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REVIEW

The Role of Ubiquitin-Proteasome System (UPS) in Asthma Pathology

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Abstract: Asthma represents a major global health concern, underscoring an imperative for further exploration into its pathogenesis to inform the development of more effective treatment strategies. As a key mechanism for intracellular protein degradation and regulation, the ubiquitin-proteasome system (UPS) plays a crucial but complex and multifaceted role in the pathological process of asthma. This study systematically reviews the functions and mechanisms of E3 ubiquitin ligases and deubiquitinases within the UPS in asthma. The study explores the impact of these mechanisms on the occurrence of inflammation and the alteration of airway hyperresponsiveness by regulating the synthesis and release of inflammatory factors, as well as the proliferation or differentiation of key inflammatory cells. A comprehensive understanding of the pathological mechanism of UPS in asthma will help to provide new theoretical basis and potential drug targets for the precision treatment, which holds great promise for the treatment of asthma in the future.

Keywords: UPS, asthma, E3 ubiquitin ligase, deubiquitinases

Introduction

Asthma is a heterogeneous airway inflammation with no certain cause, unlike chronic obstructive pulmonary disease (COPD), for which smoking is the main cause.[1] It is often driven by Th2 cell activation and associated cytokines, leading to eosinophil recruitment, mast cell activation, and excessive mucus production by airway epithelial cells.[2] This chronic inflammation is associated with hyperresponsiveness of the respiratory tract, which usually results in generalized and variable limitation of reversible expiratory circulation, leading to repeated occurrences of wheezing, breathlessness, chest tightness, and coughing.[3] According to the WHO, a significant proportion of asthma-related deaths occurs in low- and lower-middle-income countries, where the challenges of under-diagnosis and under-treatment persist.[4] Bronchospasm is an important pathophysiological feature of asthma attacks, with histamine playing a pivotal mediating role in the process of bronchospasm caused by asthma.[5] On the one hand, it causes bronchospasm or bronchial hyperreactivity through both direct and indirect effects, and on the other hand, it participates in the inflammatory response of asthma, which makes airway inflammation persist and aggravate, and consequently increases the frequency and severity of bronchospasm.[5,6] In recent years, with the deepening of our understanding of the pathogenesis of asthma, targeted therapy and specific signaling pathway therapy have gradually become the new direction of clinical asthma treatment. For instance, omalizumab is suitable for allergic asthma patients with elevated serum IgE levels and clear allergens by antagonizing IgE.[7] In addition to omalizumab, other asthma biologics, such as mepolizumab, reslizumab, and dupilumab have been employed to target specific inflammatory pathways in patients exhibiting a suboptimal response to conventional therapies such as inhaled glucocorticoids and long-acting β2-agonists.[8,9] However, asthma biologics still face serious challenges in terms of cost, delivery methods, and variability in response. Furthermore, studies on the abnormally activated inflammatory pathways such as Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT) and Phosphoinositide 3-Kinase (PI3K) in the pathogenesis of asthma have also become popular.[10] Currently commonly

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used treatments are palliative and do not address the root cause of asthma. Therefore, we want to explore the specific attack mechanism of asthma and carry out targeted therapy from the root to relieve asthma symptoms. To study the pathogenesis and development basis of asthma, scientists need to establish in vitro animal asthma models that can reflect the pathophysiology of human asthma, including IgE mediated antigen sensitivity, acute bronchoconstriction, increased airway resistance, chronic airway inflammation, etc.[11] The current common approach is to induce mice using ovalbumin (OVA) or house dust mite (HDM).[12] The scientific findings introduced in this paper are basically based on these two induction methods.

Ubiquitin-proteasome system (UPS) is a complex cascade reaction process in eukaryotic cells that ubiquitinates the corresponding protein, leading to its recognition and subsequent degradation by the proteasome.[13] This highly specific process consumes cellular energy and serves as a crucial regulator of various biological processes implicated in the development of conditions like cardiovascular disease, cancer, and inflammation-related disorders.[14] The UPS comprises key components including ubiquitin, E1 ubiquitin-activating enzymes, E2 ubiquitin-conjugating enzymes, ubiquitin-protein ligase E3, proteasomes, and deubiquitinating enzymes deubiquitinating enzymes (DUBs).[15] Notably, extensive research has focused on elucidating the roles of E3 ubiquitin ligases and DUBs in the occurrence and development of those diseases. Therefore, this review will primarily emphasize the functions of E3 enzymes and DUBs.

Ubiquitination is a multistep post-translational modification governed by the ubiquitin ligases that successively activates, conjugates, and ligates 76-amino acid proteins ubiquitin onto substrate proteins.[16] This adjustment alters important properties of the substrate protein, including its intracellular activity and localization, reaction with other proteins, and extensive half-life within the cell.[17] Therefore, ubiquitination could regulate a large cohort of crucial cellular processes and a deficiency in the ubiquitin function has been shown in several diseases, such as inflammatory diseases, immune disorders, and susceptibility to infections.[18] There are three types of ligases, E1, E2, and E3 enzymes. Of all the enzymes involved in ubiquitination, the E3 enzyme is the most abundant. E3 ubiquitin ligases fall into three families: Really Interesting New Gene (RING E3s), homologous to E6-AP C-terminus E3s (HECT E3s), and RING-between RING-RING E3s (RBR E3s) according to their structural characteristics and mechanism of action. After binding to the E2 Ub complex and substrate, RING E3s catalyzes the direct transfer of ubiquitin from E2 to the lysine residue of the substrate, while HECT and RBR E3 ligase catalyze the transfer of ubiquitin from E2 to cysteine, the active site of E3 ligase, followed by the transfer of ubiquitin to the substrate protein.[19] E3 ligase plays a vital role in the onset and progression of chronic human inflammation, including asthma, COPD, arteriosclerosis, and arthritis.[20]

Scientists have made extensive achievements in the research on the regulation of ubiquitination and its coupling and the transmission of downstream signals, but the research on deubiquitination has not made great progress until recent years. Deubiquitination is the removal of ubiquitin from modified substrates mediated by DUBs against ubiquitin couplings and ligase induced signals.[21] Human genes encode almost 100 different DUBs that break down the ubiquitin chains and their signals while recycling ubiquitin for further coupling.[22] This can be done by breaking the entire ubiquitin chain by cutting the bond between the near-end ubiquitin and the substrate, or by cutting a single ubiquitin at the far end of the chain.[22] Dysregulation or dysfunction of DUBs is associated with many major human diseases, including chronic inflammation, cancer and neurological disorders, which is often caused by abnormal signals within cells.[23] With the further elucidations of the mechanism of DUBs, its importance in clinical diagnosis and treatment has been gradually explored. In the future, DUBs may be used as new targets for the treatment of some major human diseases and improve prognosis. In this review, we will focus on the E3 ubiquitin ligases, deubiquitinases, and their roles in regulating asthma.

E3 Ligases and Their Mechanisms Involved in Asthma Pathology

E3 Ubiquitin Ligases Promote the Advancement and Course of Asthma

Only a limited subset of E3 enzymes, including autocrine motor factor receptor (AMFR), Midline 1 (MID1), Parkin, Chromobox 4 (Cbx4) and tripartite motif-containing 27 (TRIM27), positively contribute to the pathogenesis and progression of asthma as shown in Figure 1 and Table 1. These enzymes play a pivotal role in orchestrating widespread airway inflammation by regulating the production of inflammatory mediators and promoting the proliferation of immune cells. The mechanisms of these E3 ligases will be explained in more detail below in this section.

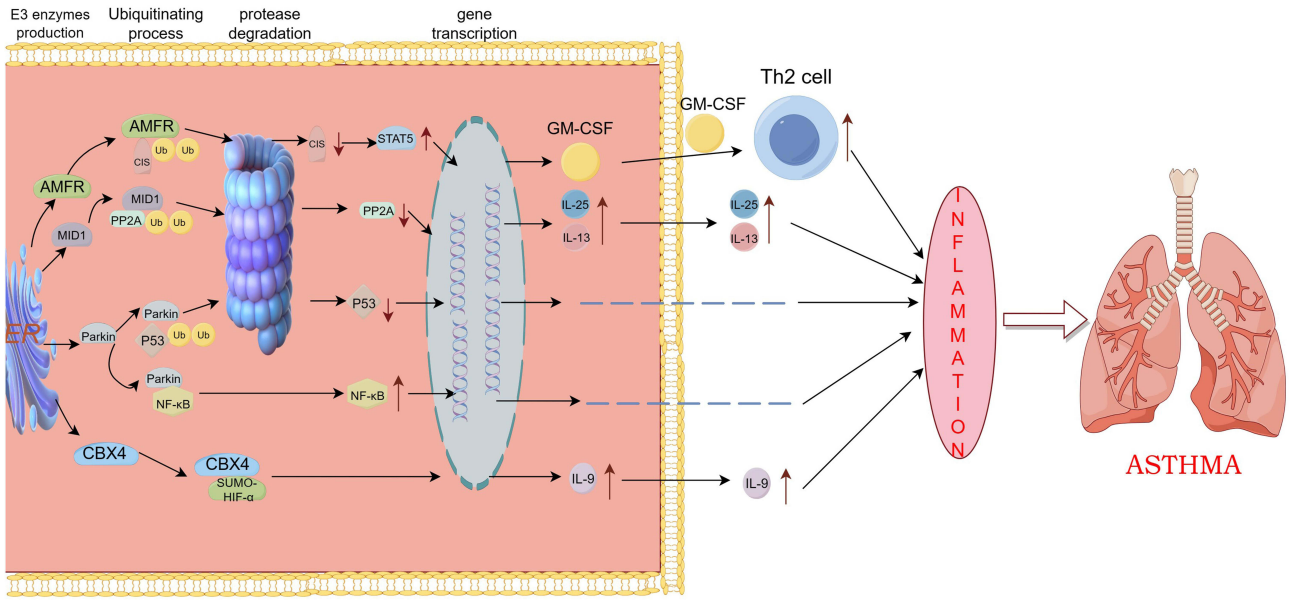

Figure 1 E3 ubiquitin ligases promote asthma pathology. Autocrine motor factor receptor (AMFR) can promote Granulocyte macrophage-colony stimulating factor (GM-CSF) production by targeting Cytokine Inducible SH2-containing protein (CIS) and facilitating its ubiquitination degradation. E3 enzyme Midline 1 (MID1) can mediate the ubiquitinating degradation of Protein Phosphatase 2A (PP2A) to inhibit the secretion of inflammatory Cytokines Interleukin-25 (IL-25) and Interleukin-13 (IL-13). E3 enzyme Parkin has exerted its function in two pathways. One is mediating the ubiquitinating degradation of P53, the other is increasing the production of inflammatory substrate Nuclear Factor Kappa-light-chain-enhancer (NF-κB). CBX4 functions as an E3 enzyme but it increases the secretion of Interleukin-9 (IL-9) through the SUMOysation of Hypoxia-inducible factor alpha (HIF-α). All these reactions promote inflammation, which ultimately leads to an increase in the course and progression of asthma.
Abbreviations: AMFR, Autocrine motor factor receptor; GM-CSF, Granulocyte macrophage-colony stimulating factor; CIS, Cytokine Inducible SH2-containing protein; MID1, Midline 1; PP2A, Protein Phosphatase 2A; IL-25, Interleukin-25; IL-13, Interleukin-13; NF-κB, Nuclear Factor Kappa-light-chain-enhancer; IL-9, Interleukin-9; HIF-α, Hypoxia-inducible factor alpha.

