



Review article

Allergies – A T cells perspective in the era beyond the T_H1/T_H2 paradigm

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ABSTRACT

Allergic diseases have emerged as a major health care burden, especially in the western hemisphere. They are defined by overshooting reactions of an aberrant immune system to harmless exogenous stimuli. The T_H1/T_H2 paradigm assumes that a dominance of T_H2 cell activation and an inadequate T_H1 cell response are responsible for the development of allergies. However, the characterization of additional T helper cell subpopulations such as T_H9 , T_H17 , T_H22 , $T_HGM-CSF$ and their interplay with regulatory T cells suggest further layers of complexity. This review summarizes state-of-the-art knowledge on T cell diversity and their induction, while revisiting the T_H1/T_H2 paradigm. With respect to these numerous contributors, it offers a new perspective on the pathogenesis of asthma, allergic rhinitis (AR) and atopic dermatitis (AD) incorporating recent discoveries in the field of T cell plasticity.

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1. Introduction

Allergies are an expanding problem throughout the western world. An estimated 40% of the EU's population, mainly young adults and

children, are affected with often dramatic consequences for their quality of life [1–3]. Moreover, allergic diseases have a significant socioeconomic impact. With 20–35% of the European workforce suffering from allergic diseases, costs accumulate up to 142 billion Euros per year. Allergic disorders comprise a large heterogeneity of diseases with multifactorial pathogenesis, including genetic and environmental influences as well as the composition of the microbiome [4]. Among the many factors contributing to the pathogenesis, T cells play a pivotal role. The $T_H1/$

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T_H2 paradigm has been the predominant concept during the last decades [1,2]. It is based on the observation that patients who suffer from allergies tend to have an increased T_H2 response to allergens. Concomitantly, the induction of a shift towards a T_H1 response was proposed as a possible treatment. In recent times, however, this concept has increasingly been challenged by a more profound understanding of T cell functions accelerated by discoveries of new T cell subsets.

In this review, we outline the role of different T cell subsets beyond T_H1 and T_H2 , including regulatory T cells, T_H9 , T_H17 , T_H22 and ThGM-CSF in selected T cell-mediated allergic diseases, namely allergic rhinitis or 'hay fever', asthma and atopic dermatitis. Furthermore, we present recent discoveries in the field of T cell plasticity.

2.1. The initiation of a T_H2 -response

T_H2 cells are known to be important in host defense against parasites, including gastrointestinal helminths [3]. They are strongly suggested to be the key T helper cell subset responsible for the pathogenesis of allergic diseases such as asthma [5]. Their differentiation is triggered by IL-4 [6] which activates their key transcription factors STAT-6 and GATA-3 [7,8]. Once activated, T_H2 cells produce IL-4, IL-5 [1], IL-13, IL-9 [9] and IL-10 [10] as their effector cytokines.

Type 2 responses can be initiated by pollen [11], house dust mite (HDM) [12] and certain foods. Factors such as the cytokine milieu and intrinsic properties of the respective antigen [12–14] are relevant for the differentiation of a naïve T cell into a T_H2 cell.

Databases of major allergens have been analyzed with regard to structural similarities of allergens. Most of the major allergens are stable proteins with a weight of less than 70 kD, a negative charge and low hydrophobicity [15].

Although it is not possible to distinguish allergen from non-allergen by structural characteristics, the structure of the allergen does seem to have an influence on the type of immune response initiated. Site-directed mutagenesis of HDM allergen Derf-2 for example leads to a complete shift towards a type 1 response in a human T cell model [16].

Furthermore there are some similarities in functional properties of allergens. Many allergens are proteases, lyases, lipid-transfer proteins, calcium-binding proteins, trypsin inhibitors or actin-binding proteins [15]. Protease activity of allergens has been studied extensively. More than 80 allergens are listed as proteases [15]. Especially cysteine and serine protease activity have been discussed as important characteristics of allergens including Der p 1 and papain. In the case of the HDM protease Der p 1, the inactive form of the enzyme or the active form in combination with a selective inhibitor do not induce type 2 responses making the protease activity seem essential for the allergenicity potential. This has been studied in both rodents [13,17] and humans [14].

A number of interleukins including IL-4 [6], IL-33 [18] and thymic stromal lymphopoietin (TSLP) [19] have been implicated in the induction of T_H2 responses. This has especially been studied in mouse models of allergic rhinitis [20]. Type 2 immune responses are thought to be initiated by dendritic cells (DCs), which present antigens to naïve $CD4^+$ T cells in an IL-4 enriched microenvironment [21]. Sokol et al. proposed basophils as the main type of antigen presenting cells [22]. This hypothesis has been refuted by the findings of Hammad et al. [21] claiming DCs to be both necessary and sufficient to initiate a T_H2 response in mice, favoring a model in which DCs initiate and basophils amplify the T_H2 response. The primary origin of IL-4 remains controversial as well. Cell types being discussed are mainly T_H2 cells themselves, mast cells [23], basophils [22], type 2 innate lymphoid cells (ILC2) [24] and others. However, T_H2 differentiation in response to allergens in an IL-4 independent manner has also been described in mouse models [25,26].

One of the most extensively studied cytokines relevant for T_H2 induction is IL-33. It is expressed by epithelial cells and fibroblasts in airways, skin and other interface organs and can also be produced by macrophages and DCs in response to epithelial damage in mice [27]. It has been proposed that IL-33 is the original inducer of IL-4 secretion

during the initiation of a type 2 response [18]. While T_H2 cells express a receptor for IL-33 (IL-33R), it remains unclear whether IL-33 induces T_H2 cells directly or via indirect pathways like IL-4 [28]. In acute allergic rhinitis, the activation of T_H2 cells in IL-33 deficient mice is lower than in wild-type mice [20]. Besides epithelial cells, DCs, and other cell types, ILC2 cells express IL-33R and secrete IL-4 and IL-13 upon stimulation [29].

