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Immune Cell-Mediated Autoimmune Responses in Severe Asthma

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Severe asthma (SA) has heterogeneous inflammatory phenotypes characterized by persistent airway inflammation (eosinophilic and/or neutrophilic inflammation) and remodeling. Various immune cells (eosinophils, neutrophils, and macrophages) become more activated and release inflammatory mediators and extracellular traps, damaging the protective barrier of airway epithelial cells and further activating other immune and structural cells. These cells play a role in autoimmune responses in asthmatic airways, where the adaptive immune system generates autoantibodies, inducing immunoglobulin G-dependent airway inflammation. Recent studies have suggested that adult asthmatics had high titers of autoantibodies associated with asthma severity, although pathogenic factors or diagnostic criteria are not well-defined. This challenge is further compounded by asthmatics with the autoimmune responses showing therapy insensitivity or failure to current pharmacological and biological treatment. This review updates emerging mechanisms of autoimmune responses in asthmatic airways and provides insights into their roles, proposing potential biomarkers and therapeutic targets for SA.

Key Words: Asthma, extracellular traps, autoimmunity, autoantibodies, epithelial cells, biomarkers

INTRODUCTION

Asthma is a chronic airway disease characterized by eosinophilic inflammation, reversible airflow limitation, and airway hyperresponsiveness to numerous pathogens (allergens, air pollutants, and microbes). It was reported that asthma affected over 300 million people with a rising tendency.[1] Increased levels of pro-inflammatory cytokines [interleukin (IL)-8, tumor necrosis factor-alpha (TNF-α), IL-6, and IL-1β] and blood/sputum neutrophilia could distinguish neutrophilic airway inflammation from eosinophilic airway inflammation that is characterized by increased production of epithelial cell-derived alarmins [thymic stromal lymphopoietin (TSLP), IL-33, and IL-25], type 2 cytokines (IL-4, IL-5, and IL-13), and blood/sputum eosinophilia.[2,3] Despite the efficacy of inhaled corticosteroid (ICS) treatment which could achieve symptom control to maintain a normal lifestyle in asthmatics with eosinophilic airway inflammation, 5%–10% of adult asthmatics still experience with uncontrolled symptoms, frequent asthma exacerbations (AEs) requiring oral corticosteroid (OCS), and/or persistent airflow limitation.[4] This phenomenon may be involved in infection-induced neutrophilic inflammation, steroid insensitivity, comorbidity (*e.g.*, obesity, chronic rhinosinusitis with nasal polyps, nonsteroidal anti-inflammatory drug hypersensitivity), allergen exposure, and smoking. Recent studies have suggested that autoimmune responses against airway epithelial cells (AECs) and immune cells may contribute to asthma severity, insensitivity to current anti-asthma medications or biologics.[5-7] It has been supposed that localized autoantibodies target structural or immune cells (mediated by self-reactive lymphocytes), resulting in tissue damage and remodeling.[7] High levels of autoantibodies in the airways induce immune cell activation, degranulation, and extracellular trap (ET) formation in association with asthma severity and therapy resistance.[5,8]

Several biologics or monoclonal antibodies [anti-immunoglobulin E (IgE), anti-IL-5, anti-IL-5Rα, and anti-IL-4Rα anti-

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bodies] have been approved to effectively control type 2-high severe asthma (SA) in aspects of reduction in AEs and OCS use (up to 50%–70%).[3,4] Besides achieving clinical response, biologics have been reported with clinical failure and partial remission in a subgroup of SA,[9,10] in which increased levels of IgG antibody against IL-5 with deposition of C1q and increased C3c levels (a marker of complement activation) in the airway secretion have been reported in patients with SA who had shown failure to mepolizumab treatment.[5] In addition, high titers of IgG and polyclonal IgE antibodies against eosinophil peroxidase (EPx) and/or anti-nuclear antibody (ANA) have been observed in patients with SA compared to healthy controls.[11,12] These findings suggest close associations between autoimmune responses against immune cells/inflammatory mediators and therapy resistance as well as asthma severity.

