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The Role of Autophagy in Eosinophilic Airway Inflammation

Jinju Lee [1], **Hun Sik Kim** [1,2,3,*]

[1]Department of Biomedical Sciences, Asan Medical Center, University of Ulsan College of Medicine, Seoul 05505, Korea
[2]Department of Microbiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul 05505, Korea
[3]Stem Cell Immunomodulation Research Center (SCIRC), Asan Medical Center, University of Ulsan College of Medicine, Seoul 05505, Korea

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***Correspondence to**
Hun Sik Kim
Department of Biomedical Sciences, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
E-mail: hunkim@amc.seoul.kr

ORCID iDs
Jinju Lee
https://orcid.org/0000-0002-5604-9925
Hun Sik Kim
https://orcid.org/0000-0002-5729-6581

Conflict of Interest
The authors declare no potential conflicts of interest.

Abbreviations
3-MA, 3-methyladenine; AHR, airway hyperresponsiveness; ASM, airway smooth muscle; ATG, autophagy-related genes; Baf-A1, bafilomycin-A1; COPD, chronic obstructive pulmonary disease; COX-2, cyclooxygenase 2; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps;

ABSTRACT

Autophagy is a homeostatic mechanism that discards not only invading pathogens but also damaged organelles and denatured proteins via lysosomal degradation. Increasing evidence suggests a role for autophagy in inflammatory diseases, including infectious diseases, Crohn's disease, cystic fibrosis, and pulmonary hypertension. These studies suggest that modulating autophagy could be a novel therapeutic option for inflammatory diseases. Eosinophils are a major type of inflammatory cell that aggravates airway inflammatory diseases, particularly corticosteroid-resistant inflammation. The eosinophil count is a useful tool for assessing which patients may benefit from inhaled corticosteroid therapy. Recent studies demonstrate that autophagy plays a role in eosinophilic airway inflammatory diseases by promoting airway remodeling and loss of function. Genetic variant in the autophagy gene *ATG5* is associated with asthma pathogenesis, and autophagy regulates apoptotic pathways in epithelial cells in individuals with chronic obstructive pulmonary disease. Moreover, autophagy dysfunction leads to severe inflammation, especially eosinophilic inflammation, in chronic rhinosinusitis. However, the mechanism underlying autophagy-mediated regulation of eosinophilic airway inflammation remains unclear. The aim of this review is to provide a general overview of the role of autophagy in eosinophilic airway inflammation. We also suggest that autophagy may be a new therapeutic target for airway inflammation, including that mediated by eosinophils.

Keywords: Autophagy; Airway inflammation; Eosinophil

INTRODUCTION

Autophagy is an essential process that maintains cellular homeostasis and cell function by delivering cytosolic constituents, including organelles, denatured proteins, or invading pathogens, to lysosomes for degradation and amino acid recycling (1-3). Through autophagy, cells eliminate damaged or harmful components, thereby ensuring survival after exposure to stressors such as hypoxia, ROS, DNA damage, aggregated proteins, damaged organelles, or intracellular pathogens (4). Aberrant regulation of autophagy can result in cancer (5), neurodegenerative disease (6), and myopathies (7). Generally, autophagy is categorized into 3 different types: macroautophagy, chaperone-mediated autophagy, and microautophagy (8). Usually, macroautophagy is regarded as "autophagy"; we also referred it as autophagy in this review.

CRSsNP, chronic rhinosinusitis without nasal polyps; CQ, chloroquine; CS, cigarette-smoke; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; DISC, death-inducing signaling complex; ECP, eosinophil cationic protein; FEV1, forced expiratory volume-1 s; hATMyofbs, human atrial myofibroblasts; LC3, light chain 3; MHV, mouse hepatitis virus; NP, nasal polyp; PGD_2, prostaglandin D_2; RANTES, regulated on activation, normal T cell expressed and secreted; SNP, single-nucleotide polymorphism

Author Contributions

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Autophagy is a dynamic process associated with the formation of autophagosomes, which are double-membrane cytoplasmic vesicles that engulf cellular components. The core proteins involved in autophagosome formation are autophagy-related genes (ATG), which comprise 4 sub-groups: 1) the ATG1/UNC-51-like kinase complex, which regulates initiation of autophagy; 2) the ubiquitin-like protein (i.e., ATG12 and ATG8/microtubule-associated protein 1 light chain 3 [LC3] conjugation system), which assists elongation of the autophagic membrane; 3) the class III PI3K/vacuolar protein sorting 34 complex I, which participates in the early stages of autophagosome formation; and 4) 2 transmembrane proteins (i.e., ATG9/mammalian Atg9 and vacuole membrane protein 1), which may contribute to the delivery process via 2 major steps: induction of autophagosomes and fusion of autophagosomes with lysosomes (9,10).

