



Resolution of allergic asthma

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Abstract

Allergic asthma is an inflammatory disease of the airways characterized by recurrent episodes of wheezing and bronchoconstriction. Chronic inflammation may finally lead cell structural damage followed by airway remodeling and of the airways. Various studies in recent years contributed to unravel important aspects of the immunopathogenesis of asthma and adapted new pharmaceutical developments. Here, I consider some novel insights into the immunopathogenesis of asthma and the protective and pathogenic roles of some innate and adaptive immune cells as well as the function of soluble mediators such as cytokines. Particular attention will be given to new concepts on resolution of chronic airway inflammation for prevention of airway structural damage.

Keywords Allergic asthma · Resolution of inflammation · Airways · Epithelium · Lymphocytes · Eosinophils

Introduction

More than 300 million people worldwide suffer from asthma, a chronic inflammatory disorder of the airways characterized by local inflammation and airway hyperresponsiveness [1]. Possible symptoms include wheezing, coughing, chest tightness, and acute exacerbation associated with breathlessness. It has been calculated that asthma leads to more than 300,000 hospital discharges a year and considerable national annual healthcare resource use (11.0 million physician office visits, 1.7 million emergency room visits, and 1.3 million hospital outpatient department visits according to the Centers for Disease Control and Prevention) in the USA. Several studies suggested a major risk to reappearance of asthma in elderly if one was affected as a child. Allergic asthma may cause debilitating daily symptoms and may be complicated by acute exacerbations of symptoms. Viral infections are common triggers of exacerbations in asthma and may impair asthma symptom control [2, 3]. In addition to viral infections, bacterial infections of the respiratory tract have been associated with

worsening or increased severity of symptoms in asthma patients [4] highlighting the concept that various infections may trigger disease exacerbations. It should be noted that asthma is characterized by a marked heterogeneity in pathophysiology and etiology in individual patients. This heterogeneity is mirrored by different disease-inducing mechanisms (allergic versus non-allergic forms of asthma), differences in immune cells acting as key drivers of disease activity (eosinophilic versus non-eosinophilic/neutrophilic forms of asthma), and varieties in both the severity (mild, moderate versus severe forms) and frequency of clinical disease manifestations.

In addition to intrinsic asthma, exogenously triggered forms of asthma exist that can be induced by exposure to allergens [5–10]. Allergic asthma is a consequence of complex gene–environment interactions and flares are frequently triggered by allergen exposure. The recommendation for the resolution of acute symptoms of this disease (e.g., wheezing, coughing, breathlessness) is to avoid contact with allergen exposure in the environment. In addition, a reduction of fat- or sugar-rich diet may be helpful. Furthermore, therapeutic asthma strategies comprise anti-inflammatory and bronchodilator treatments. In particular, inhaled corticosteroids, alone or in combination with long-acting bronchodilators, are frequently used for asthma therapy. However, symptom minimization may not be achieved in some patients leading to the manifestation of uncontrolled asthma. As specified below, asthma therapy has changed in recent years through the introduction of biological agents such as monoclonal antibodies (as outlined below). These new biological therapies for asthma,

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together with developments in the field of serum biomarkers, are important new opportunities for phenotype-specific interventions and personalized medicine in the field of asthma. The specific immunological molecules targeted by monoclonal antibodies have been identified based on the characterization of the cellular and molecular components present in the airways of asthmatic patients. In this regard, it has been recognized in the last 30 years that the airways of many asthmatic patients are filled with inflammatory cells like eosinophils during exacerbations. Thus, many biological therapies have been designed to target eosinophil activation or function in patients with asthma.

