokine ligand 1 (CCL-1) and CCL-22, which are M2-associated cytokines. However, the expression of CCL-22 can be inhibited by downregulating the genes mitochondrial division inhibitor 1 (*mdivi-1*) and PTEN-induced kinase 1 (*PINK1*), which are inhibitors of mitochondrial autophagy [76].

4.2.6 Mast Cells

Mast cells, also known as tissue basophils, are equipped with histamine, heparin, eosinophil chemokines, slow-reactive substances, and serotonin, among other substances. These cells possess the ability to release diverse bioactive mediators upon stimulation by IgE or other antigens. This initiates allergic reactions and influences airway remodeling [77]. Research has demonstrated that the asthma associated *ORMDL3* inhibits mast cell degranulation and the release of cytokines/chemokines in response to antigens [78]. This is achieved through the regulation of endoplasmic reticulum stress (ERS)-induced unfolded protein responses (UPR) and autophagy, specifically via the ATF6-UPR-autophagy-dependent pathway. Consequently, these mechanisms attenuate allergic responses [79]. It has also been observed that the inhibitory effect of *ORMDL3* overexpression on mast cell activation can be reversed by inhibiting autophagy [79].

5. The Clinical Efficacy of Known Autophagy Regulators

Corticosteroids are widely recognized as an effective therapeutic option for asthma. In a study conducted by Liu *et al.* [80,81] found that short-term glucocorticoid therapy results in the upregulation of autophagy. However, prolonged exposure to glucocorticoids is associated with a notable decline in autophagy. Corticosteroids exert their anti-inflammatory effects by inhibiting the transcription of various cytokines and receptors associated with asthma and by reducing the survival rate of specific inflammatory cells. In cases of steroid-resistant asthma, the role of autophagy in these inflammatory cells becomes increasingly important. Modulating autophagy could potentially serve as a novel therapeutic approach to SA treatment. Mounting evidence suggests that abnormal autophagy contributes to the development of asthma. Therefore, therapeutic targeting of autophagy to restore cellular homeostasis holds promise for asthmatic patients [82]. However, autophagy can be either upregulated or downregulated in different cell types depending on the cellular context, and this poses challenges for the therapeutic targeting of autophagy. Currently available drugs that have been shown to activate autophagy include rapamycin, cardiac glycosides, statins, metformin, and carbamazepine. Conversely, drugs such as chloroquine (CQ), hydroxychloroquine (HCQ), Baf-A1, 3-methyladenine, azithromycin, and melatonin have demonstrated inhibitory effects on autophagy. However, it is important to note that, because these drugs were not designed to modulate autophagy, their effects are nonspecific, making it difficult to predict the outcomes of their use in asthma treatment. Nonetheless, harnessing the considerable therapeutic potential of these drugs could be hugely beneficial for various patient populations [83]. Studies have found that the deletion of cell-specific autophagy-related genes provides a solution to the issue of nonspecific effects in such

drugs. Numerous mouse models with deletions of relevant genes have been established to investigate therapeutic autophagy regulation [84]. As a result of such research, more targeted novel drugs are currently under development as potential future therapeutics for asthma. Subsections 5.1 to 5.3, below, describe some of the autophagy modulators and targeted agents presently available.

5.1 Autophagic Agonists

Certain drugs can increase autophagy in medical conditions characterized by impaired autophagy. These drugs are potential treatment options for severe neutrophilic asthma. Rapamycin, everolimus and telrolimus activate autophagy by inhibiting mTORC1. In a study of mice with autophagy-deficient neutrophilic asthma, pretreatment with rapamycin resulted in the inhibition of Th17 cell polarization and downregulation of IL-17A expression, leading to a significant reduction in neutrophilic airway inflammation [85]. By targeting mTORC1, rapamycin has been shown to decrease the number of eosinophils and inhibit eosinophil differentiation. *In vitro*, this mechanism has been found to reduce cytokine levels, allergic airway inflammation, and mucus secretion, while promoting autophagy *in vitro* [86]. In contrast, Torin-1 inhibits mTORC1 and mTORC2 *in vitro* and facilitates eosinophil differentiation. Although there have been few clinical studies evaluating their efficacy in asthma treatment, rapamycin has been found that can restore steroid responsiveness involving IL-10 and IL-1β to dexamethasone treatment on CD14++CD16+ monocytes from steroid-resistant asthma patients [87]. And low-dose therapy with mTORC1 inhibitors has been found safe for older patients. Additionally, it has been reported that such therapy improves immune function and reduces the incidence of infections in the elderly patients [88].