Another T_H2 -stimulating cytokine is TSLP. It is constitutively expressed by epithelial cells and its secretion can be enhanced upon allergen exposure [30]. The TSLP secretion is mediated by pro-inflammatory cytokines such as TNF, IL-1 α and T_H2 cytokines such as IL-4 or IL-13 [31]. Ligation of TSLP to its receptor on DCs from human peripheral blood stimulates them to induce T_H2 responses, partly by inducing OX40L expression, which triggers naïve $CD4^+$ T cells to produce IL-4, IL-5 and IL-13 [19]. TSLP also leads to the upregulation of T_H2 cytokines in mast cells [32].

It is discussed whether allergenic potential is caused by functional activities of the allergen or by structure recognition via TLR4 or other PRRs [12,13,14]. Allergen activities like tight junction degradation by HDM protease Der p 1 enhance the distribution of the allergen and increase its chance to reach subepithelial antigen presenting cells (APCs) [33,34]. Epithelial damage can cause production of IL-33 by macrophages and DCs. Increased expression of IL-33 in DCs in mice depends on TLR4 and PI3-kinase [35]. Proteases cleave several cell-surface molecules, resulting in T_H2 induction, e.g. Der p 1 cleaves CD23, CD25 and alpha1-antitrypsin [36]. As for the pathway via TLRs, it remains unclear whether receptor activation is caused by the allergen itself or by microbial products mixed with the allergen [12].

2.2. T_H2 effector phase – a complex interplay of cytokines

The T_H2 effector cytokines IL-4, IL-5 and IL-13 are mainly released by T_H2 cells and may also derive from other cell types such as mast cells, DCs, basophils and ILC2 [37,38].

Besides its crucial role in the initiation of T_H2 responses [39], IL-4 also plays a role for the expression of VCAM-1 on endothelial cells and for inducing IL-5 [40]. IL-13 signals through the IL-4 receptor α -chain, but may activate different intracellular pathways as well [40]. Unlike IL-4, IL-13 does not regulate T cell differentiation to T_H2 cells and T lymphocytes do not directly respond to IL-13 [37,40]. However, IL-4 and IL-13 share several effector functions, such as promoting IgE isotype switching, B cell proliferation and differentiation as well as IgE production [37,40–42]. Furthermore, IL-4 and IL-13 induce mucin gene expression and hypersecretion by goblet cells, leading to airway obstruction [43,44]. Studies in animal models of disease provided evidence that IL-13, independently of other T_H2 cytokines, is both necessary and sufficient to induce all features of allergic asthma [45]. Targeting the IL-4 or IL-13 pathway has not proven to be an effective approach in the past [46]. Blocking both the IL-4 and the IL-13 pathway seems to be a more promising option for future therapies [46,47]. A recently published phase 2b trial with more than 700 patients showed that the addition of Dupilumab, a human anti-interleukin-4 receptor alpha monoclonal antibody inhibiting interleukin-4 and interleukin-13 signalling, to the existing therapy scheme of patients with uncontrolled persistent asthma significantly improved patients' lung function [48].

T cells from patients with allergic asthma also produce IL-5 in response to allergen stimulation [42], which is essential for the recruitment of eosinophils in mice [49] and in humans [50]. Yet, the definitive role of eosinophils in asthma remains unclear. They might not be necessary for the late asthmatic response and airway hyperresponsiveness [50]. But in asthma patients suffering from the eosinophilic phenotype, the anti-IL-5 antibody Mepolizumab has been able to reduce exacerbations by up to 47% [51].

Recent studies indicate that in atopic dermatitis (AD) increased levels of T_H2 cytokines, such as IL-4 and IL-13, reduce the expression of antimicrobial peptides and filaggrin, an important peptide for the

cornification in keratinocytes [52,53]. While IL-4 and IL-13 alone can induce AD symptoms, the role of IL-5, except for eosinophilia, is topic of an ongoing debate [53]. For example, Mepolizumab decreased blood levels of eosinophils in AD but did not show any clinical success [54].

3. T_H1 cells mediate pro- and anti-inflammatory processes in allergic diseases via IFN- γ

T_H1 cells are characterized by the expression of transcription factor T-bet [55] and the hallmark cytokine IFN- γ , which contributes to the eradication of intracellular pathogens. T_H1 differentiation is induced by IFN- γ together with IL-12, while IL-18 can act as a co-factor for the IL-12-induced T_H1 development and supports IFN- γ production [56].

Previous reports demonstrated that IFN- γ and the transcription factor T-bet suppress eosinophil lung infiltration and airway hyperresponsiveness. This phenomenon has partially been associated with the ability of these factors to promote T_H1 and to suppress T_H2 differentiation [56]. Indeed, T-bet as well as IFN- γ receptor deficient mice develop physiological and inflammatory features characteristic of asthma [57,58]. In addition to the T_H1-mediated counter-regulation of T_H2 responses, it has been suggested that IFN- γ may also display direct effects on airway epithelium and inhibit inflammation and obstruction by reducing mucus production. Furthermore, IFN- γ restricts eosinophilia and eosinophil generation in the bone marrow [59]. Iwamoto et al. demonstrated that administration of IFN- γ inhibits eosinophil infiltration of the trachea of sensitized BALB/c mice and decreases antigen-induced production of CD4⁺ T cells [59,60] suggesting that inhaled IFN- γ could block some symptoms in therapy refractory patients [59]. Decreased IFN- γ ⁺CD4⁺ cells were detected in patients with allergic asthma [61].