Soluble mediators like cytokines produced by immune cells have been shown to play a fundamental role in the pathophysiology of asthma. For instance, genome-wide differential gene expression in response to dust mite allergen identified cytokines such as IL-9 as gene targets that might interact with environmental dust mite to increase severe asthma exacerbations in children [11]. Moreover, pathways of innate immune stimulation by environmental or endogenous pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) play a key role in asthma pathogenesis [12]. Specifically, viral and microbial stimuli as well as factors of the airway microbiota can trigger pattern recognition receptors and may contribute to the shaping of the inflammatory response seen in asthma [4]. Activated PAMPs and DAMPs have been demonstrated to modulate mucosal immune responses of the airways via effects on cell activation and trafficking. In particular, mucosal immune cells such as dendritic cells, macrophages, granulocytes, innate lymphoid cells (ILCs), B cells, and T lymphocytes can be directly or indirectly activated via environmental triggers. Subsequently, these immune cells produce proinflammatory mediators that drive and perpetuate mucosal inflammation and airway remodeling. Cytokines of the Th2 group such as IL-4, IL-5, and IL-13 have a key role in amplifying mucosal inflammation. However, studies in recent years have clearly demonstrated that only a subgroup of patients with asthma has elevated Th2 type cytokines. In fact, only approximately 50% of asthma patients demonstrate high type 2 cytokine responses and/or elevated numbers of eosinophils. The other group of patients (“type 2-low”) is frequently characterized by a different immune phenotype associated with airway [neutrophilia](#), goblet cell hyperplasia, and obesity-related [systemic inflammation](#) [13–17]. These findings highlight the concept that several asthma phenotypes exist in clinical practice and may require individual therapeutic approaches for optimized therapy.

Immune cells and signaling pathways in asthma

The chronic inflammation in allergic asthma is associated with marked airway hyperresponsiveness and leads to recurrent

episodes of exacerbation marked by wheezing, breathlessness, chest tightness, and coughing [18]. Studies in recent decades have unequivocally shown that immune cell pathways play a crucial role in the pathogenesis of asthma. For instance, immunoglobulin E (IgE) bound to the surface of immune cells such as mast cells may bind to specific airway allergens followed by IgE cross-linking, cell activation, and mediator release [19–21]. Mediators include histamine, a potent proinflammatory substance leading to vasodilatation and local inflammation. In addition to mast cells, other mucosal immune cells in the airways such as innate lymphoid cells (ILCs), macrophages, dendritic cells, and adaptive immune cells such as B and T lymphocytes play an important role in the pathogenesis of asthma. In particular, these cell types have been shown to produce soluble mediators such as cytokines that impair or boost mucosal inflammation of the airways in allergic asthma. Moreover, these cell types may respond to cytokine signals in the local environment triggering immune cell activation and further cytokine production. For instance, eosinophils have been classically described as proinflammatory immune cells in asthma and these cells differentiate from progenitor cells derived from the bone marrow under the influence of cytokines such as IL-3, IL-5, and GM-CSF [13, 22, 23]. In addition, IL-3 has been demonstrated to contribute to the differentiation of mucosal bone marrow-derived mast cells and to basophil differentiation and activation [24]. Remarkably, these two cell types are not the predominant cells in the airways during asthma exacerbations, but they may contribute more than other inflammatory cells to the terminal exacerbation of the allergic reaction. In fact, these cell types carry the high affinity IgE receptor on their surface [18, 25], and after allergen encounter cross-link, the allergen on the IgE bound to the high affinity IgE receptor resulting in the release of potent preformed mediators like histamine that favor bronchoconstriction. In addition to histamine, mast cells in asthma may produce various other mediators including chymase, tryptase, prostaglandin D₂, and leukotriene C₄, and thus favor the induction of mucosal edema, bronchoconstriction, muscle hyperplasia and dysfunction, and mucin production through multiple pathways. The number of mast cells is significantly increased in patients with asthma. These cells are located in multiple areas within the airways including the epithelium, the submucosal glands, and the smooth muscle layers. In addition to the above mediators, mast cells have been demonstrated to produce numerous proinflammatory or pro-fibrotic cytokines including IL-4, IL-13, IL-33, TGF β 1, and TSLP. These cytokines have been suggesting to control various key features of the pathophysiology of asthma including epithelial cell shedding, goblet cell and muscle cell hyperplasia, hypervascularization, augmented collagen production, and subepithelial fibrosis [21]. Thus, mast cells emerge as key players in the pathophysiology of asthma and targeting of mast cell activation and function appears of high relevance to achieve resolution of disease.

One of the biologicals targeting activation of IgE receptor-bearing immune cells such as mast cells consists of omalizumab which is a humanized monoclonal antibody that specifically binds to free human immunoglobulin E (IgE) to affect the inflammatory process caused by mast cell activation in patients with moderate-to-severe allergic asthma [5, 26]. This therapeutic approach is like many other currently used anti-inflammatory medications positioned downstream of the allergic reaction in asthma [27]. Looking at other biological targets, it has been reasoned that eosinophils represent the predominant cell type populating the airways of patients during asthma exacerbations in many patients and they may contribute with their cytotoxic content to the destruction of the airway epithelial barrier, thus resulting in major chronic airway disorder that is difficult to reverse.