AMFR

Alveolar macrophages (AMs), an important kind of airway immune cells, play crucial roles in lung homeostasis, immune response, and airway remodeling.[31] In the mouse models of asthma induced by OVA and papain respectively, AMs can mediate the presentation of OVA-related allergic antigen and stimulate the proliferation and differentiation of Th2 cells through the production of Interleukin-1β (IL-1β), Transforming growth factor-β (TGF-β), Granulocyte macrophage-colony stimulating factor (GM-CSF) and other cellular inflammatory factors to regulate Th2 cell and eosinophilic inflammation in asthma.[32] RNA sequencing of purified AMs in these two types of OVA- and papain-induced asthmatic

Table 1 E3 Ubiquitin Ligases promoting the progression of Asthma

E3 Ligase	Promotion (+) Or Inhibition (−)	Targeted Molecules	Asthma Models	Effects in Asthma	Reference
AMFR	(+)	CIS	OVA-induced	Promote Th2 and eosinophil reaction, IL-4, IL-13 secretion.	[24]
Cbx4	(+)	HIF	HDM-induced	Promote IL-9 secretion.	[25]
MID1	(+)	PP2A	HDM-induced	Promote allergic airway inflammation and epithelial barrier dysfunction.	[26]
Parkin	(+)	NF-κB, P53	HDM-induced	Promote inflammatory response, lung damage.	[27–29]
TRIM27	(+)	NLRP3	OVA-induced	Promote AHR and the pathological changes of lung tissue, increase airway inflammation and oxidative stress.	[30]

Abbreviations: AMFR, autocrine motor factor receptor; CIS, Cytokine Inducible SH2-containing protein; OVA, ovalbumin; Th2, T helper 2; IL-4, Interleukin-4; IL-13, Interleukin-13; Cbx4, Chromobox 4; HIF-1α, hypoxia-inducing factor-1α; HDM, house dust mite; IL-9, Interleukin-9; MID1, Midline 1; PP2A, Protein Phosphatase 2A; NF-κB, Nuclear Factor Kappa-light-chain-enhancer. TRIM27, tripartite motif-containing 27; NLRP3, NOD-like receptor protein.

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mouse models revealed that the E3 ubiquitin ligase AMFR was upregulated in both types of asthmatic mice.[24] AMFR, an endoplasmic reticulum resident E3 ubiquitination enzyme, recognizes misfolded proteins for ubiquitination and subsequent proteasome degradation.[33] AMFR can positively regulate the production of GM-CSF by targeting Cytokine Inducible SH2-containing protein (CIS) and facilitating its ubiquitination degradation in UPS.[24] Thus, the overproduction of GM-CSF will drive the aggregation of eosinophils and the proliferation and differentiation of Th2 cells in asthma, intensifying the airway inflammation.[24] These studies demonstrate a new mechanism of communication between AMs and Th2 cells and eosinophils in the context of OVA- and papain-induced asthma, and AMFR selective inhibitors may become novel pharmacological targets for future asthma treatment related to these allergen-induced asthma models.

Cbx4

Cbx4 is a member of the HP1 proteins, comprising 560 amino acids.[34] In addition, Cbx4 is the sole enzymatically active member identified within the Cbx family so far. It possesses various distinctive domains and is involved in post-translational modification of substrates such as Homeodomain Interacting Protein Kinase 2 (HIPK2), septin interacting protein 1 (SIP1) and hypoxia-inducing factor-1α (HIF-1α) as a small ubiquitin-like modifier (SUMO) E3 ubiquitination enzyme.[35] In a recent study, it was reported that Cbx4 can enhance the deactivation of HIF-1α through interacting with HIF-1α and promote transcription of Interleukin-9 (IL-9), ultimately promoting T helper 9 (Th9) cell differentiation, thereby promoting the progression of asthma.[25] This study introduces a novel concept for the clinical management of asthma. Targeting Cbx4 and HIF-1α through SUMO E3 ubiquitin ligase activity inhibitors can effectively alleviate chronic lung inflammation caused by Th9 cell activation. In the context of house dust mite (HDM)-induced asthma, Cbx4 can aggravate epithelial barrier dysfunction by mediating SUMOylation of β-catenin. Knockdown of Cbx4 in vivo in the HDM-induced asthma model promotes membrane localization of β-catenin and inhibits inflammatory Wnt/β-catenin signaling, improving airway epithelial barrier function, and thereby reducing HDM-induced allergic airway inflammation and asthma epithelial barrier dysfunction.[36]

Midline-1

Midline 1 (MID) is a microtubule binding E3 ubiquitin ligase that is known to be involved in organ development and diseases such as cancer and allergic inflammation.[37,38] The occurrence and attack of asthma are often closely related to allergic airway inflammation caused by the activation of innate immune pathways by allergens. In the mouse models of acute asthma attack induced by HDM or rhinovirus infection, MID1 exhibited increased expression in mouse bronchial epithelium.[26] MID1 was found to decrease the activity of protein phosphatase 2A (PP2A) by interacting with its catalytic subunit PP2Ac, thereby promoting the expression of airway hyperreactivity and inflammation-related factors such as Interleukin-25 (IL-25), Interleukin-33 (IL-33), and C-C Motif Chemokine Ligand 20 (CCL20), and the release of Interleukin-5 (IL-5) and Interleukin-13 (IL-13) in the HDM- and rhinovirus-induced asthma models. Further studies showed that the inhibition of MID1 on PP2A inflammatory signaling pathway was regulated by upstream TNF-related apoptosis-inducing ligand (TRAIL), and TRAIL promoted asthma by up-regulating MID1. This gives us a more complete understanding of how MID1 functions in asthma.[2] In addition, it can promote the accumulation of eosinophils, T lymphocytes and dendritic cells, further promoting the development of HDM- and rhinovirus-induced asthma.[26] Specifically inhibiting MID1 or activating PP2A pharmacologically can limit the progression of allergic airway disease caused by rhinovirus or HDM.[26] These findings identify the key role and certain action sites of MID1 in allergic airway inflammation such as HDM- and rhinovirus-induced asthma and establish a bridge between the development of asthma and the activation of immune pathways in the context of these allergen-induced asthma models.

Parkin

Parkin is a cytoplasmic E3 ubiquitination enzyme expressed in the airway epithelium.[39] Parkin can ubiquitinate and activate the pro-inflammatory nuclear factor kappa-light-chain-enhancer (NF-κB) of activated B cells.[40] Parkin also promotes lipopolysaccharide (LPS)-induced lung inflammation such as lung injury by inhibiting p53 and promoting the activation of NF-κB.[41,42] Under high Interferon-γ (IFN-γ) environment, IFN-γ induced Parkin to promote the production of neutrophil chemokines (LIX and IL-8) and airway neutrophilic inflammation by decreasing the expression of Parkin inhibitor Thapp11.[27] These studies predict an important role for Parkin as a proinflammatory factor in pulmonary

inflammation. In Kris genelyn Dimasuay's study of the asthmatic airway, it was found that the mRNA levels of Parkin were significantly up-regulated in the HDM-induced asthmatic airway epithelium, which was positively correlated with mitochondrial DNA (mtDNA) release in bronchoalveolar lavage fluid (BALF).[27] Earlier reports have demonstrated mitochondrial dysfunction in mouse models of allergic asthma[28,29] The pro-inflammatory factor, IL-13, only induces mtDNA release in Parkin sufficient human tracheobronchial epithelial (HTBE) cells to aggravate mitochondrial damage but not in Parkin deficient conditions,[27] while Kris genelyn Dimasuay's study suggested that Parkin could mediate the exacerbation of airway inflammation as an E3 ubiquitin ligase induced by mtDNA release in asthmatic airway epithelium. However, the exact role of Parkin in mitochondrial dysfunction in asthma has not been fully elucidated.

TRIM27

The expression of tripartite motif-containing 27 (TRIM27) has been found to exacerbate airway hyperresponsiveness (AHR) and the pathological changes of lung tissue, as well as to significantly increase airway inflammation and oxidative stress in asthmatic mice.[30] TRIM27 knockdown effectively alleviated OVA-induced airway hyperresponsiveness (AHR) and lung pathological changes.[30] In addition, TRIM27 knockdown significantly reduced airway inflammation and oxidative stress in asthmatic mice, and in vitro analysis confirmed the favorable effects of TRIM27 deletion on inflammation and oxidative stress in mouse airway epithelial cells.[30] Further studies found that the loss of TRIM27 significantly reduced the activation of NOD-like receptor protein 3 (NLRP3) inflammasome, which provided ideas for exploring the pathological mechanism of TRIM27 promoting asthma.[30]

E3 Ubiquitin Ligases Inhibit the Development and Progression of Asthma

Most of the reported E3 enzymes can inhibit asthma pathogenesis rather than promote asthma progression shown in Figure 2 and Table 2, which may be due to the degradation of key substrates in the pathogenesis and progression of asthma by E3 enzyme-mediated ubiquitination. The mechanisms are discussed in more detail below.