Autophagy regulates immunity by eliminating invading pathogens, regulating recognition of innate pathogens, playing roles in Ag presentation via MHC class II molecules, and controlling B- and T-cell development (11). T-cells lacking *Atg5*, *Atg7*, *Atg3*, or *Beclin-1* showed impaired proliferation and increased cell death (12). Furthermore, autophagy dysfunction is related to various inflammatory diseases, including inflammatory bowel disease (13), asthma (14), and chronic rhinosinusitis (CRS) (15-17). For example, formation of double-membrane autophagosomes in fibroblasts from severe asthmatic patients has been observed by electron microscopy (18,19), and genetic variants of the autophagy gene *Atg5* are associated with promotion of airway remodeling and loss of lung function in childhood asthma (20).

Eosinophils are a major type of inflammatory cell that play an important role in airway inflammatory diseases, including asthma (21-23). Among the many proinflammatory molecules, IL-5 is involved in eosinophil-mediated inflammation. IL-5 promotes the differentiation, survival, trafficking, activation, and effector functions of eosinophils (22). Migration of eosinophils, especially to the lungs, is regulated by chemokines such as CCL5 (regulated on activation, normal T cell expressed and secreted [RANTES]), CCL7 (MCP3), CCL11 (eotaxin 1), CCL13 (MCP-4), CCL15, CCL24, and CCL26, which bind to CCR3 (23,24). Eosinophils with inflammatory lesions in the lungs produce and release a variety of proinflammatory mediators, including basic proteins (major basic protein, eosinophil cationic protein [ECP], eosinophil peroxidase, eosinophil-derived neurotoxin), cytokines (IL-2, IL-3, IL-4, IL-5, IL-10, IL-12, IL-13, IL-16, and IL-25), chemokines (CCL5, CCL11, and CCL13), growth factors (TNF and TGF-α/β) (23,25). These proteins contribute to sustained inflammation (26) and tissue damage (23,25). For example, TGF-β produced by eosinophils in asthma patients is implicated in tissue remodeling through fibroblast proliferation and increased production of collagen and glycosaminoglycans (27,28).

Although evidence suggests that autophagy and eosinophils play important roles in immune responses and airway inflammation, few studies have examined the association between autophagy and eosinophils in inflammatory diseases. Here, we focus on the role of autophagy in eosinophilic airway inflammation, and suggest modulation of autophagy as a promising therapeutic approach to treat eosinophilic inflammatory diseases.

ROLE OF AUTOPHAGY IN AIRWAY INFLAMMATION DISEASES

Asthma

Asthma is a chronic airway disease characterized by airway hyperresponsiveness (AHR) and inflammation caused by molecular and cellular responses (29). Various types of inflammatory

cell are involved in the pathogenesis of asthma, including dendritic cells, mast cells, eosinophils and lymphocytes (30). Asthma is typically associated with an imbalance between Th1 and Th2 pathways; over-driven Th2-mediated inflammation leads to airway inflammation and asthma (31). In such situation, eosinophils play important roles in augmenting AHR, mucus production, and airway remodeling in allergic asthma by producing IL-13 and leukotrienes from eosinophil lipid bodies (23,32). Blood eosinophil counts correlate with the severity of allergic asthma (33), and electron microscopy reveals large numbers of eosinophils in the bronchial mucosa of patients with severe allergic asthma (32). Accordingly, the current focus of asthma treatment is the use of anti-inflammatory drugs such as inhaled corticosteroids. However, these drugs often failed to control asthma in some patients (34). Recent studies suggest that asthma pathogenesis is largely heterogeneous and complex, which is not simply driven by allergen-specific Th2 lymphocytes as expected in allergic asthma. Some patients were characterized by the upregulation of IFN-γ, IL-17, and neutrophils in their lungs, in which airway neutrophilia correlated with asthma severity (35-38). Furthermore, consistent with the role of IL-17 in neutrophil recruitment, Th17 cells promoted neutrophilic inflammation, and contributed to the development of AHR in concert with Th2 cells in asthma animal models (39). Thus, a novel therapeutic target for treating diverse types of asthma, including eosinophilic asthma, is needed. Recent studies suggest that autophagy is a promising candidate.