There is increasing evidence that eosinophils may not only mediate Th2 responses but also potently regulate homeostatic processes at steady state, thus challenging the paradigm of eosinophils as a merely destructive and inflammatory cell type [28]. Under baseline conditions, eosinophils rapidly leave the bloodstream to enter mucosal tissues, like gut and lung, where they regulate important immune functions. These so-called resident eosinophils (rEos) have been recently demonstrated to be morphologically and phenotypically distinct from the inflammatory eosinophils (iEos) that are recruited to the lung during house dust mite (HDM)-induced allergic inflammation [29]. Moreover, rEos have been shown to prevent the development of pulmonary Th2 immunity, and thus contribute to lung homeostasis. These eosinophils have a ring-shaped nucleus and reside in the parenchyma as opposed to those iEos increased in asthma which are induced in the bronchial lumen and have a segmented nucleus. The relationship between rEos and iEos is not entirely clear; however, further investigation is needed. Some reports indicated that rEos are IL-5 independent [30] and suggested that rEos promote the development of Th1 immunity, either by directly inhibiting T cells or by impairing the ability of dendritic cells to induce Th2 immunity [29]. The discovery of this new type of eosinophils raises potential concern about therapies trying to block eosinophil function in eosinophilic asthma; as such, therapies might also affect the function of rEos, and thus tissue homeostasis. Also, considering asthma exacerbations driven by respiratory viruses like rhinovirus, eosinophils play an important role in clearing the infections. These functions of eosinophils are not well examined yet but their role in infections must be further investigated during the resolution of asthma (Fig 1).

Neutrophils have been suggested to play an important pathogenic role in asthma patients with a “type 2-low” immune response. Accordingly, various studies have addressed the contribution of neutrophils to asthma pathogenesis in recent years [31–34]. It has been suggested that tissue neutrophils in the lung may possess specific phenotypic features distinguishing them from resting blood neutrophils. Moreover, neutrophil-derived

mediators and CXCR4+-derived neutrophil extracellular traps have been suggested to amplify the underlying allergic immune response and cardinal features of allergic asthma [35]. However, further studies are needed to gain further insights into the role of neutrophils in allergic asthma.

Finally, macrophages have been implicated in asthma pathogenesis [36–39]. Monocytes recruited into mucosal tissues can interact with environmental factors leading to macrophage polarization. In this context, macrophages can differentiate in various different subsets like M1-like, classically activated or M2-like alternatively activated cells. On exposure to local microenvironments, recruited macrophages can be polarized into either classically activated or alternatively activated phenotypes. Activated macrophages have been suggested as potential indicators of oxidative stress, tissue remodeling, and disease severity in asthma [37]. Moreover, studies in macrophage-deficient mice suggested an important role of these cells in the asthmatic phenotype. Specifically, studies in CD163-deficient mice showed a marked reduction of pro-inflammatory cytokines in the bronchoalveolar lavage fluid when compared with control wild-type mice [38]. These studies suggested that macrophages may play a key role in asthma and should be considered as targets for new therapeutic approaches.

Targeting Th2 and Th9 cytokines for resolution of asthma

Th2 and Th9 cells and their signature cytokines have been shown to play a key role in asthma [40] [41, 42]. Th2 cells are characterized by production of IL-4, IL-5, IL-6, and IL-13. In addition to Th2 T cells, these cytokines can be produced by innate lymphoid type 2 cells in asthma [43]. Th2 cytokines or their receptors have been targeted in patients with asthma or murine models of disease in order to achieve resolution of asthma. In particular, studies targeting IL-13 were very successful to block allergic airway inflammation and airway hyperresponsiveness in experimental asthma. In addition to targeting single cytokines or cytokine receptors, transcription factors have been emerged as possible targets for blockade of several cytokines simultaneously. One example consists of GATA-3. Increased GATA-3 expression was noted in asthmatic airways and correlated with the presence of IL-5 mRNA+ cells. These results suggested a causal association between augmented GATA-3 expression and dysregulated IL-5 expression in atopic asthma [44]. Treatment with GATA-3 antisense DNA was effective in suppressing airway inflammation and hyperresponsiveness in experimental asthma [45]. Additionally, GATA-3 inhibition resulted in multiple downstream therapeutical effects including suppression of airways eosinophilia and mucus production. The relevance of GATA-3 for Th2 cytokine production was underlined by biomarker

analysis in this study, as biomarkers indicated an attenuation of Th2-regulated inflammatory responses upon GATA-3 blockade [46]. Other studies attempted to target the transcription factor BATF or the Janus kinase Tyk-2 to block IL-4 and IL-9 pathways, and these studies demonstrated resolution of allergic asthma upon blockade of BATF or Tyk-2, respectively [40, 47].