FBXL19

The Skp1-Cullin-1-F-box protein (SCF) ligase complex is one of the largest families of E3 ubiquitin ligases,[59] which is involved in the ubiquitination process. In this complex, the F-box contains two main domains for substrate recognition. The F-box motif binds to S-phase kinase-associated protein 1 (Skp1) to create the SCF ligase complex. Another substrate-binding motif recognizes and interacts with phosphorylated substrates.[60] The F-box protein, F-Box And Leucine Rich Repeat Protein 19 (FBXL19), has been shown to share considerable sequence similarity to the SCF protein family.[61]

In a study using ovalbumin (OVA)-induced asthma mouse models, investigators first applied MG-132 proteasome or lysosomal inhibitors to mice lung epithelial cells MLE12. They found that only MG-132 could attenuate Suppression of Tumorigenicity 2 (ST2L) degradation, but not the lysosomal inhibitors. Moreover, ST2L was found to be polyubiquitinated via co-IP assays.[43] These results indicated that ST2L degradation in lung epithelial cell lines was mediated by the ubiquitin-proteasome machinery. When FBXL19 selectively mediated the ubiquitination and degradation of ST2L, the expression of pro-inflammatory factor IL-33 is also decreased, and IL-33-induced pulmonary inflammation was alleviated. Overexpression of FBXL19 eliminated the pro-inflammatory and pro-apoptotic effects of IL-33 and effectively alleviate the severity of lung injury in OVA-induced asthmatic mice.[43] This study demonstrated that targeting the IL-33-ST2L axis via the E3 ubiquitin ligase FBXL19 was a potential strategy to alleviate OVA-induced asthma.

TRIM Family Proteins

TRIM proteins are one of the largest families of E3 ubiquitinating enzymes, which consists of more than 80 proteins. Tripartite motif-containing 21 (TRIM21, Ro52), as a member of the TRIM family, contains PRY and SPRY domains at the c-terminus.[62] As a common E3 ubiquitin ligase, TRIM21 holds significance in pathogenesis and progression of inflammation,[63,64] cancer,[65,66] and autoimmunity.[67]

In the immune microenvironment, macrophages play crucial roles in asthma pathogenesis and development.[68,69] In OVA-induced asthma mouse models and asthmatic patients, the number of alveolar macrophages is increased, and the level of alternative activation (M2) polarization of macrophages is also increased.[70] Recent studies have found that

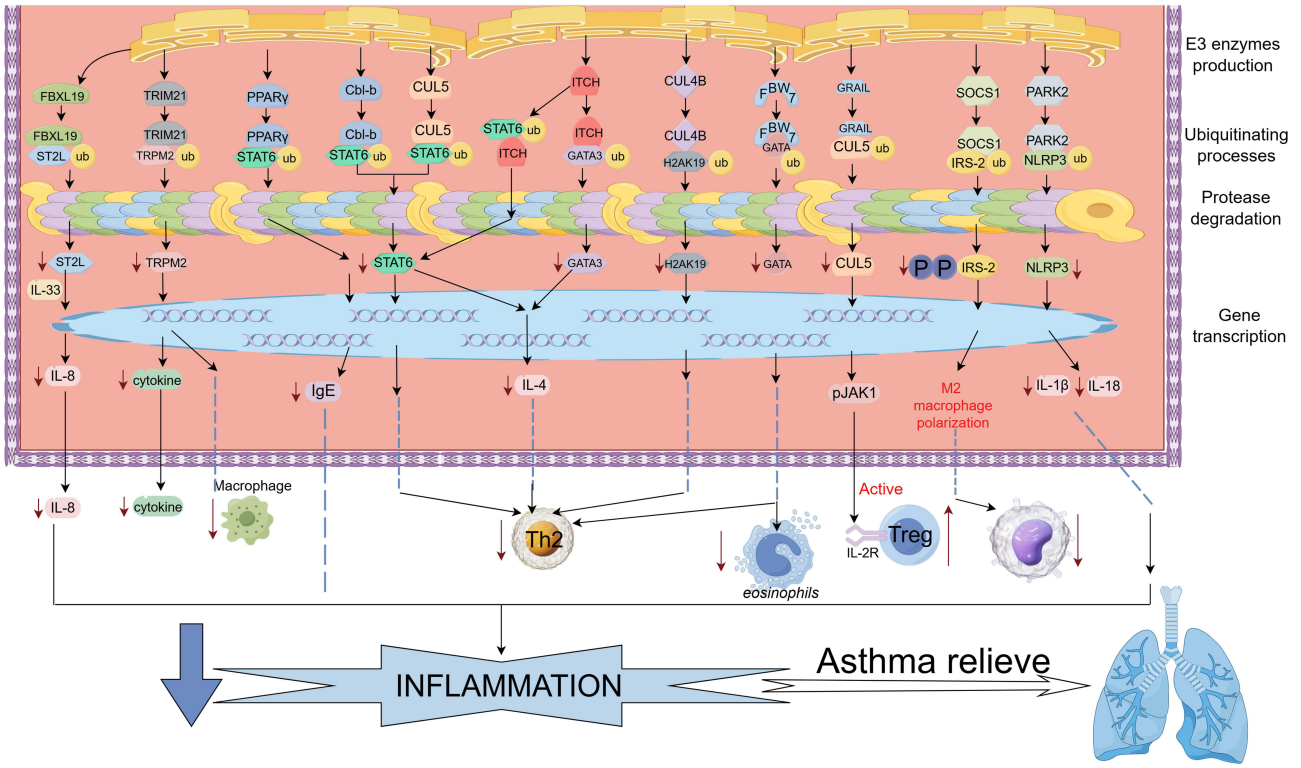

Figure 2 E3 ubiquitin ligases inhibit asthma pathology. The E3 enzyme F-box and leucine-rich repeat protein 19 (FBXL19) plays a pivotal role in orchestrating the ubiquitinating degradation of ST2L, thereby effectively suppressing Interleukin-8 (IL-8) secretion. Concurrently, Tripartite -motif protein 21 (TRIM21) acts as an essential mediator in the ubiquitinating degradation of Transient Receptor Potential Cation Channel Subfamily M Member 2 (TRPM2), leading to the inhibition of inflammatory cytokine secretion and macrophage production. Notably, E3 enzymes peroxisome proliferators-activated receptor γ (PPARγ), Casitas B lymphoma-b (Cbl-b), and Cullin-5 (CUL5) collaborate to mediate the ubiquitinating degradation of Signal Transducer and Activator of Transcription 6 (STAT6). The activation of the PPARγ signaling pathway results in the downregulation of IgE secretion, while Cbl-b and CUL5contribute to the reduction of T helper 2 (Th2) cell differentiation. ITCH, another crucial E3 enzyme, exerts its influence by facilitating the ubiquitinating degradation of both STAT6 and GATA Binding Protein 3 (GATA3). This dual degradation process leads to a decrease in Interleukin-4 (IL-4) secretion and Th2 differentiation. Furthermore, the E3 enzyme Cullin 4b (CUL4B) intervenes in the ubiquitinating degradation of H2Ak19, effectively inhibiting Th2 cell differentiation. Additionally, F-box and WD repeat domain-containing 7 (FBW7), acting as an E3 enzyme, engages in the ubiquitinating degradation of GATA Binding Protein (GATA), thereby suppressing Th2 cell differentiation and eosinophil production. The regulatory protein, An E3 ubiquitin ligase gene related to anergy in lymphocytes (GRAIL) assumes a central role in mediating the ubiquitinating degradation of CUL5. This action promotes Interleukin-2 (IL-2) activation mediated by phosphorylated Janus kinase (pJAK1), ultimately enhancing Treg activation and, consequently, inhibiting inflammation. The E3 enzyme Suppressor of cytokine signaling (SOCS1) plays a crucial role in mediating the ubiquitinating degradation of Insulin Receptor Substrate 2 (IRS-2), leading to a reduction in phosphorylated IRS-2 levels and ultimately inhibiting M2 macrophage polarization. Moreover, the E3 enzyme PARK exerts inhibitory effects on the secretion of inflammatory cytokines Interleukin-1β (IL-1β) and Interleukin-13 (IL-13), mediated by House Dust Mite (HDM). This inhibition is achieved through the ubiquitinating degradation of NOD-like receptor thermal protein domain associated protein 3 (NLRP3). Collectively, these intricate molecular interactions culminate in the inhibition of inflammation, contributing to the attenuation of asthma's course and progression.

Abbreviations: FBXL19, F-box and leucine-rich repeat protein 19; IL-8, Interleukin-8; TRIM21, Tripartite -motif protein 21; TRPM2, Transient Receptor Potential Cation Channel Subfamily M Member 2; PPARγ, peroxisome proliferators-activated receptor γ; Cbl-b, Casitas B lymphoma-b; CUL5, Cullin-5; STAT6, Signal Transducer and Activator of Transcription 6; Th2, T helper 2; GATA3, GATA Binding Protein 3; IL-4, Interleukin-4; CUL4B, Cullin 4b; FBW7, F-box and WD repeat domain-containing 7; GATA, GATA Binding Protein; GRAIL, An E3 ubiquitin ligase gene related to anergy in lymphocyte; IL-2, Interleukin-2; pJAK1, phosphorylated Janus kinase; SOCS1, Suppressor of cytokine signaling; IRS-2, Insulin Receptor Substrate 2; IL-1β, Interleukin-1β; IL-13, Interleukin-13; HDM, House Dust Mite; NLRP3, NOD-like receptor thermal protein domain associated protein 3.