The previous studies demonstrated close relationships between activated immune cells (eosinophils, neutrophils, and macrophages)-derived ETs and autoimmune mechanisms in adult patients with SA.[13] ETs from eosinophils and neutrophils were higher in patients with SA than in those with non-SA. These ETs further damaged AECs, activated immune cells, and facilitated autoimmune responses. They could induce the release of autoantigens from AECs, especially cytokeratin (CK)18, CK19, α-enolase, and tissue transglutaminase, and the production of their autoantibodies from activated B lymphocytes.[14] This review aimed to: 1) update fundamental mechanisms of autoimmune responses in the airway inflammation of SA; 2) explore potential biomarkers for predicting autoimmune responses in asthmatic airways; and 3) discuss possible therapeutic options for SA.

AUTOANTIBODIES INDUCE IMMUNE CELL ACTIVATION IN AUTOIMMUNE DISEASES

Autoimmune diseases are characterized by localized or circulating autoantibodies, which are influenced by susceptibility genes and environmental factors.[15] Genetic polymorphisms associated with autoimmune diseases, such as *IL-4 receptor alpha*,[16] *SLC22A5/A4*,[17,18] *HLA-B*, *Smad3*, *Myc*, *IKZF1*, and *IL-2R/IL-15R*,[19] have been linked to asthma pathophysiology, suggesting the crosstalk between asthma and autoimmune responses. Furthermore, environmental triggers (*e.g.*, respiratory viral infections) could incite autoimmune responses which are closely associated with the onset of asthma.[6,15] In addition, the presence of autoantibodies may initiate the activation of immune cells, contributing to asthma pathogenesis. In fact, the number of eosinophils has been found to be elevated and correlated with disease severity in patients with autoimmune conditions.[20,21] Eosinophils from patients with bullous pemphigoid expressed the high-affinity IgE receptor (FcεRIα) on their surfaces, which can potentially activate eosinophils through IgE autoantibodies.[22,23] Neutrophils play pivotal roles in systemic autoimmune diseases, which share a common trait: an immune system malfunction that leads to an inability to distinguish self from non-self, resulting in damaging various tissues and organs (*i.e.*, kidneys, vessels, and joints).[24,25] Circulating immune complexes deposit in kidney glomeruli, triggering the recruitment and aggregation of neutrophils as well as the formation of neutrophil ETs (NETs). Moreover, observational studies have revealed elevated percentages and numbers of CD-$14^{high}CD16^{high}$ monocytes and macrophages in patients with autoimmune diseases, such as systemic lupus erythematosus, primary biliary cholangitis, and inflammatory bowel disease.[26-30] These alternatives could be attributed to heightened levels of IgG autoantibodies (*e.g.*, anti-dsDNA and anti-C1q antibodies), immune complexes intertwined with microparticles, exosomes (neutrophil-derived microvesicles carrying microRNA-155), and interferon-gamma (IFN-γ)-rich environment. IFN-γ contributes to host defense against infection; however, it exhibits an essential role in the development of autoimmunity through its effects on T cell differentiation and immunoglobulin class switching on B cells. Although the particular process of how autoantibodies contribute to immune cell activation is yet unknown, these findings give insight into a possible contribution of autoimmune response in the pathogenesis of SA.

AUTOIMMUNE MECHANISM, POSSIBLE BIOMARKERS, AND NOBLE TREATMENT OPTIONS IN SA

Patients with SA suffer from persistent symptoms, lower lung function, and lower quality of life that associate with comorbidity and side effects of treatment related to OCS use.[4,31] To clarify the contribution of autoimmune responses in SA, clinical relevance of autoimmunity in asthma and immune cell-mediated autoimmune responses *in vitro* and *ex vivo* experiments are summarized in Table 1.

The roles of eosinophils

Eosinophils exhibit a defense role against parasitic helminth, bacterial, fungal, viral infection, and allergens. Persistent eosinophilia and activated eosinophils mainly maintain type 2 airway inflammation and remodeling in asthmatic airways.[23,32] Activated eosinophils have the ability to release ETs (EETs), which are a complex arrangement of DNA fibers and granular proteins [major basic protein (MBP), eosinophil cationic protein (ECP), and EPx]. Higher EETs-forming eosinophils were noted in patients with SA than in those with non-SA.[33] Numerous studies have emphasized on the role of EETs in autoimmune responses in SA.[23,32] EETs could change the morphology of AECs, downregulate tight junction proteins, prompt AECs to release alarmins, and activate type 2 innate lymphoid cells (ILC2).[34] In addition, MBP has the potential to harm AECs and

