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IL-17 and IL-22 in atopic allergic disease

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A long standing paradigm is that antigen-specific Th2 cells and their cytokines such as IL-4, IL-5, and IL-13 orchestrate the characteristic features of atopic allergy. The discovery of a role for IL-17-producing (Th17) and IL-22-producing (Th22) T helper cells in inflammatory diseases has added an additional layer of complexity to the understanding of the pathogenesis of allergic diseases. Here we re-evaluate the role of T helper cells, with special focus on the Th17 and Th22 subsets in allergic asthma and atopic dermatitis. Whereas sparse data point to a protective role of the increasing amounts of Th22 cells that are found in chronic stages of both allergies, the data on Th17 cells paint different pictures for the contribution of Th17 cells during subsequent stages of these two forms of allergy.

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Introduction

Allergic diseases, such as atopic dermatitis and allergic asthma, are caused by deregulation of the immune response to harmless environmental antigens. Allergic diseases are commonly associated with chronic inflammation characterized by infiltration and accumulation of eosinophils, T cells and mast cells. Increased disease severity is often coincided by the additional influx of neutrophils. Classically, allergic inflammation is characterized by an initial Th2-driven phase (mediated by IL-4, IL-5 and IL-13), which precedes a Th1-dominated phase. However, recent studies suggest that IL-17 and IL-22 play a role in sustained inflammation in allergic diseases. IL-17 and IL-22 are leukocyte-derived cytokines with major impact on a variety of tissue cells, in particular epithelial cells, in the inflamed tissues. IL-17 triggers expression of antimicrobial factors and promotes a vast

inflammation by inducing the production of another series of pro-inflammatory cytokines. By contrast, IL-22 primarily has a protective and regenerative function and is less pro-inflammatory. Important differences, as well as many similarities, are emerging when the biology of Th17 cells in the mouse is compared with corresponding phenomena in humans. In this review we focus on the roles of IL-17 and IL-22 in allergic asthma and atopic dermatitis, since data on these cytokines in other allergic disorders are scarce.

IL-17

IL-17A is a homodimeric protein that belongs to the IL-17 cytokine family [1]. IL-17F is the most closely related family member to IL-17A, sharing the same receptor and regulatory elements [2]. IL-17A and IL-17F are, amongst others, produced by a subpopulation of CD4⁺ T cells, namely Th17 cells, which have been implicated in the pathogenesis of various chronic inflammatory diseases [3,4]. Human Th17 cells are characterized by the production of IL-17A (IL-17) and IL-17F [5,6] and express the chemokine receptor CCR6, mediating leukocyte homing to skin and mucosal tissue [7]. The IL-17 receptor (IL-17R) is ubiquitously expressed and ligand binding causes secretion of pro-inflammatory cytokines and chemokines (mainly IL-8, and also IL-6 and CXCL1/3/5/6) [8] resulting in recruitment of neutrophils and/or macrophages to the area of inflammation as well as their activation and subsequent tissue damage [5]. The role of Th17 cells in host defense against pathogens has been characterized extensively in mouse models, with the general consensus that IL-17 is necessary for protective immunity against extracellular pathogens [9]. Although the precise role of IL-17 is not always clear in humans, recent data show that tissue-infiltrating Th17 cells are present in diverse chronic inflammatory diseases, including psoriasis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, allergic asthma and atopic eczema [10,11].

Like all specialized effector Th cell subsets, Th17 cells develop from naive T cells under the influence of T cell polarizing factors. A major factor in the development of Th17 cells is IL-23, which is primarily secreted by activated dendritic cells (DCs), monocytes and macrophages and promotes expansion and survival of Th17 cells [12]. In line with the dominant role of Th17 over Th1 cells in chronic inflammatory diseases, IL-23, rather than the Th1-inducing cytokine IL-12, was identified to be pathogenic in a number of mouse models of chronic

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inflammation, including experimental autoimmune encephalomyelitis, collagen-induced arthritis, psoriasis, inflammatory bowel diseases and eosinophilic airway inflammation [3,4^{*},13].

IL-22

IL-22, originally described as an IL-10-related T cell derived inducible factor (IL-TIF), belongs to the IL-10 cytokine family [14]. In contrast to the IL-17R, expression of IL-22R is limited mainly on nonhematopoietic tissue cells, such as epithelial cells of the digestive and respiratory systems and keratinocytes of the skin [15]. In these cells, IL-22 triggers the production of antimicrobial peptides (although less potent compared to IL-17 [16]) and expression of a series of proteins involved in cellular differentiation and survival [17]. IL-22 producing Th cells were first considered to be a variant of Th17 cells, but recent reports show that IL-22 can be produced without production of IL-17 by cells defined as Th22 cells [18^{**},19^{*}]. Th22 cells coexpress CCR6 and the skin-homing receptors CCR4 and CCR10 [20^{*}], suggesting that these cells have a prominent function in the skin.

IL-22 has both pro-inflammatory (again to a lesser extent than IL-17) and protective properties, but the dual effects of IL-22 are not yet fully understood. IL-22 deficient mice have a lower disease incidence in a rheumatoid arthritis model [21] and IL-22 induces keratinocyte migration in an *in vitro* injury model and strongly induces hyperplasia of reconstituted human epidermis [22]. In addition, while IL-22 deficient mice are highly susceptible to liver damage in an experimental hepatitis model, transfer of IL-22-expressing Th17 cells into IL-22-deficient mice results in protection [23].