TRIM21 can interact with transient receptor potential cation channel, subfamily M, member 2 (TRPM2) protein, an encoded protein is activated by oxidative stress and stressed susceptibility to cell death.[44,71] The interaction between TRIM21 and TRPM2 will promote the apoptosis of pro-inflammatory macrophages and inhibit the production of inflammatory cytokines such as Interleukin-1β (IL-1β), IL-4, IL-6, IL-10, TNF-α, and TGF-β, thus alleviating asthma symptoms.[44] The specific mechanism is that TRIM21 relies on the key site TRPM2 K1218 to degrade TRPM2 via ubiquitination, thereby reducing intracellular calcium, Reactive oxygen species (ROS) levels and the production of inflammatory factors, thus promoting the apoptosis of macrophages. The long non-coding RNA lncTRPM2-AS blocks this ubiquitination process and exacerbates macrophage inflammation in OVA-induced asthma models.[44]

Recently, with the deepening of the research on TRIM family, more and more TRIM proteins have been found to play a significant role in the pathological mechanism of asthma. TRIM31 expression can alleviate the pathological changes of

Table 2 E3 Ubiquitin Ligases suppressing the progression of Asthma

E3 Ligase	Promotion (+) Or Inhibition (–)	Targeted Molecules	Asthma Models	Effects in Asthma	Reference
FBXL19	(–)	ST2L	OVA-induced	Inhibit IL-8 and inflammation reaction.	[43]
TRIM21	(–)	TRPM2	OVA-induced	Promote macrophage apoptosis, inhibition of cytokine production.	[44]
TRIM31	(–)	NLRP3	OVA- and HDM-induced	Reduce the infiltration of inflammatory cells, inhibit NLRP3 inflammasome activation.	[45]
March1	(–)	unknown	HDM-induced	Inhibits neutrophil inflammation.	[46]
PPARγ	(–)	STAT6	OVA-induced	Inhibit IgE.	[47]
ITCH	(–)	GATA3 STAT6	OVA-induced	Inhibit IL-4 secretion, Th2 differentiation.	[48]
Cbl-b	(–)	STAT6	OVA-induced	Inhibit Th2 differentiation.	[49]
CUL5	(–)	pJAK1	OVA-induced	Inhibit Th2 differentiation.	[50]
CUL4B	(–)	H2A(K119)	OVA-induced	Inhibit Th cells differentiation.	[51]
GRAIL	(–)	CUL5	–	Promote IL-2R activation, Treg active.	[52]
FBW7	(–)	GATA	HDM-induced	Inhibit Th2 differentiation, eosinophils infiltrate into the lungs.	[53–55]
SOCS1	(–)	IRS-2	OVA-induced	Inhibit M2 polarization.	[56]
RNF125	(–)	HMGB1	OVA-induced	Inhibit epithelial autophagy, oxidative stress.	[57]
PARK2	(–)	NLRP3	HDM-induced	Inhibit inflammasome activation, IL-1β, IL-18 secretion, cellular epithelial dysfunction.	[58]

Abbreviations: FBXL19, F-box and leucine-rich repeat protein 19; ST2L, Suppression of Tumorigenicity 2; OVA, ovalbumin; IL-8, Interleukin-8; TRIM21, Tripartite -motif protein 21; TRPM2, Transient Receptor Potential Cation Channel Subfamily M Member 2; TRIM31, Tripartite -motif protein 31; NLRP3, NOD-like receptor protein 3; HDM, house dust mice; March1, membrane associated ring-CH-type finger 1; PPARγ, peroxisome proliferators-activated receptor γ; STAT6, Signal Transducer and Activator of Transcription 6; ITCH, ITCHy E3 ubiquitin protein ligase; GATA3, GATA Binding Protein 3; IL-4, Interleukin-4; Th2, T helper 2; Cbl-b, Casitas B lymphoma-b; CUL5, Cullin-5; pJAK1, phosphorylated Janus kinase 1; CUL4B, Cullin 4B; H2A, H2A clustered histone; GRAIL, also known as RNF128, ring finger protein 128; FBW7, F-box and WD repeat domain-containing 7; GATA, GATA Binding Protein; IL-2R, Interleukin 2 receptor subunit alpha; SOCS1, Suppressor of cytokine signaling; IRS-2, Insulin Receptor Substrate 2; RNF125, RING finger protein 125; HMGB1, high mobility group box 1 protein; PARK2, parkin RBR E3 ubiquitin protein ligase; IL-1β, Interleukin-1β; IL-18, Interleukin-18.

OVA-induced asthma and reduce the infiltration of inflammatory cells.[45] TRIM31 deficiency exacerbates NLRP3 inflammasome activation in OVA-induced asthmatic mice and HDM-stimulated airway epithelial cells.[45] In this extensive TRIM family, distinct proteins play varied roles in the pathological mechanism of asthma. Further exploration of the TRIM family will facilitate a more comprehensive understanding of the pathological mechanism of asthma.

PPARγ

Peroxisome proliferator-activated receptor-γ (PPAR-γ), first identified in rodents 30 years ago, belonged to the recipient family of nuclear hormones, acting on fat metabolism, insulin sensitivity, and glucose stability.[72] Recent studies indicate that PPARγ can function as an E3 ubiquitin ligase. In OVA-induced asthma models, PPARγ binds to the phosphorylated signal transducer and activator of transcription 6 (STAT6) and initiates its ubiquitination and degradation, thereby inhibiting the synthesis of serum IgE downstream.[47] It is well known that most asthma cases are linked to IgE-mediated responses, and elevated serum IgE levels are one of the hallmarks of allergic asthma.[73] PPARγ-induced downregulation of IgE would alleviate symptoms associated with allergic asthma. Additionally, a signaling pathway upstream of PPAR-γ was also explored in this study. The researchers found that serum IgE levels were significantly increased in E-prostanoid 4 (EP4) receptor deficient mice, and bioinformatics analysis showed that the inhibitory effect

of EP4 signaling on IgE was dependent on activation of the PI3K-AKT pathway.[47] In conclusion, the EP4-PI3K-AKT-PPARγ-STAT6-IgE pathway significantly contributes to the induction and pathogenesis of OVA-induced allergic asthma.

ITCH

The E3 ubiquitin ligase ITCH was named based on the genetic analysis of mutant mice showing abnormal immune phenotypes and severe skin scratching.[74] ITCH interacts with signal molecules like Jun protein, Smad2, Notch, and p73, contributing significantly to DNA damage response and cell cycle regulation.[74] Mutation in the ITCH gene is a cause of syndromic multisystem autoimmune diseases.[75] Allergic asthma is a complex inflammatory disease, which is a type II immune disease characterized by the increased number of TH2 cell-mediated inflammatory factors IL-4, IL-5, IL-13, and eosinophils.[76]

Itch$^{-/-}$ mice have increased Th2-type inflammation in the lungs and digestive tract.[74] To explore the role of ITCH in Treg cells, researchers generated Treg-specific ITCH knockout mice and challenged them with OVA in an allergic asthma model. They found that ITCH abolished Treg-specific mice had more severe lung inflammation than control mice, with specific IgE and Th2 cytokines were significantly increased.[48] With further study, ITCH-deficient Treg cells have Th2 properties and produce Interleukin-4 (IL-4) to guide the development of Th2 inflammatory responses.[48] GATA binding protein 3 (GATA3) expression in Tregs is essential for the maintenance of Treg suppressive function and stability.[77,78] However, the molecular pathway through which ITCH selectively inhibits GATA3-mediated Th2 response is crucial for controlling the progression of allergic asthma.[48] In addition, ITCH has been shown to inhibit inflammatory signaling via the nucleotide binding oligomerization domain containing 2 (NOD2) pathway through ubiquitination and degradation of inhibitor of apoptosis proteins (IAP), especially cIAP1.[79] Furthermore, ITCH has been demonstrated to inhibit asthma, Crohn's disease, sarcoidosis and other inflammatory diseases that are highly associated with the NOD2 signaling pathway.[80,81]

Cbl-b

Casitas B lineage lymphoma b (Cbl-b) is an E3 ubiquitin ligase containing multiple domains such as the protein tyrosine kinase binding (TKB) domain, RING-finger domain, and proline-rich domain.[82] These domains are required for the Cbl-b protein to recruit ubiquitin-binding enzymes, recognize ubiquitin-coupled target proteins and degrade proteins. In addition, Cbl-b is involved in T cell differentiation, B cell antigen receptor signaling, and peripheral tolerance regulation.[83,84] Cbl-b was known to affect immune/anergy switching points at multiple levels.[85]

In OVA-induced allergic asthma mouse models, compared to the normal mice, the Cbl-b$^{-/-}$ allergic asthma mice had more severe inflammatory cell infiltration in the blood vessels and around the bronchus and increased mucus secretion. In addition, respiratory resistance responses to methylamine choline (methch) aerosols showed that Cbl-b$^{-/-}$ mice remained highly responsive to methyl groups 24 hours after OVA attack, indicating that severe airway inflammation in Cbl-b$^{-/-}$ mice led to increased airway hyperreactivity (AHR), which is a classic sign of asthma.[49] Cbl-b deficiency led to elevated IL-4, IL-5, IL-9, and IL-13 production by T cells in vitro and in the bronchoalveolar of mice in vivo. Higher levels of these cytokines in lavage compared to the WT group suggested that Cbl-b negatively regulates the differentiation of Th2 and Th9 cells.[49] Further investigation showed that Cbl-b could target STAT6 for ubiquitination degradation, thereby inhibiting Th2 reaction and IL-4-STAT6 signal transduction.[49]

CUL Family

Cullin-RING E3 ubiquitin ligases (CRLs), the largest family of E3 enzymes, are responsible for the post-translational modification of nearly 20% of intracellular proteins and controlling numerous important cellular physiological and biochemical functions.[86] However, Cullin5 (CUL5) is a scaffold protein nucleating CRLs complex.[87] Nedd8, a ubiquitin-like protein, covalently attaches to CUL5 to activate its E3 ubiquitin ligase activity.[88] The Suppressor of cytokine signaling (SOCS) box domain in the SOCS protein allows it to act as a substrate receptor for the CRL5 complex, facilitating ubiquitination of the substrate.[89] It was demonstrated in a previous study that a cytokine induced CIS, a member of the SOCS protein family, restricts Th2 and Th9 differentiation, as well as lung inflammation in OVA-induced experimental asthma.[90] Mice with low CUL5 expression in T cells exhibit Th2 inflammation that will further worsen with age.[50] CUL5-deficient T cells show a propensity for Th2 and Th9 differentiation and heightened STAT6 inflammatory signaling.[50] The specific mechanism is that CUL5 forms a complex with CIS and phospho-Jak1 to promote

the ubiquitination and degradation of phospho-Jak1. CUL5 deletion will inhibit this process and increase the intracellular levels of phospho-Jak1 and phospho-Stat6, thereby reducing the threshold of IL-4 receptor signaling.[50] Thus, these CUL5-deficient $CD4^+$T cells can differentiate from Treg to Th9 even under conditions of low levels of IL-4, thereby increasing susceptibility to OVA-induced allergic asthma.[50] In addition, a recent study showed that in a mouse model, preexisting allergic insult induces CUL5 expression, impairs antiviral immunity and promotes neutrophil inflammation that exacerbates asthma.[91]