Poon et al. (20) showed that a single-nucleotide polymorphism (SNP) rs12212740 G>A of *Atg5* correlated significantly with a reduction in pre-bronchodilator forced expiratory volume-1 s (FEV1) in asthmatic patients (**Table 1**). They also used electron microscopy to show that fibroblasts and epithelial cells in bronchial biopsy tissue from asthmatic patients harbored more double-membrane autophagosomes than tissue from a healthy subject (20). Martin and colleagues (18) showed that SNPs of *Atg5* and *Atg7*, and 2 SNP variants (rs12201458 and

Table 1. Autophagy and its impact on chronic airway inflammatory diseases

Disease	Species	Autophagy modulation	Disease phenotype affected	Autophagy role	Reference
Asthma	Human	SNPs of ATG5	Reduced FEV1 Associated with severe adult asthma	Protective	Poon et al. (20)
	Human	SNPs of ATG5 and ATG7	Associated with childhood asthma	Protective	Martin et al. (18)
	Human	Baf-A1, 3-MA ATG7 knockdown in hATMyofb cells	Reduced fibrotic effect of TGF-β1	Detrimental	Ghavami et al. (42)
	Human	CQ in ASM cell	Reduced airway remodeling markers including collagen-1 and phspho-SMAD2/3	Detrimental	McAlinden et al. (43)
	Mouse	3-MA (intraperitoneal) Atg5 knockdown (intranasal)	Decreased IL-5 level AHR improved Decreased eosinophil count	Detrimental	Liu et al. (40)
	Mouse	CD11c-specific deficiency of Atg5	Th17 polarization Severe neutrophilic asthma	Protective	Suzuki et al. (41)
	Mouse	ATG5 deficiency in fibroblasts	Reduced fibrotic effect of TGF-β1	Detrimental	Ghavami et al. (42)
	Mouse	CQ (intranasal)	Decreased expression of Beclin-1 and Atg5	Detrimental	McAlinden et al. (43)
COPD	Human	Dysfunction of lung epithelium	Apoptosis activation ROS activation Emphysema	Protective	Chen et al. (52) Kim et al. (53) Chen et al. (54)
	Human	Beclin-1 or LC3B knockdown	Apoptosis inactivation Inhibition of autophagosome formation	Detrimental	Chen et al. (52) Kim et al. (53)
	Human	Beclin-1, Atg5, or Atg7 knockdown	Prevents ROS generation	Detrimental	Chen et al. (54)
CRS	Human	Reduced LC3 in NP-derived fibroblast	Increase NPs	Protective	Chen et al. (15)
	Human	Reduction of LC3 in NP-derived fibroblasts	Increased NPs Increased COX-2 expression	Protective	Wang et al. (16)
	Mouse	Myeloid cell-specific deficiency of Atg7	Increased eosinophil infiltration Increased H-PGDS expression Increased IL-1β expression by macrophages	Protective	Choi et al. (17)

H-PGDS, hematopoietic prostaglandin D_2 synthase.

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rs510432) of *Atg5* are associated with childhood asthma (**Table 1**). These findings were tested in a murine model of asthma (**Table 1**) (40,41). Inhibition of autophagy by intraperitoneal injection of 3-methyladenine (3-MA) and intranasal knockdown of *Atg5* led to a marked improvement in AHR, the number of infiltrating eosinophils, IL-5 levels in bronchoalveolar lavage fluid, and histological inflammatory features (40). However, Suzuki et al. (41) showed that deficiency of CD11c-specific autophagy promotes neutrophilic airway inflammation in a murine asthma model. They found that impaired autophagy induced Th17 polarization, resulting in refractory asthma (41). Although they demonstrated a role for autophagy in neutrophilic airway inflammation, but not eosinophilic inflammation, the results suggest that autophagy plays an important and diverse role in asthma.