In line with the concept that T_H1 can counterregulate T_H2 responses, patients with atopic dermatitis display decreased IFN- γ production compared to healthy controls [62]. Furthermore, IFN- γ production is decreased in individuals suffering from seasonal allergic rhinitis [63] and no increased IFN- γ levels were detected in patients with perennial allergic rhinitis (PAR) [64].

However, T_H1 cells and IFN- γ can also contribute to the exacerbation of allergic diseases, especially in the chronic phase. High levels of T_H1 cytokines have been found in humans and mice with severe asthma. In addition, IFN- γ has an effect on cells involved in acute phase of asthmatic disease. The IFN- γ receptor is expressed on mast cells and in a mouse model of chronic allergic asthma it was shown that this can contribute to the development of characteristic features of the disease such as neutrophilic and eosinophilic inflammation and airway remodelling as well as expression of several cytokines in the lung [65].

Similar to this, in patients suffering from chronic AD mRNA levels of the T_H1 cytokine IFN- γ were increased in severe exacerbated skin lesions [66]. In a transgenic mice model for atopic dermatitis increased T_H1 cytokine mRNAs were detected as the disease progressed [67].

In summary, the T_H1 cytokine IFN- γ has multiple effects in allergies and can contribute to both anti-inflammatory and pro-inflammatory processes.

4. T_H17 responses are likely to have regulatory functions in atopic conditions

T_H17 cells were identified in 2005 as a novel T helper cell subset with major implications for the pathogenesis of autoimmune diseases and the clearance of extracellular bacteria and fungi [68,69]. Their discovery challenged the prevailing concept of the T_H1/T_H2 dualism and initiated the quest for other T helper cell subsets. T_H17 cells are named after their signature cytokine IL-17 and are regulated by their master transcription factor ROR γ t [70]. Recent studies, however, revealed a heterogeneity of effector cytokines within the T_H17 cell subset, which translates into different and even opposing T cell functionalities such

as pro- and anti-inflammatory pathways based on differential co-expression of IL-10 [71,72].

Enhanced levels of IL-17 were found in the bronchoalveolar lavage (BAL) and in lung biopsies of patients with a clinical presentation of asthma [73,74]. Asthma, however, is nowadays regarded as a heterogeneous disease with different phenotypes and endotypes [75]. The neutrophilic form of asthma is, in contrast to the eosinophilic Th2 mediated variant, associated with a more severe phenotype, a higher frequency of exacerbations and higher resistance to corticosteroids [76]. IL-17 has the ability to recruit neutrophils via increased secretion of neutrophil chemokines by airway epithelial cells [77]. BALs from IL-17 over-expressing mice showed elevated numbers of neutrophils [78]. In asthma with a severe phenotype, the amount of IL-17A⁺ cells is significantly increased compared to healthy individuals and patients with mild or moderate asthma. Interestingly, there is no significant increase of IL-17A⁺ cells in mild asthma compared to healthy controls [79]. Furthermore, IL-17 promotes the development of severe allergic asthma. Sorbello et al. showed that the number of IL-17 producing cells in the lamina propria of both, the upper and lower respiratory tract, is significantly increased in patients suffering from asthma with a severe clinical phenotype. A positive correlation between the number of IL-17 producing cells, the number of neutrophils and the number of clinical exacerbations was also observed [80]. Apart from its role in attracting neutrophils, IL-17 seems to be involved in the development of airway hyper-reactivity, increased mucus production due to goblet cell hyperplasia and airway remodelling, as shown in IL-17 transduced mice [78]. In conclusion, T_H17 cells are likely to play an important role especially in severe asthma, due to their link to airway neutrophilia. However, a regulatory role for IL-17 in established asthma has also been proposed [81].

There is strong evidence that IL-17 producing cells play a role in the pathogenesis for AR as well. IL-17 deficient mice exhibited less allergic symptoms, mucosal eosinophilia and IgE levels [82]. In line with this data, increased numbers of T_H17 cells in the peripheral blood of allergic individuals [83,84] and elevated IL-17 expression in the nasal mucosa of AR patients could be detected upon allergen challenge [85]. Moreover, serum levels of IL-17 correlate with clinical severity of AR [86].

In conclusion, T_H17 cells are associated with AR due to increased T_H17 responses both in the peripheral blood and at sites of allergic inflammation.

Apart from the established role of IL-17 producing cells in psoriasis, there are strong hints that these cells also contribute to the pathogenesis of AD, which is usually described as a T_H2/T_H22 cell derived disease [87]. Increased amounts of IL-17A producing cells in the peripheral blood of patients suffering from severe AD have been reported. IL-17 is also locally elevated in the typical skin lesions of acute AD but interestingly, there is no further increase in IL-17 levels for chronic AD [87, 88]. Additionally, higher levels of T_H17 regulated products were present in AD skin lesions [88]. It has been shown that the microbiome is important for IL-17A expression and neutrophil skin invasion in AD mouse models [89]. In another mouse model of AD-like skin lesions induced by epicutaneous Oxazolone-exposure, IL-17 deficient mice displayed diminished swelling and signs of skin barrier dysfunctions. In particular, a decrease in eosinophilic recruitment and in T_H2-like cytokine levels could be observed in these lesions compared to wild-type mice [90]. Barrier dysfunctions in AD are likely caused by a genetic defect affecting filaggrin. Indeed, filaggrin deficient mice develop AD like skin lesions and show elevated levels of IL-17 [91].