Like CUL5, Cullin 4B (CUL4B) is also a scaffold protein of its corresponding complex CRL4B, which plays an important role in various physiological, biochemical, and developmental degradations.[92] Disruption of the CUL4B gene results in X-linked mental retardation in humans and severely inhibits a range of developmental processes such as cell proliferation, hematopoiesis, and neurogenesis in mice.[93–96] In addition, CUL4B also plays a key role in Th cell differentiation.[51] In OVA-induced mouse models of asthma, CUL4B-deficient mice have a more severe Th2 response than controls.[51] CUL4B depletion enhances $CD4^+$ T cell differentiation into Th1 and Th2 cells in vitro.[51] In addition to classical transcription factors, several epigenetic factors have also emerged as key regulators in $CD4^+$T cell differentiation.[97,98] For example, IL-4 in Th1 cells and Ifng in Th2 cells are marked by the repressive mark trimethylated histone H3 at lysine 27 (H3K27me3).[99] Polycom repression complex 2 (PRC2) plays a key role in catalyzing H3K27 in this process.[100] Thus, when PRC2-mediated trimethylation of H3K27me3 is inhibited, $CD4^+$T cells will enhance their differentiation into Th1 and Th2 cells.[100] In addition, polycomb repression complex 1 (PRC1) recognizes H3K27me3 established by PRC2 to enhance PRC2 action, and PRC1 catalyzes H2AK119ub1, which is essential for the efficient recruitment and activity of PRC2 on its target genes.[101] CRL4B during this series of compounds by promoting H2AK119 single ubiquitin (H2AK119ub1) and PRC2 mediated H3K27me3 three methylation, which inhibits their expression in the process of Th cell differentiation.[51]

GRAIL

Allergic asthma can develop due to defects in peripheral regulatory T cells (Tregs).[102] In previous studies, the use of low-dose Interleukin-2 (IL-2) has been reported to successfully treat autoimmune diseases caused by Tregs.[103,104] Researchers have isolated equal numbers of Tregs from patients with allergic asthma and patients with autoimmune diseases and compared their responses to low doses of IL-2 in vitro. The results showed that it is not a defect in Treg numbers that influences disease development but that Tregs in these patients lose their suppressive regulatory role in IL-2R desensitization.[105] In this process, Tregs from healthy people can inhibit IL-2R desensitization and prolong the sustained expression of key factors (eg pSTAT5 and Deptor) of its downstream pathways, thereby maintaining Treg stability by promoting STAT5 transcription as well as mTOR inhibition.[106–108] However, when activated by IL-2, CRL degradation of pJAK1 and Deptor associated with the IL-2Rβ chain occurs, and sustained expression of pSTAT5 and Deptor is suppressed, resulting in a loss of Treg stability.[105]

An E3 ubiquitin ligase gene related to anergy in lymphocytes (GRAIL) was abundantly expressed in healthy controls.[52] GRAIL can ubiquitinate the lysine (K724) on CUL5 protein, which is required for CRL activation to degrade Deptor and pJAK1 by SUMOylating.[52,108] Therefore, GRAIL can be used as a competitive inhibitor of this SUMOylating modification to block the activation of CUL5 CRLs complex, thereby preserving the protein activity and expression of pJAK1 and Deptor.[50,87,109] At this point, the treatment idea for allergic asthma can be transformed from immunosuppression to self-tolerance recovery.

FBW7

Allergic asthma involves persistent eosinophilic airway inflammation due to Th2 cells released-cytokines like IL-4 and IL-5.[110] Therefore, inhibiting the development of Th2 cells and the differentiation of $CD4^+$ T cells into Th2 cells are beneficial measures to treat or relieve the symptoms of allergic asthma. However, the classical JAK/STAT6 signal transduction pathway is closely linked to T cell development, Th2 differentiation, and the regulation of Th1/Th2 balance.[111,112] The mechanism is that activated STAT6 initiates transcription in the downstream region of Th2-specific genes by up-regulating GATA3 to induce the functional differentiation of $CD4^+$ T cells into Th2 cells.[113] The E3 ubiquitin ligase F-box and WD repeat domain-containing 7 (FBW7), part of the F-box protein family, plays a crucial role

in tumor development.[114,115] In addition, FBW7 can regulate the ubiquitination of GATA3, thereby disrupting its structure, and conditionally inactivating FBW7 in the T cell lineage, which results in the reduction of thymic CD4 single-positive cells and splenic $CD4^+$ and $CD8^+$ T cells.[53,54] Therefore, enhancing FBW7 function can effectively inhibit Th2 cell development and prevent the development of allergic asthma. This conclusion has been demonstrated experimentally. Ken-Ichi Suehiro's group found that SRY-Box Transcription Factor 12 ($Sox12^{-/-}$) mice showed increased eosinophil infiltration into the lungs and exacerbated Th2 cell differentiation in response to HDM.[55] Moreover, Sox12 enhanced FBW7-mediated ubiquitination of GATA3, a process demonstrated by the elimination of Sox12 repression of GATA3 upon FBW7 knockdown.[55]

SOCS1

SOCS family proteins can act as inhibitory signals in a negative feedback loop in the JAK-STAT pathway.[116] These proteins feature a central SH2 domain and a C-terminal SOCS box domain and interact with RING finger proteins, Culin proteins, and elongin B and C to exert E3 ubiquitinating enzyme activity.[89,117–120] As one of the most potent signaling suppressors of the SOCS family, SOCS1 can regulate the polarization of the M2 phenotype.[121] Numerous studies in asthmatic patients have shown that the presence of M2 macrophages in the lungs and airways correlates with the severity of pneumonia as well as poor lung function.[121,122] Inhibiting the polarization of M2 macrophages will be the key to reducing allergic pulmonary inflammation. In macrophages, IL-4 activates insulin receptor substrate (IRS)-2 upon binding to its corresponding IL-4 receptor, thereby inducing differentiation of M2 macrophages.[123–125] SOCS1 was found to be highly induced in human monocytes upon IL-4 receptor activation, and knockdown of SOCS1 by siRNA resulted in extended IRS-2 tyrosine phosphorylation and heightened M2 differentiation.[56] In addition, healthy monocytes with higher SOCS1 content showed higher IRS-2 ubiquitination and lower M2 polarization than allergic monocytes upon IL-4 stimulation.[56] In this process, SOCS1 shortens IRS-2 tyrosine phosphorylation by promoting ubiquitination of IRS-2, which in turn inhibits the transduction of downstream signals and ultimately inhibits M2 differentiation.[56]

RNF125

RING finger protein 125 (RNF125) is an E3 ubiquitin ligase in the RING domain family,[126] interacting with the high mobility group (HMG) B-box domain of high mobility group box 1 protein (HMGB1) and degrade it through UPS system, thereby inhibiting autophagy and oxidative stress in airway epithelium and alleviating the progression of asthma.[57] RNF125 expression was significantly decreased in asthmatic patients and mice, and further studies showed that RNF125 hypermethylation was the cause of RNF125 low expression in primary airway epithelial cells of OVA-treated mice.[57] Therefore, demethylation therapy targeting RNF125 may be one of the methods for precision treatment of OVA-induced asthma in the future.

PARK2

As an E3 ubiquitin ligase, PARK2 is involved in various cellular processes through ubiquitination degradation, and research on PARK2 has mainly focused on Parkinson's disease.[127] Ge and his team used HDM to induce airway epithelial cells BEAS-2B to mimic allergic asthma in vitro[58] and found that the expression of PARK2 is significantly down-regulated in HDM-induced asthma models, which can effectively alleviate asthma inflammation.[58] The specific mechanism by which PARK2 exerts its effects is as follows: it promotes the ubiquitination of NLRP3 inflammasome, negatively regulates NLRP3 protein, suppresses NLRP3 inflammasome activation, and reduces the secretion and release of pro-inflammatory factors IL-1β and IL-18. This ultimately protects the airway epithelial cell barrier.[58] PARK2 will eventually relieve the symptoms of HDM-induced allergic asthma.

Deubiquitinases and Their Mechanisms Involved in Asthma Pathology

The reported studies on the effects of deubiquitinases like Ubiquitin-specific protease (USP) family, A20, Cylindromatosis gene (CYLD), ovarian tumor domain protease domain-containing ubiquitin aldehyde-binding protein 1 (OTUB1) and BRCA1/BRCA2-containing complex subunit 3 (BRCC3) on asthma pathology exhibit both pro- and anti-asthmatic properties, as depicted in Figure 3 and Table 3. The mechanisms of action of these deubiquitinases will be explained in more detail below.