In addition, recent studies demonstrated that autophagy plays a crucial role in airway remodeling in airway smooth muscle (ASM) cells (**Table 1**). Ghavami et al. (42) showed that autophagy is a regulator of fibrogenesis induced by TGF-β1 in primary human atrial myofibroblasts (hATMyofbs). TGF-β1 promoted collagen-1 and fibronectin synthesis in hATMyofbs, which correlated with autophagic activation in these cells. Autophagy inhibition by ATG5 deficiency or treatment with bafilomycin-A1 (Baf-A1) and 3-MA decreased the fibrotic effect of TGF-β1 (42). McAlinden et al. (43) investigated the correlation between autophagy activation and asthma airway remodeling; human asthmatic tissues showed thickened epithelium, greater lamina propria depth, and increase in ASM bundles with higher expression of Beclin1 and ATG5 along with reduced p62 compared with non-asthmatic controls. They also showed that TGF-β1 induces upregulation of airway remodeling markers, collagen-1 and SMAD2/3 phosphorylation (pro-fibrotic signaling) along with the increased expression of Beclin-1 and LC3B-II (a marker of autophagosome formation) in ASM cells, which was reversed by an autophagy inhibitor, chloroquine (CQ). CQ also prevented accumulation of collagen in the lung of murine asthma models (43).

Furthermore, autophagy is a critical mediator of asthma exacerbations due to viral infection as well as allergic asthma (14). Viral infection is associated with exacerbation of acute asthma. Rhinovirus, severe respiratory syncytial virus, influenza viruses, coronaviruses, and adenoviruses are often detected in the airways of asthma patients (14). Treatment with Baf-A1 inhibited vacuolar-type H+-ATPase-mediated degradation of sequestered material and blocked autophagy flux by interfering with late-stage autophagosome-lysosome fusion in lung epithelial cells, resulting in growth inhibition of influenza A viruses (44). An experimental model based on mouse hepatitis virus (MHV), a prototype coronavirus used in replication and function studies, revealed that autophagy is required for viral replication, particularly for the formation of double membrane vesicle-bound MHC replication complexes (45). Further study revealed that a coronavirus non-structural protein 6 expressed by the MHV and severe acute respiratory syndrome coronavirus activates autophagy by generating autophagosomes independently of starvation (14,46). Thus, given its significant impact on asthma pathogenesis, further studies are needed to investigate the role of autophagy in the context of different cell types and to establish a therapeutic strategy for its regulation.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

COPD, a major global health epidemic, is associated with chronic inflammation of the airways and lung parenchyma (47,48). The main symptoms are shortness of breath, chronic cough, and excessive production of sputum. Chronic exposure of the airways to environmental

pollution is a main cause of COPD; indeed, approximately 15% of smokers suffer from this disease (49). COPD differs from asthma in that the main characteristic is irreversible airflow obstruction (49,50). The physiological abnormalities that characterize COPD are emphysema and obliteration of small airways (50). Although emphysema can occur independently of small airway narrowing, and vice versa, these 2 pathologies usually coexist in COPD (50). Narrowing of the small airways is caused by inflammation, increased airway muscle mass and fibrosis in the airway wall, and accumulation of inflammatory mucus exudates in the lumen (50).

Although the major inflammatory cells involved in COPD are $CD8^+$ T cells, neutrophils and macrophages, some patients have eosinophil involvement (similar to that in asthma) (47). As mentioned before, eosinophils migrate in response to cytokines (IL-5 in particular) and specific chemokines (such as eotaxin I and RANTES). Exacerbation of COPD is triggered by persistent inflammation, which is itself caused by eosinophil-derived proinflammatory mediators such as basic proteins, cytokines, and growth factors (51).

Recent studies demonstrate an association between autophagy and COPD (**Table 1**) (52-54). Chen et al. (52) showed that expression of LC3B-II, ATG4, ATG5, ATG12, and ATG7 is higher in individuals with COPD than in those without, and that treatment of primary human bronchial epithelial cells with aqueous cigarette-smoke (CS) extract induces LC3B-II. They also demonstrated a regulatory role for LC3B during epithelial cell apoptosis in a CS-induced lung cell injury model (52,53). Apoptosis is implicated in the pathogenesis of COPD. Treatment of epithelial cells with CS extract initiates the extrinsic apoptosis pathway, which involves assembly of the Fas-dependent death-inducing signaling complex (DISC) and activation of caspase-8; it also induced expression and conversion of the autophagic regulator LC3B, increased autophagosome formation, and increased caspase-3 activation. siRNA-mediated knockdown of autophagic proteins Beclin-1 or LC3B in epithelial cells inhibits assembly of the Fas-dependent DISC (52,53). Moreover, apoptotic indices and emphysema development were reduced markedly in LC3B knock-out mice exposed to CS (54).