Cardiac glycosides, such as digoxin, digitalis, and ouabain, are widely used to treat heart disease, but also show potential for use in targeted cancer therapy. These compounds have been found to activate autophagy. In human non-small cell lung cancer (NSCLC) cells, cardiac glycosides induce autophagy by downregulating rapamycin (mTOR) signaling and activating extracellular signaling to regulate kinase 1/2 (ERK1/2) signaling [89]. Furthermore, they can restore autophagosome maturation in AECs and reverse defective autophagy fluxes [90]. However, under certain conditions, cardiac glycosides may exert inhibitory effects on autophagy and autophagic cell death by inhibiting sodium-potassium pump (Na+/K+-ATPase) activity. For instance, in situations such as starvation, autophagy-inducing peptide therapy, and hypoxic-ischemic injury of the neonatal hippocampus [91].

Statins such as atorvastatin and simvastatin, have shown promise for improved asthma control and reduced asthma exacerbations [92]. Specifically, simvastatin has been found to activate autophagy in bronchial smooth muscle cells (BSMCs) in mouse models of asthma, leading to the inhibition of airway inflammation and airway remodeling [93]. Additionally, short-term combination therapy with atorvastatin and inhaled corticosteroids has been shown to reduce inflammatory sputum mediators in smokers with mild to moderate asthma who do not respond adequately to inhaled corticosteroids alone [94]. Recent studies indicate that it is capable of controlling inflammatory responses in asthma by inhibiting macrophage autophagy and promoting the production of IL-10 [66]. Studies have found that mevalonate pathway regulates cell size homeostasis and proteostasis through autophagy involving the Rab GTPases. And statins, inhibitors of the mevalonate pathway, reduce cell proliferation and increase cell size and cellular protein density in various cell types [95].

Metformin, commonly used in the clinical treatment of diabetes and metabolic syndrome, has shown potential as a means of reducing asthma exacerbations and has been used in adult cohorts with comorbid asthma and diabetes mellitus [96]. *In vivo* studies using mice with sensitized asthma have demonstrated that metformin can effectively mitigate injury-induced airway inflammation and remodeling [97]. Metformin has been found to induce mitophagy by downregulating p53 and promoting Parkin activity. However, metformin also exerts various effects unrelated to AMPK, and the relationships between these effects and autophagy activation have not been confirmed. Carbamazepine is another medication that activates autophagy. This is clinically used for the treatment of seizures and bipolar disorder. It activates autophagy by inhibiting phosphoinositide 3-kinase (PI3K) signaling. However, it also inhibits various neuronal functions [98], and, to date, there have been no clinical trials on the treatment of asthma with carbamazepine.

5.2 Autophagic Inhibitors

Certain drugs have the ability to reduce autophagy in diseases, where it is excessive. These are potential candidates for eosinophilic asthma treatments. CQ, an antimalarial drug, inhibits autophagy by impeding the fusion of autophagosomes and lysosomes. It is important to note that CQ treatment does not disrupt lysosomal acidity. Conversely, the autophagy flux inhibitor HCQ elevates lysosomal pH, blocks lysosomal acidification, and inhibits autophagosome-lysosomal fusion, resulting in the accumulation of autophagic components [99]. However, CQ and HCQ have various additional effects, including disruptions to the Golgi apparatus and lysosomal network [100,101]. Furthermore, the anticancer effects of these drugs have not been consistently observed in certain clinical trials, suggesting that their efficacy may not be solely dependent on autophagy modulation.

Baf-A1 is a macrolide antibiotic that inhibits the acidification of autolysosomes by targeting vacuolar H+-V-ATPase, effectively blocking late-stage autophagy [102, 103]. Another macrolide antibiotic, azithromycin, has been

used in the long-term treatment of chronic inflammatory lung disease; however, this application carries a risk of infection with nontuberculous mycobacteria (NTM). This is attributed to the antibiotic's ability to hinder lysosomal acidification, impede autophagosome clearance, impair autophagy, and hinder phagosome degradation [104]. However, research has shown long-term, low-dose macrolide antibiotic therapy to effectively reduce airway inflammation and steroid resistance [105]. Yet, this approach has some drawbacks, including the potential induction of drug resistance and increased susceptibility to mycobacterial infections [106].