Th9 cells are a specific subgroup of activated lymphocytes characterized by the production of IL-9 [48–52]. These cells are associated with the expression of the transcription factor PU.1 [50, 53]. In mice, increased levels of IL-9 in the airways of naive animals induced lung eosinophilia and serum total IgE levels, which are 2 clinical features of asthma. These data supported a central role for the IL-9 pathway in the pathogenesis of allergic inflammation [54]. Furthermore, p-STAT6 and PU.1 were associated with Th9 cells and IL-9 production in allergen-induced airway inflammation [55]. In humans, genetic studies suggested a link between the IL-9R locus and

asthma in patients. Studies in humans further revealed that patients with allergic asthma have increased peripheral blood Th9 cell counts and serum IL-9, while eosinophil apoptosis was inversely related to IL-9 concentration [56]. B lymphocyte-induced maturation protein 1 (Blimp-1), a negative regulator of Th9 development, appeared to orchestrate the resolution of airway inflammation in patients with allergic asthma [57]. These findings indicated that IL-9 is specifically upregulated after local allergen challenge in the lungs of atopic asthmatic patients. The increased expression and its correlation with eosinophil numbers suggested a potential role for IL-9 in the late phase of the allergic response [58]. Moreover, IL-9R was expressed on neutrophils from patients with asthma and additional studies demonstrated that IL-9 stimulation results in production of IL-8 [59] highlighting a potential role of IL-9 for mucosal inflammation in asthma. Additionally, IFN-gamma stimulated airway epithelial cells expressed IL-9R suggesting that IL-9 signaling may affect mucosal immune