The mechanism by which CS induces autophagy in epithelial cells is unclear; however, oxidative stress is a possible link that connects COPD to autophagy. Oxidative stress can damage lipids, proteins and DNA, and also activate autophagy (55). Furthermore, it is recognized as a major factor that predisposes an individual to developing COPD (56). Various types of inflammatory cell including eosinophils and structural cells produce ROS in the airways of a COPD patient (56,57). Treatment with the antioxidants such as N-acetyl-L-cysteine reverses starvation-induced autophagosome formation (which is associated with intracellular ROS production) in cultured cells (58). H_2O_2-induced autophagic cell death can be prevented by knockdown of ATG such as *Beclin-1*, *Atg5*, and *Atg7* (59). Indeed, exposure to CS induces pro-oxidant states in several cell types, including epithelial cells (60). In addition, chemical inhibitors of NADPH oxidase, a membrane-dependent source of ROS, inhibit CS extract-induced activation of LC3B (54). The evidence cited above suggests that increased activation of autophagic pathways may trigger or exacerbate COPD. Thus, resolution of autophagy should be studied with respect to alleviating COPD.

CRS

CRS is characterized by chronic inflammation of the sinonasal mucosa. Clinical symptoms include sinus pressure, nasal congestion, rhinorrhea, and a reduced sense of smell persisting

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for more than 12 wk (61). It is commonly categorized into 2 groups based on the presence or absence of nasal polyps (NPs): chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP) (62). The 2 groups show distinct inflammatory patterns. Whereas CRSsNP is characterized by type 1 inflammation with increased levels of IFN-γ in the inflamed sinus mucosa and low ECP/myeloperoxidase ratios, CRSwNP is typically characterized by type 2 inflammation, which is associated with a typical Th2-skewed eosinophilic inflammation with high IL-5 and ECP concentrations in the polyps (63,64). IL-5 is a potent activator and survival factor for eosinophils. Several reports show that eosinophilic inflammation is dominant in patients with severe refractory CRS (65,66). However, recent findings in Eastern Asia countries showed that CRSwNP can be classified into eosinophilic and non-eosinophilic type (67). NP from Caucasian patients are mainly eosinophil-dominant with robust Th2 response (>80%), whereas NP from Asian patients (Korea, Japan, and China) are characterized by less infiltration of eosinophils but are largely neutrophil-dominant (>50%) with mixed Th1 or Th17 type inflammation (68-72). Of interest, NP from Asian patients born and resided in the United States appears non-eosiniphil-dominant, suggesting the contribution of genetic factors to eosinophilic inflammation in NP (73).

Another core pathologic feature of CRS is elevated prostaglandin D_2 (PGD_2) levels. Upregulation of PGD_2 in NPs correlates strongly with the number of mast cells that mainly produce PGD_2 and play an important role in orchestrating eosinophil infiltration in patients with CRS (74-76). Also, expression of PGD_2 synthase is increased in patients with CRSwNP and correlates positively with eosinophilic inflammation (77). However, it is unclear why these pathologic features occur in CRS.

Previous reports suggest that autophagy plays an important role in CRS (**Table 1**) (15,16). Chen et al. (15) showed that expression of LC3 protein fell markedly, but Akt/mTOR signaling (a negative regulator of autophagy) was activated, in NPs from patients with CRSwNP but not in individuals with normal nasal mucosa. In addition, they demonstrated a negative correlation between autophagy and NPs; also, formation of LC3 puncta (an alternative indicator of autophagy) decreased in NP-derived fibroblasts (15). In another report, Wang et al. (16) showed that NP tissues are deficient in autophagy and that cyclooxygenase 2 (COX-2) is negatively regulated by autophagy in NP-derived fibroblasts. LC3 and COX-2 (a common indicator of inflammation) were analyzed by immunoblotting in fresh tissues from NPs and control nasal mucosa. LC3 expression was decreased, while COX-2 expression increased significantly, in fresh NP tissues compared with control nasal mucosa (16). In addition, COX-2 expression by NP-derived fibroblasts and nasal mucosa-derived fibroblasts was reduced by starvation-induced autophagy and by overexpression of LC3; however, it increased upon inhibition of autophagy by 3-MA (16).