5. T_H22 cells in atopic diseases

Until the recent description of T_H22 cells, T_H1 and T_H17 cells were considered to be the main producers of IL-22 [92–95]. T_H22 cells are positive for the chemokine receptors CCR4, CCR6, and CCR10. They produce IL-22 but in contrast to T_H17 cells neither IL-17 nor IFN- γ [96].

T_H22 cell induction is accomplished through the interaction of naïve CD4⁺ cells with plasmacytoid DCs [97] in the presence of TNF and IL-6 [96] and can be inhibited by TGF- β [96]. The function of IL-22 cells can be modulated by IL-20 and STAT-3 as well as by TNF [98].

IL-22 has both pro-inflammatory and tissue-protective properties, depending on the context [99]. In the skin, IL-22 has a regenerative and moreover protective influence on epithelial cells as it induces the re-epithelialization of tissue and supports migration and proliferation of epithelial cells [100–102]. Thus, it is of importance for wound healing [102,103].

In contrast to its protective effects, dysregulation of the T_H22 system seems to sustain and support atopic diseases: in AD, T_H2 polarization was thought to be the major inducer of disease until enhanced IL-22 levels were observed pointing towards a major role for T_H22 [104]. The IL-22 mediated effect on epithelial proliferation and acanthosis is in line with the hyperplasia of the epidermal layer which is present in atopic dermatitis [105]. While in AD patients IL-17 levels remained unaltered during the chronic phase of disease, numbers of T_H2 and T_H22 cells were increased, strengthening the role of T_H22 cells in maintaining the disease [106]. IL-22 plasma levels also increased with the severity of the disease [107]. Interestingly, while it has been demonstrated that IL-22 contributes to chronic atopic dermatitis in adults, in children AD was dominated by T_H2 cells rather than T_H22 [108].

In patients suffering from AR, IL-22 levels were also found to be increased [109,110]. In addition, enhanced IL-22 mRNA expression was observed in the peripheral blood mononuclear cells (PBMCs) of asthmatic children and of children suffering from AR. In the latter case, IL-17 mRNA expression was additionally increased. In both, AD and AR, levels of IL-22 mRNA expression correlated with the expression of serum levels of IgE [111].

5. T_H9 derived IL-9 promotes allergic responses

IL-9 has long been considered a T_H2 cytokine, as it promotes allergic inflammation and is associated with various T_H2 responses. Recently it has been proposed that a distinct subset, the T_H9 cell, represents the main producer of IL-9 [112]. T_H9 cells can be generated from naïve T cells in the presence of TGF- β and IL-4 or can be differentiated from T_H2 cells by activation of TGF- β signalling, which promotes loss of GATA-3, IL-4, IL-5 and IL-13, while inducing an up-regulation of IL-9 expression [113–115].

Although a T_H9-specific transcription factor has not been clearly identified, the transcription factor BATF (*B cell activating transcription factor-like*), IRF4 [116] and PU.1 are essential for T_H9 cell development [39].

IL-9 plays a major role in allergic responses, as originally shown in IL-9-transgenic and IL-9 knock-out mice [117,118]. IL-9 deficient mice did not develop goblet cell hyperplasia and mastocytosis [117]. In transgenic mice over-expression of IL-9 led to massive pulmonary inflammation but was dependent on further stimulation factors such as IL-4, IL-5 and IL-13 [118]. IL-9 largely contributes to thymic stromal lymphopoietin (TSLP)-induced allergic inflammation in vivo [119] and exacerbates allergic diseases through various mechanisms, mainly by increasing the number of mast cells within the airway epithelium and promoting pulmonary goblet cell hyperplasia [39,120–124]. Lately, it has been demonstrated in a papain-induced lung airway hyper-reactivity mouse model that another source of IL-9 in vivo is represented by type 2 innate lymphoid cells (ILC2) and that transient IL-9 expression by ILC2 acts to promote their survival and proliferation in an autocrine manner [125].

T_H9 cells are major contributors to human atopic diseases, including atopic dermatitis, asthma and food allergies. Asthma patients have an increased number of circulating T_H9 cells but no significant difference was found between healthy individuals and AR patients. However, in both eosinophilic asthma and eosinophilic AR the T_H9/T_H1 ratio was

elevated [126]. Also, enhanced IL-9 expression was present in AD skin lesions [127].

Taking together current findings, increased levels of IL-9 in atopic diseases suggest a role of IL-9 as an important mediator of inflammation.

7. GM-CSF producing T helper cells are associated with severity of atopic diseases

GM-CSF (*granulocyte macrophage colony-stimulating factor*) is a hematopoietic growth factor. Only recently GM-CSF came back into focus as a cytokine relevant for the pathogenic potential of T_H17 cells [128,129]. In mice, GM-CSF expression is co-regulated by the T_H17 cell program. This is controlled by ROR γ t and additionally requires IL-1b and IL-23 for its induction [128]. In humans, however, the situation is surprisingly different. STAT-3 activating cytokines, such as IL-6 and IL-23, known to favor the T_H17 program, rather suppress GM-CSF induction. Instead, GM-CSF expression is promoted by the T_H1 pathway [130]. Particularly, the autocrine activation-dependent IL-2 production promoted the upregulation of GM-CSF via STAT-5 phosphorylation [131]. This is in line with GM-CSF expression in T_H1 but not T_H17 cells in humans, which are known to be poor producers of IL-2 [132]. In addition, T cells producing GM-CSF in the absence of any other lineage defining cytokine have been identified. They are also negative for the expression of master transcription factors specific for T_H1, T_H2 or T_H17 cells respectively, and could be considered a separate T helper cell subset due to their segregation from any of the so far delineated T helper cell subsets. In humans, they can be identified ex vivo based on the combination of the three chemokine receptor surface markers CCR6, CCR10 and CCR4 [130].