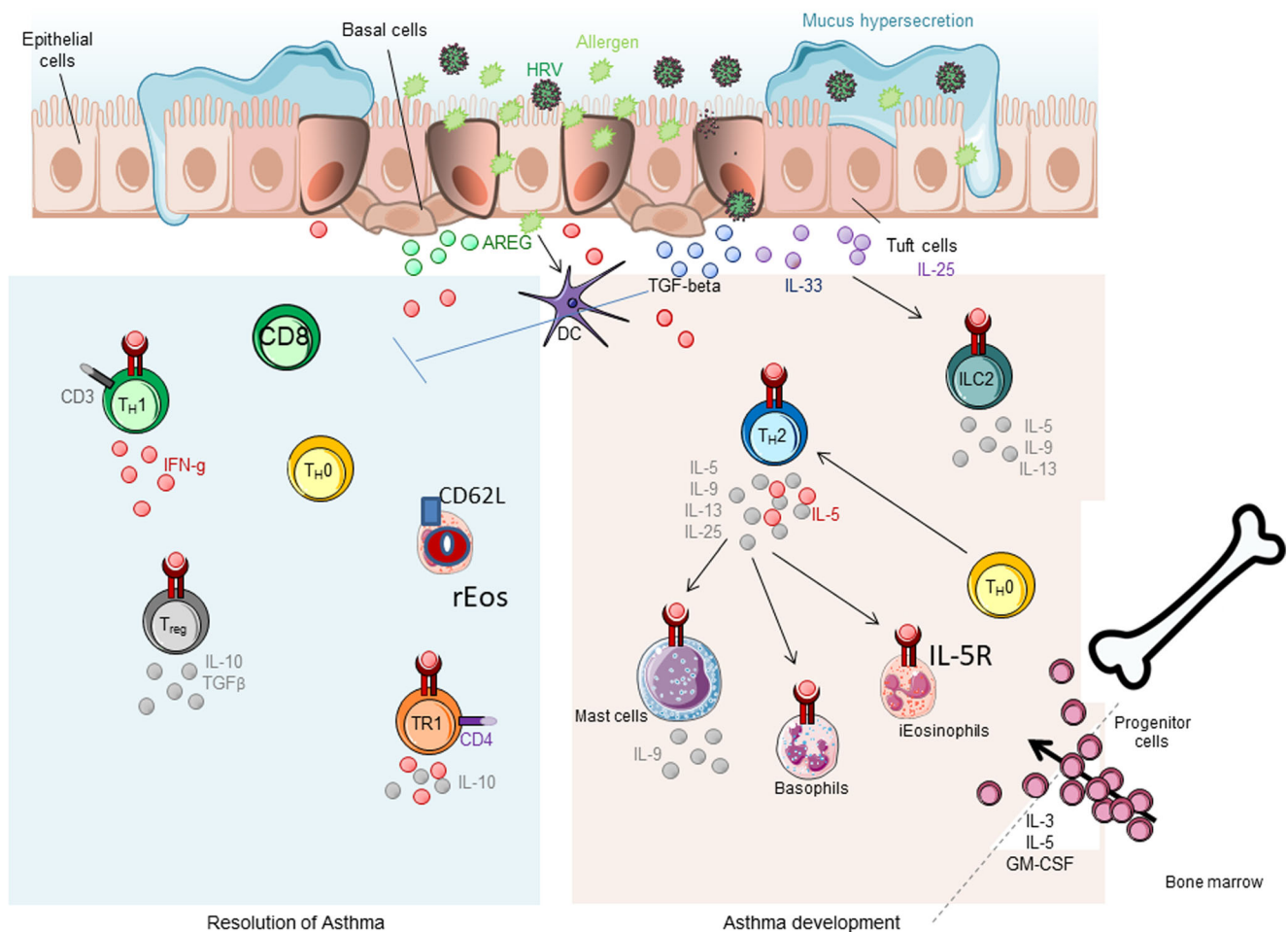


Fig. 1 Resolution of allergic asthma. Allergic asthma exacerbations are associated with increased accumulation in the airways of Th2 cells which release TH2 (Th2) cytokines like IL-5, IL-9, and IL-13. These cytokines recruit inflammatory cells belonging to the innate immunity. Usually, the immune asthmatic reaction is reversible and this resolution is associated with decreased inflammatory cells like Th2 cells, mast cells, basophils,

inflammatory eosinophils (iEos), and induction of resident eosinophils rEos and TH1 (Th1) and Tregulatory cells producing IL-10 (TR1=Tr1) or TGF-beta and IL-10. Chronic asthma is a condition in which the Th2-driven inflammation does not resolve and results in a profound airway remodeling dominated by pro-fibrotic cytokines like TGF-beta

regulation via several independent pathways [60]. Moreover, anti-IL-9 antibody treatment suppressed production of IL-4, IL-5, and IL-13 in bronchoalveolar lavage fluid suggesting that blockade of IL-9 might be useful for treatment of asthma [61]. Finally, additional studies revealed that IL-9 levels are highly correlated to expression levels of the calcium-activated chloride channel HCLCA1 and mucus production of airway epithelium in asthma suggesting that this cytokine is a potential marker for atopic asthma [62, 63]. However, a clinical trial using a neutralizing IL-9 antibody (MEDI-528) to existing asthma controller medications showed no improvement in asthma exacerbation rates or FEV1 values [64].

Interferons and viral infections in asthma

Common exacerbations of asthma especially in children have been associated with the detection of rhinovirus in the airways. Rhinovirus, a member of the picornaviridae family, is often detected in the airways of asthmatic children during symptomatic visits to the hospital because of an ongoing infection in the airways [65]. The immune responses to rhinovirus comprise the upregulation of interferon pathways [66]. Especially type I and type III interferons were found to be associated with rhinovirus infection of the airways [67]. Dysregulated interferon responses have been observed in asthmatic patients during rhinovirus-induced exacerbations in non-controlled asthmatics [68]. During acute rhinovirus infection, IFN type I was found to be induced in serum of the cohort of preschool children with asthma in symptomatic visits. *In vitro* exposure of peripheral blood mononuclear cells (PBMCs) from asthmatic and control children to rhinovirus demonstrated in PBMCs of asthmatic children RV-induced upregulation of genes of the IFN pathway like STAT1/2, IRF1, but also programmed cell death protein 1 ligand (PDL1), a gene induced by IFN but implicated in T cell exhaustion [66, 69] and cytotoxic T lymphocyte-associated protein 4 (CTLA4), a regulatory protein that downregulates mucosal immune responses. Thus, viral infections such as those induced by rhinoviruses lead to complex alterations of mucosal immune responses in the airways with particular changes in IFN regulation. In summary, our findings in preschool children with asthma indicate that their immune system is still able to react during acute exacerbation of disease with IFN type I and III immune responses. However, this reaction remains associated with induced immune inhibitory pathways like PDL1 and CTLA4 that need further attention. Similarly, we found that acute rhinovirus infections, endogenous TGF- β is retained intracellularly in rhinovirus-infected cells, resulting in a T-bet-mediated immune response. However, rhinovirus infection also activates TGF- β present in the environment, as in patients with chronic asthma, to replicate and inhibit effective antiviral immune responses. Thus, it is possible that