Table 1. Autoantibodies Reported in SA

Autoantibodies	Year	Study subjects	Method	Sample	Key findings
α-enolase-specific IgG	2006[42]	HCs (n=58) Mild-to-moderate (n=83) SA (n=78)	Immunoblotting	Serum	Higher prevalence of positive a-enolase-specific IgG in patients with SA than in those with mild-to-moderate asthma or HCs
EPx-specific IgG ANA	2018[6]	HCs (n=15) NA (n=13) MA (n=18) ICS-dependent EA (n=13) OCS-dependent EA (n=20)	ELISA Immunoassay	Sputum	Higher levels of EPx-specific IgG and ANA in patients with OCS-dependent EA and MA than in those with ICS-dependent EA and NA
PR3-, P0-, SS-A-, SS-B-, Scl-70-, Jo-1-, U1-SnRNP-, Sm-, MPO-, and TPO-specific IgG	2019[36]	HCs (n=24) Mild asthma (n=15) Moderate asthma (n=18) SA (n=17)	ELISA	Serum Sputum	Higher levels of U1-SnRNP- and Sm-specific IgG in sputum and TPO-specific IgG in serum of SA than in those with mild asthma or HCs Positive correlations between sputum U1-SnRNP-specific IgG levels and sputum eosinophil count/FeNO
ANA	2021[41]	Non-SA (n=29) SA (n=17)	ELISA	Sputum	Higher levels of ANA in patients with SA than in those with non-SA Positive correlations between ANA and MPO levels
EPx-specific IgG ANA	2022[35]	HCs (n=8) Moderate EA (n=10) ICS-dependent SEA (n=18) OCS-dependent SEA (n=8)	ELISA Immunoassay	Sputum	Higher levels of ANA in patients with OCS-dependent SEA than in HCs
EPx-specific IgG MARCO-specific IgG	2023[54]	HCs (n=18) SA (n=143)	ELISA	Sputum	Higher levels of MARCO- and EPx-specific IgG in patients with MEA than in HCs Positive correlations between MACRO-specific IgG and EPx-specific IgG levels
EPx- and ECP-specific IgG EPx-and ECP-specific IgE	2023[12]	HCs (n=60) Mild asthma (n=83) Moderate-to-SA (n=78)	ELISA	Serum	Higher levels of EPx/ECP-specific IgG/IgE in patients with moderate-to-SA than in either those with mild asthma or HCs
Collagen V-, EPx-, TREM1-, and IL-1R2-specific IgG ANCA	2023[37]	HCs (n=30) EGPA (n=17) SEA (n=63)	ELISA	Serum	Higher levels of collagen V-, TREM1-specific IgG and ANCA in patients with SEA than in HCs
CK18-specific IgG	2022[13]	HCs (n=26) Non-SA (n=41) SA (n=11)	ELISA	Serum	Higher levels of CK18-specific IgG in patients with SA than those in with non-SA Negative correlation between CK18-specific IgG levels and FEV_1

ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; CK18, cytokeratin 18; EA, eosinophilic asthma; ECP, eosinophil cationic protein; EPx, eosinophil peroxidase; EGPA, eosinophilic granulomatosis with polyangiitis; FeNO, fractioned exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; HCs, healthy controls; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IgG, immunoglobulin G; IL-1R2, interleukin 1 receptor 2; Jo-1, anti-histidyl transfer RNA synthetase; MA, mixed granulocytic asthma; MARCO, macrophage receptor with collagenous structure; MPO, myeloperoxidase; NA, neutrophilic asthma; OCS, oral corticosteroid; PR-3, proteinase 3; SA, severe asthma; Scl-70, topoisomerase I; SEA, severe eosinophilic asthma; Sm, Smith; TPO, thyroid peroxidase; TREM1, triggering receptor expressed on myeloid cells-1; U1-SnRNP, U1 small nuclear ribonucleoprotein.