Recent findings suggest an important role for GM-CSF and GM-CSF producing T cells in the pathogenesis of allergic diseases. In a mouse model of allergic asthma, severity of the disease increased with the level of GM-CSF production of airway epithelial cells, which was upregulated via EGFR-signalling and independent of IgE or T_H1, T_H2 and T_H17 cytokines [133]. Moreover, GM-CSF prolongs and potentiates inflammatory infiltration in allergic airway inflammation [134]. In line with these findings, administration of antibodies against GM-CSF blocked the hyper-responsiveness of epithelial cells [135].

In patients with allergic rhinitis increased levels of GM-CSF were found in the nasal lavage during the birch-pollen high season in addition to increased levels of eosinophils in the nasal mucosa [136].

Its role in the pathogenesis of atopic dermatitis has been of wide interest, as keratinocytes of patients with atopic dermatitis presented increased levels of GM-CSF [137]. As GM-CSF enhances proliferation of DCs, basophils, eosinophils and monocytes, recruits and activates monocytes, it additionally modulates the function of Langerhans cells [138]. It has been suggested that increased levels of GM-CSF and thus the severity of the disease are due to promoter gene polymorphisms. This would allow predictions of an individual's predisposition to atopic dermatitis [139,140]. However, findings on polymorphism are not consistent across populations and need further investigation [141].

8. T_{reg} cells limit the severity of allergic diseases

The role of regulatory T cells (T_{reg} cells) as modulators of adaptive and innate immunity has been increasingly recognized. A multitude of different T_{reg} subgroups have been described. In this review, we focus on CD4⁺CD25⁺Foxp3⁺ T_{reg} cells in the context of allergies [142]. Foxp3⁺ T_{reg} cells can be dissected into thymic (tT_{reg} cells) or peripherally induced T_{reg} cells (pT_{reg} cells). In the thymus, the cytokines IL-2 and a moderate self antigen binding avidity of the T cell receptor are required for FoxP3⁺ tT_{reg} differentiation [143], while FoxP3⁺ pT_{reg} cells in mice differentiate from naïve CD4⁺ T cells in the periphery, facilitated by high amounts of TGF- β and IL-2 when they encounter non-self antigens [144,145] FoxP3⁺ tT_{reg} cells are thought to control systemic and

tissue-specific autoimmunity. In contrast, FoxP3⁺ pT_{reg} cells have been proposed to play a crucial role in preventing allergic inflammation in the mouse model [146]. Interestingly, it has been recently shown in mice that a major fraction of intestinal FoxP3⁺ pT_{reg} cells coexpress ROR γ t and that this particular pT_{reg} subset especially regulates T_H2 responses [147].

The critical role of T_{reg} cells in regulating autoimmunity has been shown in patients with dysfunctional T_{reg} cells due to FoxP3 gene mutations (IPEX syndrome) or in mice (scurfy mice), which suffer from multi-organ autoimmunity. As a result, patients develop diseases such as type 1 diabetes mellitus, hypothyroidism, severe enterocolitis, arthritis and psoriasis. Interestingly, these patients also suffer from allergic manifestations such as atopic dermatitis, food allergies, elevated eosinophils, and serum IgE levels due to the loss of function of FoxP3 [148, 149].

It has been shown that expansion and suppressive potential of Foxp3⁺ T_{reg} differs between atopic and non-atopic children with non-atopic children having an earlier and greater global Foxp3 expression [150].

The functions of Foxp3⁺ T_{reg} cells in the human immune response upon allergen exposure in peripheral tissues include suppression of migration of T_H1, T_H2 and T_H17 cells, inhibition of dendritic cells, mast cells, basophils and eosinophils and limitation of IgE production in B cells in favor of IgG4 [151,152]. Recently, an additional pathway was discovered by Ulges et al. [153] who showed that the casein kinase CK2 in pT_{reg} cells suppresses excessive T_H2 responses in mice. CK2 controls the suppression of immunoglobulin-like transcript 3 (ILT3), an inhibitory receptor expressed on monocytes, macrophages and DCs. If the β -subunit is removed in T_{reg} cells, a subpopulation of ILT3⁺ T_{reg} cells arises that cannot limit the proliferation of IRF4⁺ PD⁺ L2⁺ dendritic cells which are needed for T_H2 expansion in vivo. Therefore, ILT3⁺ T_{reg} cells limit T_H2 responses in a CK2 dependent manner [153].

In mouse models of atopic dermatitis, T_{reg} cells are increased in response to allergen exposure, confining the eczema. A depletion of

Foxp3⁺ T_{reg} cells consequently leads to an exacerbation of skin inflammation alongside increased serum IgE levels and T_H2 cytokines [154].

Along these lines, T_{reg} cells seem to play a vital role in the prevention of antigen-induced airway inflammation models of asthma, as they control T_H2 mediated lung inflammation. One important way is the control of T_H2 differentiation via the type E3 ubiquitin ligase Itch, which inhibits GATA-3 and STAT-6 and therefore the IL-4 production. Itch deficient mice produce IL-4 that activates T_H2 cells [155]. On the other hand, IL-4 dominance in atopic mouse models compromises T_{reg} function via the IL-4R-STAT-6 pathway and favors T_H2 differentiation [156,157]. In support of these findings, T_{reg} cells prevent asthma if present in sufficient quantity in early childhood [158,159]. Interestingly, pneumococcal components induce T_{reg} cells upon intratracheal administration and thus suppress hyper-inflammation [160]. This opens up new perspectives for asthma therapy like sublingual immunotherapy using the positive influence of T_{reg} cells upon aberrant inflammation.