children with acute asthma are able to induce an effective anti-rhinovirus immune response during acute exacerbation. By contrast, in patients with chronic asthma, active TGF- β is induced and released by structural cells. It can be that in chronic asthma rhinovirus induces the effect of the exogenous TGF- β resulting in TH1 and TC1 depletion. These data open new avenues for our understanding of the role of rhinovirus-mediated asthma in children (Fig 1).

Th1 and Th17 cytokines and cytokines produced by regulatory T cells in asthma

Th1 T lymphocytes are characterized by the production of IFN- γ and other immunoregulatory cytokines such as TNF. These T cells develop via IL-12 stimulation and express the transcription factors STAT1, STAT4, and T-bet [70–73]. Initial studies in patients with asthma detected a marked suppression of T-bet levels suggesting a regulatory role of this transcription factor in asthma pathogenesis [74]. Consistently, mice deficient in T-bet displayed some features of asthma upon OVA sensitization including airway inflammation and hyperresponsiveness underlining a key role of T-bet in airway inflammation [74]. Additional studies indicated that modulation of Th1 responses may affect lung immunology and experimental asthma. In fact, it was found that preventive intranasal administration of IL-27 induces a Th1 environment in the lung that helps to alleviate Th2-mediated allergic asthma by boosting the STAT1 rather than the STAT4 pathway [75].

Th17 produce various immunoregulatory cytokines such as IL-17A, IL-17F, IL-21, and IL-22 [76, 77]. These cells are characterized by the expression of the transcription factor ROR γ . Several studies implicated a role of Th17 cells in asthma pathogenesis [78–82]. In particular, elevated production of IL-17 was found in a subset of patients with severe asthma exhibiting a “type 2-low” phenotype. It has been suggested that the differentiation of IL-17-producing cells is favored in severe asthma via a microenvironment rich in IL-6 and TGF- β . Particularly high levels of IL-17 were noted in geriatric asthma. In fact, a study in geriatric asthma showed that serum IgE, IL-17A, IL-17F, and TGF- β levels were significantly elevated in patients with moderate or severe asthma as compared to young patients with moderate asthma and control patients [83]. Asthma patients with high levels of IL-17 displayed mainly features of neutrophilic asthma with goblet cell and smooth muscle hyperplasia, high mucus production, and airway inflammation dominated by neutrophils. As airway epithelial cells and smooth muscle cells may express IL-17R, these findings suggested that IL-17 may drive airway remodeling in asthma. Although pleiotropic roles of IL-17 were noted in experimental asthma in mice, the above findings suggested that IL-17 may play an important role in airway pathophysiology. Finally, it was found that Th17 cytokines

are associated with steroid resistance in asthma suggesting that these cytokines may play an active role in molecular resistance against therapy.

The balance between Th17 cells and regulatory T cells (Treg cells) has been suggested to have a key role in the pathogenesis of asthma [78–82]. Various studies indicated that the homeostatic balance between Treg and Th17 cells is markedly altered in asthma exacerbation and correlates with asthma severity [84]. Regulatory T cells are known to produce immunosuppressive cytokines such as IL-10 and TGF- β [69, 85, 86]. These cytokines may suppress proinflammatory mucosal immune responses in asthma [87]. For instance, in a murine model of asthma induced by repeated house dust mite inhalation, a mixed IL-13/IL-17A cytokine response and an accumulation of IL-10-producing T cells was noted in the lungs. Ablation of T cell-derived IL-10 boosted IFN- γ and IL-17A cytokine responses in experimental asthma suggesting that IL-10 from effector T cells signals to CD11c⁺ myeloid cells to suppress a pathogenic cytokine response in asthma [88]. In patients with severe asthma, suppression of IL-10 levels was noted indicating an impaired capacity of the lung immune system to counteract proinflammatory signals [89]. Although IL-10 and TGF- β may suppress inflammation, they may also cause structural alterations, as TGF- β has been identified as pro-fibrotic cytokine that markedly affects lung fibrosis and airway remodeling in asthma [87, 90, 91].