compromise barrier integrity. Increasing evidence supports the contribution of circulating autoantibodies on eosinophil activation in SA. This is reinforced by the correlation between autoimmune responses, B cell counts, and activated eosinophils in the airways of patients with SA.[7,12,35] Polyclonal IgE against EPx and ECP has been reported to be higher patients with SA than in healthy controls.[12] In addition, patients with OCS-dependent SA have been reported to have elevated levels of EPx-specific IgG autoantibody and ANA in their sputa.[7] Immunoprecipitated IgG in the sputum of patients with heightened autoantibody levels triggered eosinophil degranulation and EET release.[6,7] Later studies have reported the presence of IgG autoantibodies in patients with severe eosinophilic asthma, such as U1 small nuclear ribonucleoprotein-, Smith- and thyroid peroxidase-specific IgG, anti-neutrophil cytoplasmic antibodies [myeloperoxidase (MPO)-specific IgG and proteinase 3-specific IgG], collagen V-, triggering receptor expressed on myeloid cells-1, and IL-1R2-specific IgG, although the function of these autoantibodies has not been studied.[36,37] Collectively, a subgroup of patients with type 2-high SA presents autoimmune responses including IgG and IgE antibodies against components of eosinophils and/or neutrophils.

IL-5 is a primary cytokine released from T helper 2 (T_h2) and ILC2, and it is able to recruit, survive, and activate eosinophils. Anti-IL-5/IL-5 receptor antibodies (approved for patients with SA) may modulate EET-mediated airway inflam-

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mation. However, worsening asthma symptoms were found in 13.6% of patients with type 2-high SA who had received anti-IL-5 antibody,[38] which may be involved in the presence of autoimmune responses in airways with the formation of autoantibodies and heterocomplexes and the activation of complement system. Thus, the identification of potential autoimmune responses should be considered for patients with type 2-high SA before commencing biologics.

The roles of neutrophils

Neutrophils have the fundamental function in combating pathogens via phagocytosis, degranulation, and reactive oxygen species (ROS) production.[39] Researchers have honed in on the role of neutrophils in chronic inflammatory conditions and steroid insensitivity, as a strong association was observed between blood/sputum neutrophils and SA in both cluster analyses and longitudinal studies.[31,40] In addition, higher levels of NETs [containing chromatin structures (DNA-histone complexes) and neutrophilic granular proteins] were released from activated neutrophils in patients with SA, which were associated with autoantigens and autoantibody generation. When compared to patients with non-SA, sputum ANA levels were elevated in patients with SA and had a positive correlation with sputum MPO levels (abundantly expressed in neutrophils and NETs),[41] suggesting that autoimmune responses may be associated with neutrophil activation/NET formation in SA. NETs have been reported to induce autoantigens from AECs and promote autoantibody production from activated B cells.[14,42] Furthermore, NETs play a crucial role in damaging AECs and activating eosinophils, thereby remarkably contributing to airway inflammation and remodeling in SA. High levels of autoantibodies against NETs were observed in patients with COVID-19, and low levels of serum DNases (break down NETs) linked to disease severity.[43] These results indicate the close interplay between these autoantibodies and neutrophil activation/NET formation in SA.

NETs have intricate structures consisting of MPO, neutrophil elastase (NE), and S100 calcium-binding protein A9 (S100A9).[44] Of note, NE triggers mucous gland hyperplasia, mucous secretion, and the proliferation of airway smooth muscle cells, while MPO contributes to hypochlorous acid production. These factors collectively inflict damage on resident lung cells.[45,46] Elevated S100A9 levels have been reported in both sputa and sera obtained from patients with severe NA, inducing the formation of NETs, damaging AECs, and contributing to airway remodeling.[47,48] These results indicate that S100A9 may serve as a potential biomarker for predicting neutrophilic airway inflammation in SA. Despite the pivotal role of neutrophils in the autoimmune endotype of SA, therapeutic approaches targeting neutrophil recruitment and activation have been concerning. The formation of NETs is modulated by the IL-8 pathway. IL-8-stimulated neutrophils from SA patients were reported to have higher levels of NETs/dsDNA than those from non-SA.[49] However, anti-IL-8 receptor antibodies (AZD6059 and SCH 527123) showed disappointing results in clinical trials, despite their potential to suppress neutrophil numbers.[50,51] Further potential therapeutics (*e.g.*, microRNAs, exosomes, and stem cell therapies) targeting neutrophilic airway inflammation are needed to investigate for early prevention of airway autoimmunity in SA.