9. Mechanisms of T helper cell plasticity

In the light of increasing complexity among T cell subsets and their influence on the pathogenesis of allergic diseases as shown above (Fig. 1), it is not surprising that the perception of terminally differentiated non-plastic T helper cell fates has shifted towards a concept of T cell plasticity over the recent years.

In this regard, Brugnolo et al. have originally shown that allergen-specific T_H2 cells can be driven into an IFN- γ -producing phenotype [161,162]. This has led to the idea of an autoregulatory loop initiated by either IFN- γ production that inhibits T_H2 differentiation and proliferation [163,164] or the essential role of IFN- γ in creating T_H1/T_H2 hybrids [165,166]. More recently, Peine et al. were able to show that T_H1/T_H2 hybrids can occur naturally during parasite infections in a mouse model. A transfer of either the hybrids or the distinct subsets into a T_H1 or T_H2 inflammation model demonstrated reduced immunopathology for the hybrid conditions compared to the distinct subsets. These

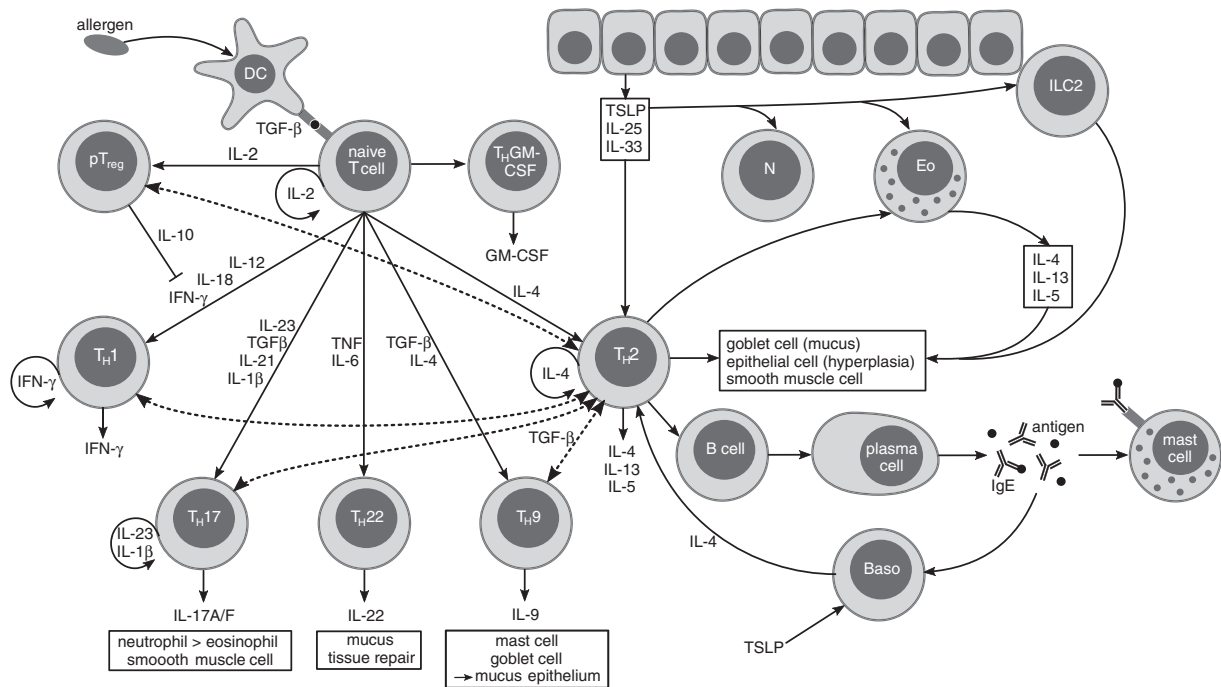


Fig. 1. Mechanisms of allergic sensitization. DC's located in epithelial tissue present processed antigens to naive T helper cells (T_H0) which differentiate into effector T cells depending on surrounding cytokine milieu. These subsets are classified according to their production of hallmark cytokines. In line with the concept of T cell plasticity, this differentiation is not definite and cytokine secretion profiles can change (for more details please see Fig. 2). This diagram outlines distinct effects cytokine combinations can have on cells, like causing reactions known to allergic conditions in epithelial or smooth muscle cells or modulating immune responses. Auto stimulating effects are indicated by circular arrows.

findings are opening the field to the possibility of more diverse T cell subsets with different functions in comparison to the so far established subsets, which could play an important role in the course of immunopathologies, such as allergies [165,166].

Another example relevant in the context of allergies was the identification of the aforementioned pro-inflammatory T_H9 cells developing from T_H2 cells in the presence of TGF- β , which are therefore associated with various T_H2 mediated pathologies [115]. Thus, it is indispensable to add T cell transitions between the defined subsets to our model in order to gain a better understanding of the pathogenesis of allergies.