In asthmatic patients, the inhibition of autophagy and the induction of IL-10 have been observed in alveolar macrophages treated with 3-methyladenine (3-MA) [66]. This inhibition is achieved by the suppression of autophagosome formation through the inhibition of class III PI3Ks [107]. Moreover, 3-MA has also been shown to reduce oxidative stress and lung inflammation by inhibiting the formation of EETs [14,27,80,108]. But, 3-MA is also associated with cytotoxic effects and DNA damage, resulting in reduced cell viability across various cell lines [109]. Melatonin has been investigated in clinical trials as a potential therapeutic agent for various diseases. It has been shown to protect against ischemia-reperfusion (I/R) damage in rat brains by inhibiting autophagy and activating the PI3K/Akt survival pathway. However, it should be noted that melatonin can interfere with ROS-sensitive processes [110]. Furthermore, it has been observed that several current asthma medications, such as dexamethasone, montelukast, anti-IL-5, and anti-IgE antibodies, also inhibit autophagy [107]. Specifically, dexamethasone significantly decreases IL-5-induced autophagy in the peripheral blood eosinophils of patients with NSA, with less pronounced effects in patients with SA [11].

More specific inhibitors that target the autophagy pathway are currently under preclinical development. These include the lysosomal inhibitor Lys05, inhibitors of mitochondrial autophagy, ULK1 inhibitors (MRT67307, MRT68921, and SBI-0206965), and VPS34 selective inhibitors (SAR405, LY294002, VPS34-IN1, and Wortmannin) [109]. A recent study proposed that the compromised glucose metabolism and impaired cytokine secretion observed in ATG5-deficient ILC2s can be restored by treatment with exogenous pyruvate or supplementing with free fatty acid supplements. These interventions effectively target ILC2-dependent inflammation [20].

5.3 Biological Agents

In 2020, whole human anti-IL-5 antibodies and anti-IL-5 receptor antibodies were utilized in the management of steroid-refractory asthma. These antibodies specifically target the autophagy-mediated activation pathways of eosinophils, reducing LC3 levels and the eosinophil count in bronchoalveolar lavage fluid (BALF) [80]. Treatment with anti-IL-5 monoclonal antibodies was found to improve AHR [111]. Early-stage human studies have demonstrated that IL-1β receptor antagonists, such as anakinra, can alleviate neutrophilic airway inflammation. These antagonists can serve as a rescue treatment for acute asthma attacks [112]. Research has shown that the NLRP3 inhibitor MCC950 effectively inhibits IL-1β and is an efficacious treatment for mouse models of severe steroid-resistant neutrophil-allergic airway disease [113]. Whole human anti-IL-4 and anti-IL-13 monoclonal antibodies have progressed to phase III clinical trials, while anti-IL-17 monoclonal antibodies are currently in phase II clinical trials. However, existing research did not find anti-IL-17R antibodies, such as brodalumab to yield therapeutic effects in individuals with asthma [114]. Conversely, anti-IL-6R antibodies, such as tocilizumab have been effectively employed as an adjunctive treatment in children suffering from severe persistent non-atopic asthma [115]. Omalizumab is a monoclonal antibody designed to treat allergic asthma patients who display elevated serum IgE levels. It has a proven ability to prevent persistent severe allergic asthma exacerbations and to reduce the need to utilize systemic corticosteroids in asthmatics, regardless there blood eosinophil count [116].

Dupilumab, a recently developed monoclonal antibody, functions by blocking the signaling pathways of both IL-4 and IL-13. Clinical evidence suggests that this antibody is highly effective in managing severe type 2 (T2) asthma and can help prevent acute exacerbations [117]. In patients aged 12 months and older with SA, treatment with tezepelumab, a humanized TSLP IgG2 antibody, has also demonstrated significant clinical benefits, including improved lung function and reduced frequency of exacerbations. However, further validation by larger phase III clinical trials is required [118]. Cahill *et al.* [119] have demonstrated that imatinib treatment effectively reduces AHR, mast cell count, and the release of tryptase (a marker of mast cell activation). Maun *et al.* [120] found that treatment with allosteric anti-tryptase antibodies can effectively decrease the incidence of anaphylaxis. Studies with murine models of asthma have found anti-nerve growth factor (anti-NGF) antibodies to effectively reduce Th2 airway inflammation through the downregulation of lung autophagy levels [121], while oral astragalus supplementation has been found to alleviate ROS-facilitated bronchial fibrosis by inhibiting the formation of autophagosomes [122]. Luteolin is known for its anti-inflammatory, anti-allergic, and immune-enhancing properties, and has recently been found to activate the PI3K/Akt/mTOR signaling pathway, inhibit autophagy, promote cell survival, improve lung function, and alleviate airway inflammation in mice with allergic asthma. Luteolin has no effect at low doses [123].