The roles of macrophages

Macrophages play vital roles in maintaining homeostasis in both physiological and inflammatory conditions through clearing infectious, toxic, and allergic particles.[52] The precise regulatory mechanisms underlying the role of macrophages in the development of autoimmune diseases remain elusive, and a growing consensus suggests that their abnormal activation holds significant relevance.[53] Indeed, autoantibodies against the macrophage receptor with collagenous structure (MARCO) have correlations with anti-dsDNA antibodies and disease progression in patients with autoimmune diseases. High levels of MARCO-specific IgG were noted in asthmatic patients with mixed granulocytic phenotype (presenting both eosinophilia and neutrophilia in sputum) and recurrent infestion,[54] especially higher in those required OCS treatment than in those receiving ICS treatment. The presence of airway anti-MARCO IgG hindered macrophage functions in vitro by impairing the uptake of bacteria, contributing to infection susceptibility.[54] Macrophages differentiate into distinct subsets, namely M1 and M2 macrophages. M1 macrophages could release ETs (M1ETs) underlying the stimulation of LPS, IFN-γ, and TNF-α, which were more elevated in patients with SA than in those with non-SA.[52,55,56] Functional studies have recently demonstrated that M1ETs activated neutrophils, ILC1, and ILC3.[56] These findings suggest that macrophage function could be considered in novel therapies for SA.

Activated macrophages may play a pivotal role in crosslinking autoinflammation and autoimmunity through perpetuating T_h1 responses, which may contribute to autoimmune responses in SA. Macrophages release IFN-γ and CCL-2, which play potential roles in the expression of B-lymphocyte stimulators in monocytes and monocyte recruitment into inflammatory environments.[53] The overproduction of IFN-γ from macrophages and ILC1 could be induced by M1ETs.[53] The increased levels of IFN-γ cause several detrimental effects: 1) increased expression of CXCL-10 and down-regulation of secretory leukocyte protease inhibitors, resulting in increased airway hyperresponsiveness and steroid resistance; 2) the stimulation of immature dendritic cells to release B cell-activating factors (*e.g.*, B cell-activating chemokine 1) and induce B cell maturation, proliferation, and survival; and 3) the activation of neutrophils and macrophages.[56-60] Macrophages release a range of proinflammatory cytokines (*e.g.*, IL-1β, IL-6, TNF-α, and ROS), resulting in local and systemic inflammation and promoting fibrosis and degradation of cartilage.[53]

Moreover, M1ETs could directly induce the release of neutrophil activation-related cytokines from AECs and simulate neutrophils to release NETs, further aggravating neutrophilic inflammation in SA.[56] Clinical efficacy and limitations of anti-IL-1, anti-TNF-α, and anti-IL-6 antibodies have been reported in clinical trials on patients with pulmonary diseases.[61-63] Novel therapeutics targeting upstream signaling in the pathway of the production of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) have been focused on investigation [*e.g.*, NLR family pyrin domain containing 3 inflammasome/nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB)].

The roles of AECs

AECs can detect invading pathogens through the expression of transmembrane or intracellular pattern recognition receptors (PRRs).[64,65] Autoantigens (*e.g.*, CK18, CK19, α-enolase, and tissue transglutaminase) could be released from activated AECs in response to EETs, NETs, or occupational irritants. A recent investigation demonstrated that higher levels of circulating CK18-specific IgG were noted in SA with a correlation with low lung function parameters.[13] EETs were reported to have a feedback role in the production of epithelial cell-derived CK18 and CK18-specific IgG, further enhancing eosinophilic airway inflammation.[13] Upon PRR activation, cascade signaling pathways were triggered, leading to the release of alarmins (*e.g.*, TSLP, IL-33, and IL-25) as a response to allergens and stimuli.[66] These alarmins were traditionally thought to instigate eosinophilic airway inflammation through activating T_h2 and ILC2 in a dependent/independent dendritic cell activation manner, which facilitates rapid recruitment of eosinophils from the circulation into the inflammatory lungs. Furthermore, these alarmins contribute to the shift from IgG to IgE class-switching, a process that subsequently triggers mast cell activation and degranulation, thereby maintaining eosinophilic airway inflammation.[66] However, IL-33 has distinct functions in inducing neutrophilic airway inflammation and autoimmunity via recruiting, activating neutrophils and inducing IFN-γ release.