Wang et al. were able to drive murine T_H2 cells into an IL-17 producing phenotype via pro-inflammatory cytokines. These IL-4 and IL-17 double producers reveal synergistic effects of these two cytokines on the exacerbation of allergic asthma with enhanced production of chemokines by lung epithelial cells and subsequently increased eosinophil and neutrophil recruitment [167]. In 2014, Irvin et al. described a similar GATA-3⁺ ROR γ t⁺ co-expressing and IL-4 and IL-17 co-producing T cell population in the BAL of asthmatic patients. In this study, they were able to correlate more severe forms of asthma and increased airway obstruction to subgroups of asthmatic patients displaying high numbers of GATA-3⁺ and ROR γ t⁺ T cells in their BAL. Furthermore, in vitro dexamethasone treatment could suppress IL-4 single-producing T_H2 cells but did not show an inhibitory effect on the IL-4 IL-17 double-producing T cell population, indicating the relevance of this subtype for patients suffering from glucocorticoid-resistant asthma [168]. Other groups, such as Panzer et al., have shown that a similar IL-4 and IL-17 double-producing subset can be generated from T_H17 cells [169].

In fact, it has become evident that many CD4⁺ T cell subsets can express more than one so far considered specific transcription factors. For example, it has been reported that besides in ROR γ t⁺ T_H17 cells, T-bet can also be expressed in GATA3⁺ T_H2 cells [170,171] and FoxP3⁺ T_{reg} cells [172,173].

Additionally, the interplay between T_H2 and T_{reg} cells has recently been highlighted in the context of allergies. Studies in an allergy

mouse model reported a successful conversion of p T_{reg} cells into an IL-4 producing cell type, while losing expression of their master transcription factor FoxP3 [169]. It is known that IL-4 suppresses the TGF- β -mediated differentiation of naïve T cells into p T_{reg} cells [174]. This goes in line with findings of reduced FoxP3 protein levels in PBMCs of asthmatic patients, resembling their deficiency of T_{reg} cells and an over-expansion of T_H2 cells [175]. In a mouse model of food allergy with enhanced IL-4R signalling in T_{reg} cells IL-4 cytokines did not only decrease the formation of allergen-specific T_{reg} cells but also lead to a reprogramming of T_{reg} cells into a GATA-3 expressing IL-4 producing T_H2 -like phenotype. The PBMCs of a small cohort of food-allergic children subsequently showed that FoxP3⁺ cells started to produce IL-4 upon allergen stimulation [176].

Plasticity among the regulatory T helper cells has recently become another field of interest, as evidence of many immune-mediated pathologies being caused by a deregulated homeostasis between these T_{reg} subtypes is arising [177]. Besides the aforementioned T_H2/T_{reg} intermediates, ROR γ t⁺ FoxP3⁺ double expressing cells have been described to play a vivid role during allergic pathologies [147,178]. Encounters with commensal microbiota and intestinal Vitamin A induce a p T_{reg} population expressing ROR γ t [179] which regulates Type 2 immune responses [147,180]. Accordingly, in mice lacking ROR γ t⁺ T_{reg} cells, higher amounts of GATA-3⁺ T_H2 cells and increased levels of IL-4, IL-5 and IgE could be observed alongside with exacerbated T_H2 responses [147].

Our knowledge in this field has grown exponentially during the last few years and studies such as those carried out by the group around Marc Panzer which successfully repolarized T_H1 and T_H17 cells into partial, as well as complete T_H2 phenotypes by infecting mice with the gastrointestinal helminth *Nippostrongylus brasiliensis* [181] suggest that even more heterogeneity between T cell subsets will soon be uncovered.

In allergies, the individual functional share of T cell populations producing cytokines of several subsets remains to be investigated to eventually discover new therapeutic targets in these more specified immunologic mechanisms.