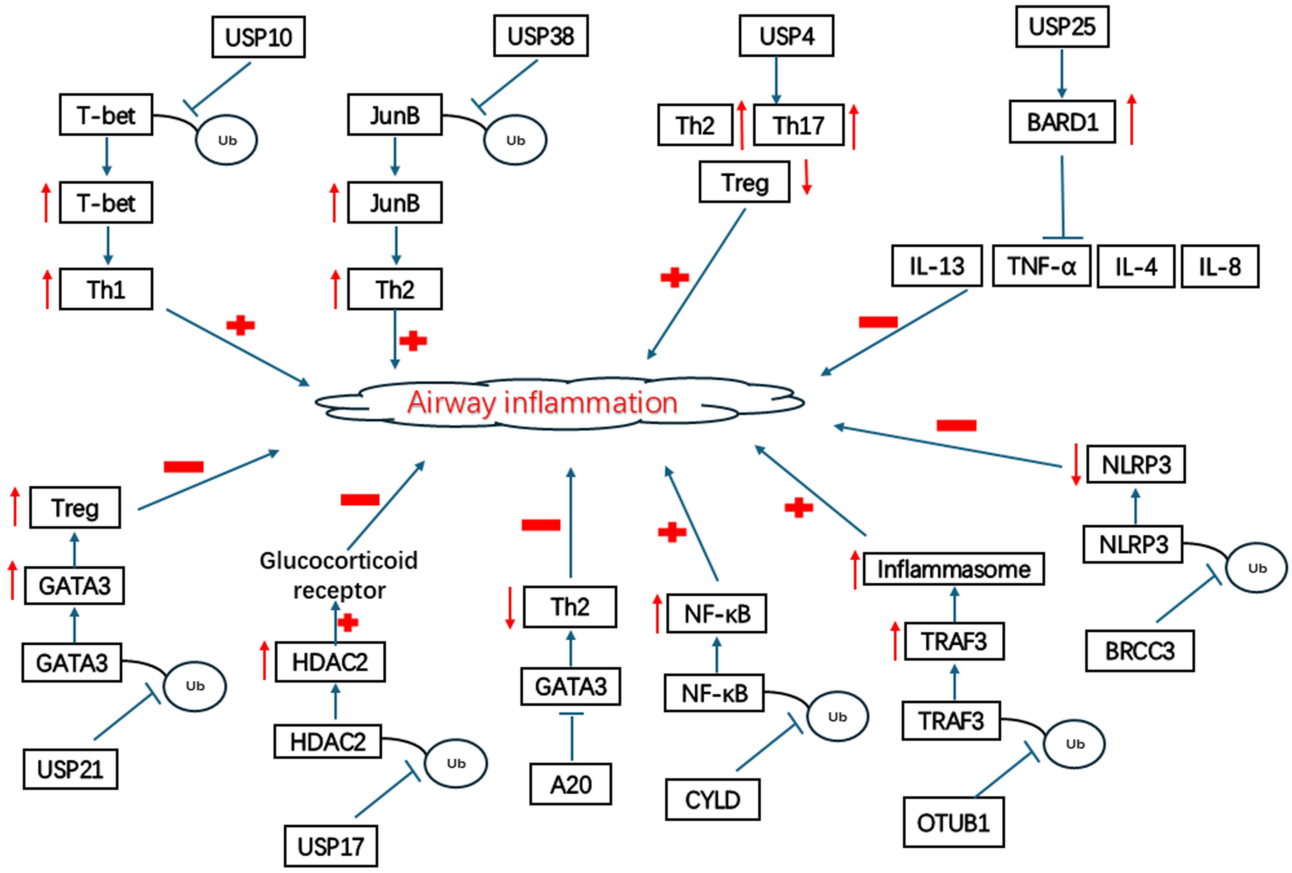

Figure 3 Deubiquitinases functioning in asthma pathology. The deubiquitinating enzyme Ubiquitin specific protease 10 (USP10) can inhibit the degradation of T-bet by removing the ubiquitin residues connected to T-bet, thereby promoting the proliferation and differentiation of T helper 1 (Th1) cells, and ultimately promoting the development of airway inflammation. Similarly, Ubiquitin specific protease 38 (USP38) promotes T helper 2 (Th2) cell proliferation and differentiation by inhibiting JunB ubiquitination and degradation. Ubiquitin specific protease (USP4) can promote the development of airway inflammation by promoting the proliferation of Th2 and T helper 17 (Th17) cells and inhibiting the proliferation of Treg cells. Ubiquitin specific protease 25 (USP25) inhibits airway inflammation by promoting BRCA1 Associated RING Domain 1 (BARD1), which in turn inhibits the secretion of inflammatory factors Interleukin-13 (IL-13), Tumor Necrosis Factor (TNF-α), Interleukin-4 (IL-4) and Interleukin-8 (IL-8). Ubiquitin specific protease 21 (USP21) can inhibit the ubiquitination of GATA Binding Protein 3 (GATA3), thereby increasing the expression of GATA3, promoting the function of Treg, and ultimately inhibiting airway inflammation. A20, as a common deubiquitinating enzyme, can inhibit the expression of GATA3, thereby inhibiting the proliferation and differentiation of Th2 cells, and then inhibiting airway inflammation. Cylindromatosis (CYLD) can inhibit the ubiquitination and degradation of Nuclear Factor Kappa-light-chain-enhancer (NF-κB), thereby activating the NF-κB inflammatory pathway and promoting airway inflammation. OTU domain-containing ubiquitin aldehyde-binding protein 1 (OTUB1) promotes the formation of inflammasome by inhibiting the ubiquitination and degradation of Tumor necrosis factor Receptor-Associated Factors (TRAF3), which ultimately promotes airway inflammation. BRCA1/BRCA2-containing complex subunit 3 (BRCC3) inhibits the activation of NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome by reducing the ubiquitination level of NLRP3, thereby reducing airway inflammation in asthma.

Abbreviations: USP10, Ubiquitin specific protease 10; Th1, T helper 1; USP38, Ubiquitin specific protease 38; Th2, T helper 2; USP4, Ubiquitin specific protease; Th17, T helper 17; USP25, Ubiquitin specific protease 25; BARD1, BRCA1 Associated RING Domain 1; IL-13, Interleukin-13; TNF-α, Tumor Necrosis Factor; IL-4, Interleukin-4; IL-8, Interleukin-8; USP21, Ubiquitin specific protease 21; GATA3, GATA Binding Protein 3; CYLD, Cylindromatosis; NF-κB, Nuclear Factor Kappa-light-chain-enhancer; OTUB1, OTU domain-containing ubiquitin aldehyde-binding protein 1; TRAF3, Tumor necrosis factor Receptor-Associated Factors; BRCC3, BRCA1/BRCA2-containing complex subunit 3; NLRP3, NOD-like receptor protein 3.

Ubiquitin Specific Protease Family

Ubiquitin-specific proteases (USPs) are the largest subfamily of deubiquitinating enzymes (DUBs) with 58 vertebrate members.[141] USPs are cysteine proteases with three parts of the USP conservation region called the finger, thumb, and palm.[142,143] To endow USPs with substrate specificity, not only the terminal extension, but also the ubiquitous associated domain (UBA), ubiquitous interacting motif (UIM) and zinc finger ubiquitous specific protease domain (ZnF-UBP) are included.[142,144] USPs play a crucial role in cancer development by regulating the cell cycle and aiding in DNA damage repair.[145,146] In addition to their roles in the regulation of cancer, USPs play important roles in some metabolic diseases such as obesity, diabetes, and atherosclerosis.[147–149] Nowadays, the effects of USPs on asthma have also been studied increasingly. In this part of the review, we will summarize the role of USPs in asthma pathogenesis.

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Table 3 Deubiquitinases Functioning in Asthma

Deubiquitinases	Promotion (+) Or Inhibition (−)	Targeted Molecules	Asthma Models	Effects in Asthma	Reference
USP10	**(+)**	T-bet	–	Promotes the development and differentiation of Th1 cells and drives Th1 immune response.	[128]
USP38	**(+)**	JUNB	OVA- and HDM-induced	Promotes IL-4 secretion and Th2 cell response.	[129]
USP25	**(−)**	BARD1	HDM-used	Inhibits nuclear damage, inflammation in the body, and TNF-α, IL-4, IL-8, IL-13 production.	[130–132]
USP21	**(+)**	FOXP3/ GATA3	–	Inhibits the stability of Treg.	[133–135]
USP17	**(−)**	HDAC2	–	Promote the production of glucocorticoid receptors and inhibit the activation of inflammatory genes.	[136]
A20	**(−)**	GATA3/ NF-κB	OVA-and HDM-induced	Inhibits Th2 cell differentiation and the production of inflammatory cytokines.	[137]
CYLD	**(+)**	NF-κB	OVA-induced	Promotes the production of inflammatory factors.	[138]
OTUB1	**(+)**	TRAF3	–	Promotes TGF-β-induced cellular inflammation and remodeling.	[139]
BRCC3	**(+)**	NLRP3	OVA-and HDM-induced	Increase the expression levels of NLRP3 inflammasome, cleaved Caspase-1, cleaved Gasdermin, IL-1β and IL-18	[140]

Abbreviations: USP10, Ubiquitin specific protease 10; T-bet, T-box expressed in T cells; Th1, T helper 1; USP38, Ubiquitin specific protease 38; JUNB, JunB Proto-Oncogene; OVA, ovalbumin; HDM, house dust mite; IL-4, Interleukin-4; Th2, T helper 2; USP25, Ubiquitin specific protease 25; BARD1, BRCA1 Associated RING Domain 1; TNF-α, Tumor Necrosis Factor; IL-8, Interleukin-8; IL-13, Interleukin-13; USP21, Ubiquitin specific protease 21; FOXP3, Forkhead Box P3; GATA3, GATA Binding Protein 3; USP17, Ubiquitin specific protease 17; HDAC2, histone deacetylase 2; NF-κB, Nuclear Factor Kappa-light-chain-enhancer; CYLD, Cylindromatosis; OTUB1, OTU domain-containing ubiquitin aldehyde-binding protein 1; TRAF3, Tumor necrosis factor Receptor-Associated Factors; TGF-β, Transforming growth factor-β; BRCC3, BRCA1/BRCA2-containing complex subunit 3; NLRP3, NOD-like receptor thermal protein domain associated protein 3; IL-1β, Interleukin-β; IL-18, Interleukin-18.