The expression of IL-33 and its receptor (ST2) were elevated in patients with SA. Elevated levels of IL-33 transcripts were noted in the biopsy samples from patients with SA.[67] A meta-analysis of serum IL-33 levels concluded that patients with moderate-to-SA exhibited higher serum IL-33 levels compared to those with mild asthma.[68] ST2 exists in two forms with contrasting functions: a soluble form (sST2), which acts as a decoy receptor by capturing and neutralizing free IL-33; and a membrane-bound form (ST2L), which triggers cell activation.[69,70] However, the increased levels of sST2 could also enhance the effects of IL-33 on airway inflammation in the context of NA.[71] Elevated serum sST2 levels (above 18 ng/mL) have been found to predict AEs in SA with a positive correlation with serum IL-8 levels.[71,72] Consistently, these studies demonstrated significantly higher serum sST2 levels in patients with uncontrolled asthma than in those with partly controlled or well-controlled asthma, suggesting that IL-33/ST2 signaling pathway may be a potential biomarkers and therapeutic targets to control neutrophilic airway inflammation in SA.

When IL-33 is released into the extracellular environment, it activates downstream inflammatory responses in collaboration with other inflammatory cytokines, such as IL-12 and IL-23, leading to more than 10-fold increase in IFN-γ release from natural killer cells and natural killer T cells.[73] IFN-γ stimulates AECs to further release IL-33 into the extracellular spaces, establishing a self-perpetuating autoinflammatory cycle.[58,59] Moreover, IL-33 possesses the capability to induce the formation of NETs from activated neutrophils and IFN-γ production from macrophages in patients with uncontrolled asthma, which may contribute to maintaining autoimmune responses in SA. To control this signaling pathway, two potential therapeutic approaches have been suggested: anti-IL-33 and anti-ST2 antibodies. Although the efficacy of anti-IL-33 antibody remains unexplored in randomized controlled trials for SA, the effectiveness of two biologics targeting the ST2 receptor has been reported in randomized controlled phase 2 trials involving patients with moderate-to-severe uncontrolled asthma.[74,75] Taken together, since the IL-33/ST2 pathway emerges as a crucial signaling pathway not only in regulating eosinophilic airway inflammation but also in contributing to neutrophilic airway inflammation in SA, it could be candidate targets for the phenotype of SA with autoimmune responses.

REGULATORY T CELLS AND $CD8^+$ T CELLS: MECHANISMS AND TARGETING APPROACHES IN SA

Besides and beyond potential targets involving activated AECs-derived cytokines or immune cells-released ETs/granulocytes, other targets could be considered for the phenotype of SA with autoimmune responses. Regulatory T cells (Tregs) possess the ability to suppress T cell activation through various mechanisms, including the production of immunosuppressive cytokines, induction of cell death, generation of immunosuppressive adenosine, downregulation of costimulatory molecules, and the consumption of IL-2 cytokine via IL-2R.[76,77] In addition, $CD8^+$ T cells can contribute to autoimmune responses through the production of IFN-γ, thereby triggering macrophage-related autoimmune mechanisms. Strategies to enhance Tregs and limit $CD8^+$ T cells hold the promise as potential therapies for autoimmune responses in SA.[78,79] Intravenous immunoglobulin (IVIG), derived from pooled human immunoglobulins from healthy donors, has shown beneficial outcomes in various autoimmune diseases through its effects on the reciprocal regulation of Treg cells and effector T cells, the inhibition of innate immune cell activation, and the neutralization of activated complements.[80] Further investigations and

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preclinical trials are required to validate their therapeutic potentials in SA with airway autoimmunity.

CONCLUSION

SA presents a significant challenge in research and clinical management, characterized by persistent airway inflammation (eosinophilic and/or neutrophilic inflammation) and progressive decline in lung function even on maintenance anti-inflammatory medication. Although several type 2-targeting biologics have been prescribed, some patients with SA do not respond to these treatments related to autoimmune responses. The detection of autoantibodies in the blood and sputum of SA has provided valuable insights into the mechanisms of persistent activation of AECs and immune cells (especially eosinophils and neutrophils) and resistance to current drugs. These autoantibodies induce the formation of ETs from immune cells (*e.g.*, eosinophils, neutrophils, and macrophages); ETs contribute to production of autoantibody against cellular components with close interactions with AECs. Although this review suggests several autoantibodies as potential biomarkers and therapeutic targets for SA, there is a need for translational studies to apply these findings in clinical practice in a larger scaled multi-center randomized trial.

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