As a novel therapeutic strategy, biologics can target specific phenotypic or endotypic mechanisms of asthma pathophysiology mediated by autophagy, and precisely

modulate the intermediate pathways of immune response in inflammation. This approach significantly improves the therapeutic efficacy of refractory and severe asthma patients. Therefore, it is necessary to explore and validate more new biologics in clinical practice to achieve personalized asthma treatment.

6. Discussion

The involvement of autophagy in the pathogenesis of asthma is currently under extensive investigation. Moreover, researchers are increasingly directing their attention toward the exploration of both the non-immune and immune cells implicated in asthma. Such research aims to determine whether autophagy modulation is a viable therapeutic approach for asthma treatment. Our current understanding of autophagy in asthma is primarily based on preclinical evidence. It remains uncertain whether drugs that affect the autophagy signaling pathway are targeting autophagy directly or indirectly, via cytokine modulation and the production of various cell types. Germic *et al*. [124] propose that both structural pulmonary cells and inflammatory cells in asthmatics can induce autophagy. However, again, the exact role of this in the pathogenesis of asthma is unclear. Consequently, it would be premature to suggest asthma treatment strategies solely based on autophagy suppression [124]. Currently available autophagy inhibitors and agonists interfere with other cellular processes, apart from autophagy. Therefore, further pharmacological studies and genetic methodologies are necessary to fully comprehend the function of autophagy and avoid potential cytotoxicity from these drugs. Numerous studies have demonstrated the diverse effects of different drugs, as well as differing doses of the same drug, on autophagy levels, and their targeting of different points within autophagy pathways. Hence, combination therapies using drugs that activate upstream autophagy in conjunction with those that enhance lysosomal degradation may prove most effective [98].

More specific approaches involve the selective knockout or knockdown of autophagy-related genes in specific cell types. However, a major obstacle to this approach is that autophagy-related proteins have other functions independent of autophagy, including involvement in cell death. After evaluating the transcriptome data of a cohort of asthmatic patients, Yang *et al*. [125] concluded that high expression of autophagy-related genes (*ARGs*) is often associated with good asthma control. They suggest that using ARG expression-based typing methods could guide appropriate hormone dosages for SA patients [125]. Therefore, elucidating the relationship between *ARGs*, immune cells, and asthma will provide valuable insights and enable more accurate prediction of treatment responses and prognoses in individual asthma patients [126]. Lv *et al*. [127] have evidenced multiple cross-links between ferroptosis and autophagy in asthma, occurring across different cell types. Galle-Treger *et al*. [20] have provided support for the hypothesis that autophagy reprogramming induces metabolic reprogramming. Their experiments demonstrate significant autophagy involvement in the regulation of metabolites such as glucose and fatty acids and the maintenance of equilibrium in metabolic pathways responsible for energy production in various immune cell populations [20].

In conclusion, future research on the therapeutic use of autophagy regulators to target different types of cells implicated in asthma must address several key issues. This should include determining whether the drug studied can be effectively targeted at the disease site, whether it can target specific cells with sufficient accuracy, whether it can eliminate cells before they activate and release inflammatory mediators, and establishing any cellular damage that may be caused by the knockdown of the relevant autophagy-related gene. If more precise autophagy-regulating drugs are to be developed, it is also crucial to elucidate the molecular mechanisms of autophagy in various cell types. The achievement of these research goals will facilitate improved treatment outcomes in clinically associated diseases.

Author Contributions

JP and LS designed the research study. JP and NL performed the research and wrote the manuscript. LS and HL provided help and advice on researching study, organizing materials and providing guidance. SH contributed to the conception and revised this manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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