USP10

T-box expressed in T cells (T-bet), a transcription factor, governs the development and differentiation of naive $CD4^+$ T cells into Th1 cells.[150] It can drive Th1 immune responses by promoting the expression of IFN-γ, a hallmark cytokine of Th1 cells.[151] The endogenous co-immunoprecipitation assay demonstrated the interaction between the deubiquitinating enzyme USP10 and T-bet, while their co-localization in the nucleus were confirmed by immunofluorescence assay after transfection with HA-T-bet and Myc-USP10.[128] Specifically, USP10 promotes the deubiquitination of T-bet via its enzymatic activity, thereby preventing its post-ubiquitination degradation and enhancing the stability.[128] Lys-313 has been reported to be a key site for the interaction of T-bet with the IFN-γ gene promoter, and the expression of T-bet is controlled by the ubiquitin-proteasome degradation pathway at the Lys-313 site.[128] This provides an idea for the exploration of the interaction site between USP10 and T-bet, but the specific mechanism remains unknown. In addition, the expression of USP10 and IFN-γ and the transcriptional level of T-bet are highly up-regulated in peripheral blood mononuclear cells (PBMCS) from asthma patients, suggesting that USP10 may maintain high levels of T-bet and IFN-γ, promote Th1 responses to combat Th2-dominated asthma.[128] In this study, the provenance of the samples from asthma patients was not specified with regard to the particular allergen exposure situation. However, it is speculated that the samples may in fact represent a group of asthma patients induced by various allergens.

USP38

Th2 cells, by producing signature cytokines IL-4 and IL-5, play a pivotal role in allergic asthma pathogenesis.[110,152] USP38 can be induced by T-cell receptor (TCR) activation, and genome-wide association studies have indicated its

presence at chromosomal loci associated with human asthma.[153] In USP38-deficient allergic asthma models induced by OVA and aluminum, the total number of cells, eosinophils, and lymphocytes in BALF were significantly decreased, as well as the percentage and absolute count of Th2 cells in mediastinal lymph nodes detected by flow cytometry.[129] In addition, depletion of USP38 in HDM-induced allergic asthma has similar results to OVA-induced allergic asthma,[129] suggesting that USP38 is an essential regulator of allergic asthma. Mechanistically, USP38 interacts with JunB Proto-Oncogene (JunB) to maintain the stability of JunB by removing polyubiquitination of JunB.[129] JunB is a TCR-activated transcription factor that plays a specific role in Th2 development by promoting IL-4 transcription.[154] However, some E3 ubiquitin ligases such as ITCH participate in JunB ubiquitination and degradation, thereby disrupting JunB function in inflammatory diseases.[155,156] USP38 deubiquitinates Lys-48-linked JunB polyubiquitylation, thereby blocking TCR-induced JunB turnover.[129] USP38 deubiquitinase is a specific site that mediates Th2 immunity and related asthma, which provides a target for the precise diagnosis and treatment of asthma in the future.

In these two models, the researchers induced asthma with specific allergens (OVA or HDM) to simulate the pathogenesis of allergic asthma and systematically detected the changes in related cytokines, cell numbers, and transcription factors to explore the role of USP38.

USP4

As a deubiquitinase, USP4 functions as a key regulator in various cellular pathways. USP4 can inhibit the tumor suppressor effect of p53, thus acting as a potential oncogene.[157] In addition to its role in cancer development, USP4 also plays an important role in autoimmune diseases, and the USP4 inhibitor Vialinin A is an important anti-inflammatory compound.[158,159] In vitro, USP4 can act as a key regulator of Treg and Th17 cells, which play important roles in the pathogenesis of chronic asthma.[157,160–163] In an OVA-induced mouse model of asthma, USP4 null mice have lower airway hyperresponsiveness and airway inflammation in the lung, as well as reduced production of Th2 and Th17-related cytokines and increased percentage of Forkhead Box P3 ($Foxp3^{+}$) Treg cells compared with controls.[164] Since FoxP3-driven gene expression patterns can largely determine Treg regulatory function,[165] USP4 can lead to impaired Treg cell suppressive function by down-regulating Foxp3, thereby promoting further inflammation development. However, the USP4 inhibitor Vialinin A can decrease the inflammatory cell infiltration in the lungs of OVA-induced mice.[164] Therefore, USP4 may be a distinct inhibitory target for the treatment of asthma and other chronic airway diseases.

In these studies, the OVA-induced asthma model was used to systematically observe the effects of USP4 knockout or inhibition on asthma-related inflammatory indicators, cytokines, and immune cells, thereby revealing its role and potential therapeutic value in the pathogenesis of asthma.

USP25

In allergic asthma patients, many genotoxic reactive oxygen species and reactive nitrogen species are produced in immune cells in response to allergen exposure such as HDM.[166] These RONS can damage biological macromolecules such as nucleic acids and proteins, thus further aggravating the deterioration of asthma patients.[167] Among them, DNA double-strand breaks are one of the most cytotoxic forms, which can lead to genomic instability and even cell death.[168] It has recently been shown that USP25 can promote the stability of DNA repair-related proteins in lung epithelial cells of patients with lung lesions due to frequent smoking.[130] In an in vitro allergic asthma model of HDM-induced BEAS-2B cells, USP25 inhibited HDM-induced DNA damage and reduced the production of pro-inflammatory cytokines TNF-α, IL-4, IL-8, and IL-13, while knockdown of USP25 had the opposite effect. USP25 can inhibit HDM-induced DNA damage and inflammation in vivo by enhancing BARD1 protein expression.[131] BARD1 is one of the key proteins in the process of homologous recombination to repair DNA damage, and its loss will lead to genomic instability.[132]

The studies above focused on the HDM-induced asthma model. Both in vitro cell experiments and in vivo animal experiments were carried out in the context of HDM, a specific allergen, to thoroughly investigate the role of USP25 in mitigating HDM-induced asthma-related damage (such as DNA damage and inflammatory response) and its relationship with DNA repair-related proteins.

USP21

Treg cells play an important role in asthma disease, and their deficiency will lead to allergic inflammation in mice, which in turn will trigger the pathological features of asthma.[169] As the severity of asthma increases, the proportion of Treg cells in patients decreases significantly.[170] The E3 deubiquitinase USP21 can increase the stability of GATA3 and up-regulate its expression in Treg cells by removing its polyubiquitination.[133,134] In another regulatory mechanism, USP21 and the serine/threonine kinase PIM2, which can phosphorylate FOXP3 and thereby activate FOXP3 function, are increased in Treg cells from asthmatic patients.[135,171] GATA3 is a key transcription factor that co-works with FOXP3 to attenuate the immune effects of Treg cells, so USP21 suppresses the limiting effect of Treg cells on Th2-type inflammatory responses in asthma by stabilizing them.[172,173]

The present section of the study is mainly based on clinical observations of asthma patients and related cell mechanism studies. Although the specific allergen-induced situation was not explicitly delineated, it elaborated on the role of USP21 in regulating Treg cell function and asthma inflammatory response within the overall context of asthma, providing an important basis for understanding the immune imbalance in asthma.

USP17

Smoking is one of the most common causes of asthma. Studies on smoking-induced asthma have found that oxidative stress caused by cigarette smoking leads to inactivation of histone deacetylase 2 (HDAC2).[174,175] HDAC2 can inhibit the activation of inflammatory genes by acetylating glucocorticoid receptors, and it plays a crucial role in regulating inflammatory genes and mediating the anti-inflammatory effects of glucocorticoids in a variety of chronic inflammation such as asthma.[176,177] In addition to interacting with HDAC2 in co-immunoprecipitation assays, USP17 can remove the K48 and K63 linked ubiquitin chains covalently bound to HDAC2, suggesting that USP17 can stabilize HDAC2 by deubiquitination and inhibit its degradation.[136] USP17 is significantly reduced in airway epithelial cells exposed to cigarette smoke extract compared with healthy airway epithelium, leading to HDAC2 hyper ubiquitination and degradation, which can be reversed by overexpression of USP17.[136] Therefore, USP17 can be used as a target for precision treatment in asthma and provides a new direction for the treatment of glucocorticoid resistance.

This study focused on smoking as an inducer of asthma. By analyzing the effects of cigarette smoke on USP17 and HDAC2 in airway epithelial cells, it revealed the potential role and therapeutic significance of USP17 in the pathogenesis of smoking-induced asthma, thus providing a new idea for asthma treatment.

A20

A20, as a common deubiquitinase, plays a crucial role in the regulation of human inflammatory pathways mainly via down-regulation of the NF-κB inflammatory pathway.[178,179] Its role in asthma has also been explored in recent years. Mice lacking A20 expression have more severe allergic airway inflammation, mucus production, and higher airway responsiveness and Th2 cytokine expression than control mice under the conditions of HDM-induced allergic asthma.[180] The expression of GATA3 factor, which induces Th2 cell differentiation, is significantly increased in $CD4^+$ T cells with A20 deletion, indicating that A20 can control the occurrence and progression of asthma by stabilizing the expression level of GATA3 and preventing excessive Th2 differentiation.[180]

Treatment of allergic airway inflammation by A20 has also been reported. Nam-In Kang and colleagues used an adenovirus containing A20 cDNA (Ad-A20) to treat allergic airway inflammation induced by OVA in mice.[137] It was found that Ad-A20 could attenuate airway inflammatory cell recruitment and peribronchiolar validation by inhibiting NF-κB signaling and the production of various inflammatory cytokines in the bronchoalveolar.[137] There are no human studies of A20 yet, but we still believe that A20 has great potential for the treatment of human chronic inflammation such as asthma.

In this part of the study, the HDM-induced asthma model was used to study the effect of A20 deletion on the pathological features of asthma. Concurrently, the OVA-induced asthma model was employed to explore the effect of A20 gene therapy, revealing the potential value of A20 in the pathogenesis and treatment of asthma from different perspectives.

CYLD

The Cylindromatosis gene (CYLD) encodes a common deubiquitinase that can affect the activity of the inflammatory factor NF-κB by removing ubiquitin residues.[181,182] In addition to the suppression of thymic and peripheral CD4 - and CD8-positive T cell development in CYLD knockout mice, CYLD also plays an important role in tumorigenesis.[183–185] The experimenter bred a transgenic mouse that can overexpress the naturally occurring short isoform (sCYLD).[138] In an OVA-induced model of allergic asthma, these mutant mice have more eosinophils and lung mucus production than wild-type mice.[138] Further studies found that sCYLD could promote the overexpression of T cell-derived IL-9 allergic pro-factor.[138] Therefore, the sCYLD mutation can be reversed by inhibiting the IL-9 factor, which provides a new idea for the treatment of asthma by targeting the IL-9 factor.