Choi et al. (17) used a murine model of CRS (mice in which *Atg7* is conditionally deleted in a myeloid cell-specific manner) to show that disruption of autophagy in CRS is linked to dysregulation of PGD_2 production and eosinophilic inflammation (**Table 1**). Indeed, more severe exacerbation of CRS was induced in myeloid cell-specific *Atg7*-deficient mice than in wild-type mice with increased infiltration of eosinophils and production of PGD_2 (17). In addition, depletion of autophagy-deficient macrophages alleviated eosinophilic inflammation and PGD_2 dysregulation significantly (17). These findings suggest a critical role of autophagy in exacerbating eosinophilic inflammation and in the pathologic features associated with CRS. Also, it suggests the possibility that autophagy may be a valuable therapeutic target for resolution of eosinophilic inflammation in CRS.

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CONCLUSION

Undoubtedly, the role of eosinophils in airway inflammation is important. Here, we describe the importance of autophagy in asthma, COPD, and CRS, focusing on eosinophil-mediated airway inflammations.

SNP rs12212740 G>A of *Atg5* correlates significantly with loss of pre-bronchodilator FEV1 in asthmatic patients. Inhibition of autophagy in a murine asthma model improves AHR, reduces the number of infiltrating eosinophils, and reduces IL-5 levels in bronchoalveolar lavage fluid. In addition, autophagy is a potential link between virus infection and asthma. However, deficiency of CD11c-specific autophagy promotes neutrophilic inflammation in a murine asthma model. These results suggest that autophagy plays different roles depending on the cell type and/or the disease model employed. Thus, further studies are necessary if autophagy is to be targeted successfully to treat asthma.

With respect to COPD, autophagy is an important regulator of epithelial cell apoptosis, which contributes to the pathogenesis of COPD. CS extract induces not only apoptosis pathway, e.g., DISC and caspase-8, but also activates LC3B, autophagosome formation and, eventually, caspase-3 in epithelial cells. These pathways are inhibited either by siRNA-mediated knockdown of *Beclin-1* or *LC3B*, or by an inhibitor of autophagy such as 3-MA. Indeed, autophagosome formation is higher in COPD patients than in healthy controls. It is suggested that oxidative stress is a critical mediator of apoptosis in COPD. Exposure to CS induces pro-oxidant-mediated stress in epithelial cells. Chemical inhibitors of NADPH oxidase, a membrane-dependent source of ROS, inhibit CS extract-induced activation of LC3B and apoptosis. These data implicate autophagy as an important regulator of epithelial cell apoptosis and in the pathogenesis of CS-induced COPD.

Autophagy is also linked to eosinophilic inflammation in CRS. CRSwNP is associated with a typical Th2-skewed eosinophilic inflammation, with high IL-5 and ECP levels in NPs. Another core pathologic feature of CRS is increased expression of PGD_2. Upregulation of PGD_2 in NPs correlates strongly with the number of mast cells, which produce PGD_2 and play an important role in orchestrating eosinophil infiltration in patients with CRS. Although it is not clear how these 2 factors are linked, we provide evidence that autophagy is a key mediator. Observational studies suggest that autophagy is involved in CRS. For example, expression of LC3 protein correlates negatively with NP development and expression of COX-2. In addition, increased eosinophilic inflammation and PGD_2 production induce more severe CRS in myeloid cell-specific *Atg7*-deficient mice than in wild-type mice. These findings reveal the critical role of autophagy in exacerbating CRS.

Although autophagy plays diverse roles, either protective or detrimental, in chronic airway inflammatory (depending on the type of cell affected and the disease model used), it holds promise as a novel therapeutic target. However, the molecular mechanism underlying disease pathogenesis is not clear. In addition to its role in regulating eosinophilic or neutrophilic inflammation, autophagy has a broad effect on diverse Th responses, likely by controlling innate immune cells. Autophagy-deficient macrophages promote production of the Th1 cytokine IFN-γ during GalN/LPS-induced liver injury (78) and dextran sulfate sodium-induced colitis (79). Autophagy-deficient myeloid cells also promote Th17 responses during *Mycobacterium tuberculosis* infection (80), as well as Th2 responses during eosinophilic CRS (17). These results suggest that autophagy is a versatile immune modulator that will require

careful modulation to achieve therapeutic benefit. Thus, further studies are needed to demonstrate how autophagy contributes to the pathogenesis of various airway inflammatory diseases, and to establish an appropriate therapeutic strategy dependent of the unique context of different diseases.

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