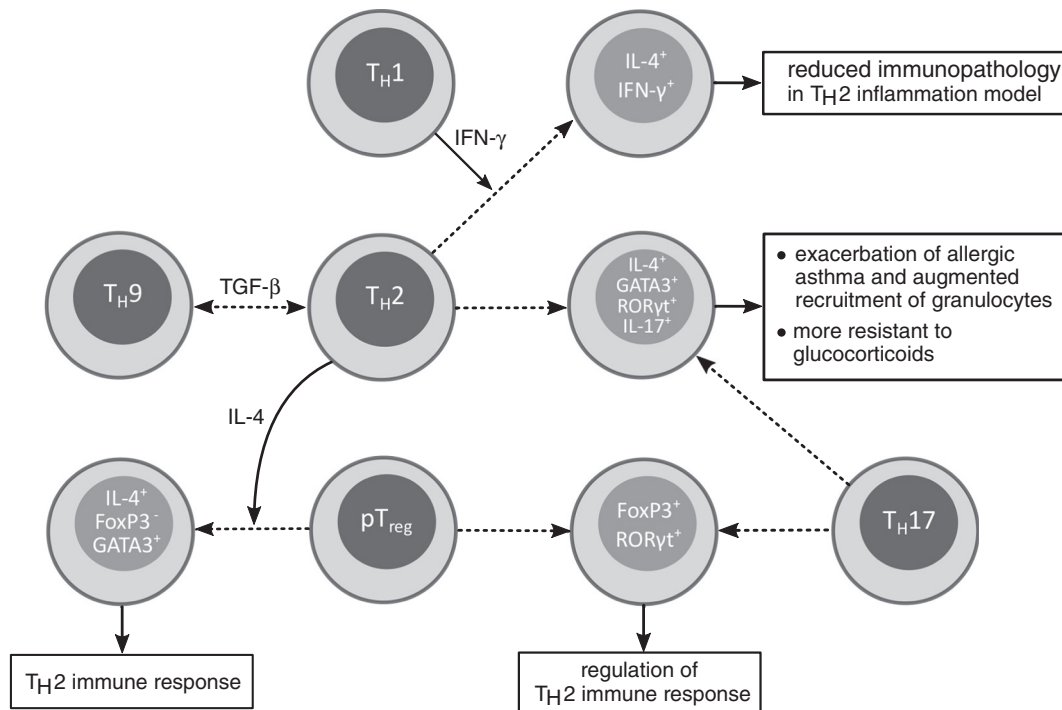


Fig. 2. T cell plasticity in allergies. Alterations in the micro milieu of T helper cells can lead to substantial changes in their effector phenotype and expression of transcription factors (dotted arrows). In this manner, IL-4 producing T_H2 cells, which are crucial to the pathophysiology of allergies, can be driven into co-production of IFN- γ or IL-17, causing the pathology to either aggravate or alleviate. Similarly, IL-4 enriched environments can cause p T_{reg} cells to lose FoxP3 expression for GATA3, leading to an over-expansion of T_H2 cells and deficiency of T_{reg} s in asthmatic patients. On the other hand, protective effects have been described for intermediates of p T_{reg} and T_H17 cells like the FoxP3 ROR γ t double-positive population.

10. Outlook: future challenges

For the future, it could be thought of blocking any cytokine, receptor or chemokine that seems to be relevant in the allergic cascade like IL-4, IL-5, IL-9, IL-13, TNF and others [182].

Nevertheless, only few of them have shown promising results in patients so far, which might reflect the large heterogeneity of clinical symptoms and immunopathological manifestations in allergic patients. Thus, identification of new biomarkers is necessary to be able to distinguish between patients that will benefit of certain therapies and non-responders.

This requirement for prospective therapies represents a future challenge in the field [183]. Apart from the role of the immune system one has to remember that the epithelial barrier has to be taken into account as well [184]. Cytokines like IL-25, IL-33 and TSLP are secreted by epithelial cells and play an important role in the development of allergies as we have seen above. This makes them a prospective target for future therapies as some of them like IL-33 are already studied in mouse models [185,186].

Therefore, a deeper understanding of the underlying pathological mechanisms of allergic diseases is required. As we know now, the T_H1/T_H2 paradigm fails to be the all-embracing explanation that it was believed to be. Characterization of new T cell subsets and of their plasticity has highlighted a further degree of complexity, which will possibly help to further clarify the immunopathogenesis of atopic diseases and to develop new potential therapeutic targets.

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Appendix A. Supplementary data

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function	biological/drug (clinical study by company/institution)	disease	clinical phase	publication or/and clinicaltrials.gov-ID (study completion date month/year)
anti-IL-2	Daclizumab (Facet Biotech)	chronic persistent asthma	phase II	Busse et al. 2008/ NCT00028288 (12/2003)
anti-IL-5	Mepolizumab/Bosatria® (GlaxoSmithKline)	asthma atopic dermatitis	phase III phase IIIA ongoing	NCT01842607 (03/2015) NCT02135692
	Reslizumab/Cinqair (Teva Pharmaceutical Industries)	asthma	phase III phase III ongoing	Castro et al. 2015/ NCT01287039 (03/2014), NCT01285323 (04/2014) NCT02501629, NCT02452190
anti-IL-5Rα	Benralizumab (MedImmune/AstraZeneca)	asthma	phase III	Nowak et al. 2015/ NCT00768079 (05/2011)
anti-IL-4Rα	Dupilumab (Sanofi/Regeneron Pharmaceuticals)	asthma atopic dermatitis	phase III ongoing phase III ongoing	NCT02528214 NCT02414854 NCT02755649
	Pitrakinra (Aerovance)	asthma atopic dermatitis	phase II phase IIa	NCT00801853 (02/2010) NCT00676884 (08/2006)
anti-IL-9	MEDI-528 (MedImmune)	asthma	phase IIa	NCT00968669(01/2012)/ Oh et al. 2013
anti-IL-12p40	Ustekinumab (Rockefeller University)	atopic dermatitis	phase II ongoing	NCT01806662
anti-IL-13	Lebrikizumab (Genentech/Roche)	uncontrolled asthma asthma atopic dermatitis	phase III ongoing phase II ongoing phase II ongoing	NCT01875003 NCT01987492 NCT02340234
	GSK679586 (GlaxoSmithKline)	asthma	phase II	NCT00843193 (07/2010)
	Tralokinumab (MedImmune/AstraZeneca)	asthma	phase III ongoing	NCT02281357 NCT02194699
anti-IL-17	Secukinumab	asthma atopic dermatitis	phase II terminated phase II ongoing	NCT01478360 (11/2014) NCT02594098
anti-IL-31	BMS-981164 (Bristol-Myers-Squibb)	atopic dermatitis	phase I	NCT01614756 (04/2015)
anti-TSLP-R	MEDI9929/AMG 157 (MedImmune/Amgen)	severe asthma mild asthma atopic dermatitis	phase III ongoing phase I ongoing phase II ongoing	NCT02054130 NCT02512900 NCT02525094
CRTH2 inhibitor	QAW039 (Novartis)	asthma	phase III ongoing	NCT02563067 NCT02555683
	QAV680 (Novartis)	atopic dermatitis allergic rhinitis	phase II phase II	NCT01785602 (11/2014) NCT01804400 (10/2013)
JAK inhibitor	Tofacitinib (Pfizer)	atopic dermatitis	phase IIa	NCT02001181 (09/2014)
TLR-9 agonist	CYT003-QbG10 (Cytos Biotechnology AG)	asthma	phase II	Beeh et al. 2013/ NCT00890734 (11/2010)