Treatment of patients with asthma: targeting of resolution via immunotherapy

Allergen-specific immunotherapy represents a possibly effective treatment for allergic asthma in experimental model systems and patients with active disease [92]. This therapeutic approach is based on repeated administration of small amounts of the sensitizing allergen. Experimental studies have indicated that allergen immunotherapy induces IL-10 production and antigen-specific Foxp3⁺ Treg cells and that such Treg cells control and orchestrate the anti-inflammatory pathways driving resolution of inflammation [93]. Meta-analyses of clinical studies suggested that allergen-specific immunotherapy may lead to reductions in symptom and medication scores. However, no clear, consistent evidence was obtained that this therapeutic approach improves measures of lung function [94, 95].

In addition to allergen immunotherapy, additional immunotherapies for allergic asthma exist that are based on suppression of IgE or mucosal cytokine responses. For instance, omalizumab, a recombinant humanized IgG1 monoclonal antibody, was approved in the USA as an add-on treatment in moderate-to-severe allergic asthma and in Europe for severe allergic asthma. This antibody binds to the Fc region of IgE [96, 97]. Thereby, omalizumab binds to circulating IgE and forms biologically inert IgE–anti-IgE complexes which do not

activate the complement cascade. In clinical trials, omalizumab reduced both early- and late-phase asthmatic responses after allergen inhalation challenge and suppressed the numbers of eosinophils in sputum as well as Fc ϵ RI expression on various immune cell subsets. It has been suggested that the reduction in the expression of Fc ϵ RI on dendritic cells may impair allergen processing in asthma [5, 98, 99]. Numerous clinical studies now underline the long-term effectiveness of omalizumab for reduction of asthma exacerbations and improvement of lung function [96, 97].

Several additional antibodies have been tested in clinical trials for asthma: mepolizumab, reslizumab, and benralizumab [100] [7, 101] [102, 103]. These antibodies target the function of IL-5 and IL-5 signaling in eosinophilic asthma. Eosinophil differentiation, survival, and activation are regulated by IL-5, a cytokine whose receptor is present on the cell surface of eosinophils or basophils. The monoclonal antibody benralizumab binds specifically to the IL-5R and thereby blocks IL-5 signaling and subsequent eosinophil differentiation. Furthermore, benralizumab binds to the RIIIa region of the Fc γ receptor on immune cells followed by induction of cytotoxicity in eosinophils. By taking advantage of these two independent pathways, benralizumab has been shown to cause effective depletion of eosinophils. The benralizumab-induced depletion of eosinophils is more pronounced as compared to that induced by IL-5 blockers such as mepolizumab and reslizumab [7, 101]. Recent 2 years of safety studies reported no major safety concern upon long-term eosinophil depletion [104]. In addition to antibodies targeting IL-5 or IL-5R in asthma, recent studies also addressed the effects of dupilumab in asthma. This antibody blocks the α subunit of the IL-4 and IL-13 receptors, and thus has a dual mechanism of action by inhibiting the activity of two cytokines simultaneously. Clinical trials suggested that the addition of dupilumab is associated with a reduced risk of severe asthma exacerbations and improvement in FEV1 in patients with uncontrolled asthma [105–110]. Thus, there are many new current and future options for immunotherapy in asthma that may allow novel approaches for individualized therapy in subgroups of the disease.

Summary

Studies in recent years have highlighted a crucial role of immunotherapy in asthma. In some cases, such immunotherapy has led to complete resolution of the asthmatic phenotype. The discovery of subgroups of immune phenotypes in asthma, however, suggests that personalized medicine is needed to achieve symptom control and improvement of lung function in larger groups of patients. Future studies are needed to identify novel targets for immunotherapy that control resolution of the disease.

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Compliance with ethical standards

Conflict of Interest The author declares that she has no conflict of interest.

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