OTUB1

OTU domain-containing ubiquitin aldehyde-binding protein 1 (OTUB1) is a common deubiquitinase that plays a crucial role in various physiological processes, including cell metabolism, proliferation, and differentiation.[186] OTUB1 has been reported to play a key role in the development of numerous lung diseases, and OTUB1 can promote the progression of non-small cell lung cancer and pulmonary fibrosis.[187,188] In addition to this, OTUB1 has been proposed as a potential biomarker for chronic fibrotic idiopathic interstitial pneumonia.[189] Recently, OTUB1 has also been reported to play an important role in the progression of asthma.[139] The expression of OTUB1 was increased in asthmatic bronchial mucosa and in TGF-β1-induced BEAS-2B cells. Inhibition of OTUB1 expression reduces TGF-β1-induced airway inflammation and remodeling.[139] This suggests that OTUB1 may have a progressive role in the progression of asthma. Mechanistically, OTUB1 enhances the stability of tumor necrosis factor receptor-associated factor 3 (TRAF3) by removing its ubiquitination, thereby promoting the activation of NLRP3 inflammasome.[139] NLRP3 inflammasome activation then promotes chronic inflammation in the allergic airway of bronchial asthma, Th2 differentiation as well as allergic airway inflammation.[190,191]

The preceding researches were mainly based on samples of bronchial mucosa from asthma patients and an in vitro cell model (TGF-β1-induced BEAS-2B cells), which revealed the role and mechanism of OTUB1 in the process of asthma airway inflammation and remodeling, thus providing a new perspective for understanding the progression of asthma.

BRCC3

BRCA1/BRCA2-containing complex subunit 3 (BRCC3) is a subunit of BRCC3-containing isopeptidase complex that possesses deubiquitinating enzyme activity.[192] The expression of BRCC3 has been shown to be elevated in OVA-induced asthma in murine models. In comparison with wild type (WT) mice, BRCC3 knockout (KO) mice exhibited a marked improvement following OVA stimulation, as demonstrated by reduced inflammatory cell infiltration and decreased levels of inflammatory cytokines.[140] Furthermore, the NLRP3 inflammasome is found to be highly activated in asthmatic mice, and that BRCC3 knockout resulted in decreased expression of the NLRP3 inflammasome, ASC, cleaved Caspase-1, cleaved Gasdermin D (GSDMD), IL-1β and IL-18. In vitro studies have showed that BRCC3 levels in airway epithelial cells are increased under the stimulation of HDM.[140] Further investigation revealed that silencing BRCC3 could increase the ubiquitination level of NLRP3, while overexpression of BRCC3 could reduce its ubiquitination level.[140] Consequently, the study suggests that BRCC3 could be a viable target for asthma treatment by inhibiting the activation of the NLRP3 inflammasome, thereby alleviating airway inflammation in asthma.

Future Directions and Clinical Implications

The UPS system, as a specific biomarker, has been widely used in disease diagnosis, disease detection and prognosis evaluation. E3 ligase Trim35, a highly effective and active biomarker, has been shown to predict the prognosis of non-small cell lung cancer (NSCLC) treated with targeted therapy and immunotherapy.[193] In addition, E3 ligases have shown superiority in the early monitoring of pancreatic cancer, Alzheimer's disease, esophageal cancer and other diseases.[194–196] Further study of the UPS system is expected to reveal biomarkers indicative of the activity of UPS-related enzymes, the levels of substrates or products, as well as inflammatory factors or immune cell-related molecules regulated by UPS.

The monitoring of these biomarkers enables physicians to make more accurate diagnoses of asthma patients, to make timely adjustments to the treatment plans, and to enhance treatment outcomes.

The study of UPS-related enzymes in asthma is of significant clinical importance. Proteasome inhibitors have been proved to be effective new drugs for the treatment of multiple myeloma and mantle cell lymphoma.[197–199] In addition, many proteasome targeted therapies are in clinical trials.[200] Proteasome inhibitors such as bortezomib, carfilzomib and ixazomib have been approved by the US Food and Drug Administration (FDA) since 2003.[200–202] By regulating the UPS, it may be possible to intervene in the inflammatory response and immune imbalance that characterize asthma. For example, the development of specific inhibitors against the E3 enzyme that promotes asthma could become a new therapeutic strategy. Furthermore, the enhancement of the activity or function of enzymes that inhibit asthma, such as GRAIL and USP21, may also contribute to the alleviation of asthma symptoms. In addition, UPS-based treatment strategies may offer enhanced personalization potential, given the potential for varied abnormal regulation of UPS among different patients. In the future, personalized UPS targeted therapy can be developed according to the gene expression profile or proteomic characteristics of patients to improve the effectiveness of treatment.

Despite the advancement in research, there are still significant research gaps in the study of the relationship between UPS and asthma. Firstly, further in-depth studies on the mechanism of UPS in different asthma subtypes are required, given the heterogeneity of asthma and the potential involvement of different molecular pathways in different subtypes. Secondly, further exploration into the interaction network between the UPS and other signaling pathways is necessary to achieve a comprehensive understanding of the pathogenesis of asthma. In addition, the development of more potent modulators or inhibitors of UPS-related enzymes and the conduct of preclinical and clinical trials are important directions for future research. Concurrently, the exploration of the potential of UPS to regulate immune cell function, particularly in the context of T cell subset balance and macrophage polarization, holds promise for novel therapeutic interventions for asthma. Finally, the search for novel biomarkers for early diagnosis, disease monitoring, and treatment response assessment is also one of the key areas for future research.

Conclusion

Post-translational modification represents a pivotal regulatory mechanism for gene expression, with ubiquitination being a critical component of this process. The E3 ubiquitin ligase is a pivotal component of this process, impacting the function and physiological state of substrate proteins. A comprehensive review of recent studies on E3 ubiquitinases and deubiquitinases in the context of chronic lung inflammation and asthma has been undertaken. It is well established that Th2 cell inflammation is a key feature of allergic asthma, and the majority of related enzymes affect its pathogenesis by regulating Th2 cell differentiation. For instance, AMFR promotes Th2 cell proliferation/differentiation, while ITCH inhibits asthma by reducing Th2 cytokine production. USP38 has been identified as a promoter of asthma pathogenesis, and immune imbalance (Treg function) has also been found to be a contributing factor. USP21, on the other hand, has been shown to inhibit Treg function. There has been an increase in the number of clinical reports on ubiquitination in the treatment of asthma. The nano-vaccine with A20 and OVA in PLGA can inhibit Th2 response and promote Treg production. However, the mechanisms underlying certain E3 enzymes, such as March1, remain to be fully elucidated. In OVA-induced asthma models, March1 shows complex effects on lung inflammation. Asthma, a global health concern, necessitates prolonged treatment regimens.

In the studies discussed in this review, the vast majority of mouse asthma models were generated with OVA or HDM. Among them, AMFR, TRIM27, FBXL19, TRIM21, PPARγ, ITCH, Cbl-b, CUL5, CUL4B, RNF 125, USP 4, and CYLD have been demonstrated to be implicated in OVA-induced models, while Cbx4, MID1, FBW7, PARK2, USP 25 have been implicated in HDM-induced models. Notably, both OVA and HDM have been used in the investigation of the mechanisms underlying TRIM31, USP 38, A20 and BRCC3. OVA-and HDM-induced mouse asthma models exhibit notable parallels in terms of inflammatory cell infiltration, cytokine expression, airway hyperresponsiveness, and airway remodeling. The two models primarily elicit Th2-type immune responses, with Th2 cells being activated in both, leading to increased secretion of Th2-type cytokines, such as IL-4, IL-5, and IL-13. In addition, both result in the infiltration of inflammatory cells in the airways and lungs. A significant accumulation of eosinophils in the surrounding tissues of the airway has been observed, resulting in the secretion of inflammatory mediators, damage to airway epithelial cells, and impairment of the airway

epithelial barrier function.[203] In the two models, eosinophils predominate in the inflammatory cell infiltration observed in the OVA-induced model, although eosinophil infiltration is also evident in the HDM model, albeit with a more complex inflammatory cell infiltration pattern. By contrast, neutrophils infiltration may be more pronounced in HDM-induced asthma model, especially in the case of acute exacerbations of asthma or in conjunction with bacterial infection. Additionally, HDM may also lead to increased activation and infiltration of other inflammatory cells such as mast cells.[203] Therefore, OVA-and HDM-induced mouse asthma models share similarities in several aspects, which reflect the basic pathological features of asthma and provide an important experimental model basis for studying the pathogenesis and treatment of asthma. Nevertheless, there are also some discrepancies, and it is necessary to select the most appropriate model according to the research objective and specific research problem. The potential for combining these two asthma models, as has been achieved by TRIM31, USP38, A20 and BRCC3, holds great promise in offering more scientific and comprehensive conclusions.

A plethora of studies have been conducted that utilize murine models to elucidate the mechanisms of the unfolded protein response (UPS) in asthma. However, it is imperative to acknowledge the inherent differences between murine models and human asthma. In mouse models, specific genetic manipulations or pharmacological interventions may produce distinct phenotypic changes, but the translation of these results into human asthma requires careful consideration. For instance, the relevance of altered expression and function of certain E3 enzymes or deubiquitinating enzymes in mouse models of asthma to human asthma has not been fully defined. In the future, more clinical studies are needed to directly detect the expression and activity of UPS-related components in asthmatic patients and analyze their relationship with clinical indicators such as disease severity and treatment response, to better translate findings in mouse models into understanding and treatment strategies for human asthma. Furthermore, histamine and bronchospasm are closely related in the pathogenesis of asthma. A study has shown that TRIM26 may affect aspirin-induced bronchospasm, and this gene can be used as a candidate gene for the diagnosis of Aspirin-exacerbated respiratory disease.[204] However, their association with the UPS system remains unclear and needs to be explored.

Data Sharing Statement

The data supporting this review are from previously reported studies and datasets, which have been cited. The processed data are available from the corresponding author upon request.

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Author Contributions

Shuzhou Deng drafted the manuscript and prepared figures and tables. Le Ding and Yisong Qian edited and revised the manuscript. Xuan Huang conceived and revised the manuscript for final submission. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors do not have any competing interests in this work.

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