Allergic asthma

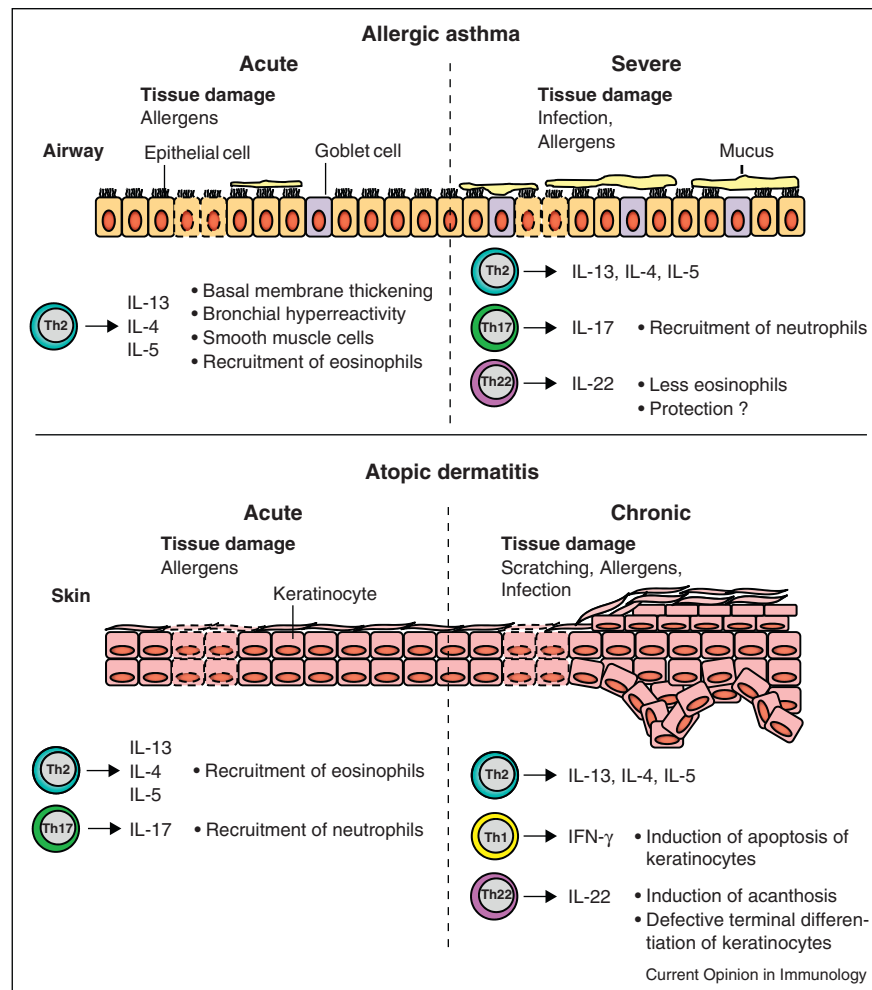
Allergic asthma is characterized by elevated IgE serum levels, chronic airway inflammation with intense eosinophil and lymphocyte infiltration, mucus hyperproduction and airway hyperresponsiveness to a large variety of stimuli. Accumulating evidence indicates that antigen-specific Th2 cells and their cytokines, such as IL-4, IL-5 and IL-13 together with inflammatory mediators from activated mast cells orchestrate these characteristic features of asthma. Patients with severe asthma demonstrate higher numbers of neutrophils in bronchoalveolar lavage (BAL) fluid and bronchial biopsy specimens than mild-moderate asthmatic patients of control subjects [24].

In line with the presence of neutrophils, IL-17 is moderately increased in lung tissue, BAL fluid, sputum and serum from asthmatic patients [25]. Moreover, IL-17 and IL-8 mRNA in sputum correlated with the presence of neutrophils in the sputum from asthmatic patients with increasing disease severity [26]. Surprisingly, in addition to IL-17 expression by T cells, IL-17A is also expressed by eosinophils in the airways of asthmatic patients [27].

However, this study did not reveal to what extent IL-17 was actually secreted by these cells. Taken together, these findings are compatible with IL-17 contributing to local accumulation of neutrophils in asthma (Figure 1). Further evidence for a role of IL-17 in allergic asthma is that, besides elevated numbers of IL-4 producing Th2 cells, peripheral blood from allergic asthmatics also harbor elevated numbers of Th17 cells compared to healthy controls. In line with increased levels of IL-17 in the lung of severe asthmatics, the percentages of Th17 cells as well as the plasma concentrations of IL-17 and IL-22 tended to increase with disease severity [28].

Mechanisms of induction of Th17 and the pathogenic role of IL-17 in airway inflammation have been subject of study in many mouse model systems. Signaling through the IL-17R is critically required to develop allergic asthma since IL-17R-deficient mice fail to develop allergic asthma in response to intranasal ovalbumin (OVA) after intraperitoneal sensitization [29]. However, differences in mouse strains, and type of allergens and protocols used to induce allergic airway disease all appeared to contribute to the importance of IL-17 in the induction and maintenance of allergic airway disease (reviewed in [30]). Recently, Wilson *et al.* showed that after sensitization with intraperitoneal OVA, a single allergen challenge primed a strong Th2-dominated inflammation characterized by increased levels of IL-4, IL-5, IL-13 and eosinophils in BAL, but not airway hyperreactivity (AHR). In comparison, allergic sensitization through the airway primed only modest Th2 responses and strong Th17-mediated responses. As a result of IL-17 release into the airway by lung-homing Th17 cells, these mice developed IL-17-dependent airway neutrophilia and AHR [31^{**}]. Studies on IL-17-neutralization during OVA challenge show decreased neutrophil recruitment and no effect on AHR [32] or suppression of AHR [33]. All together, these data suggest that the method of sensitization may affect IL-17 response in mouse models of allergic airway inflammation. Even so, most studies using mouse models of asthma have shown that IL-17 expression in the airways is upregulated after sensitization and challenged with antigen. Expression of the Th1 transcription factor T-Bet induces IFN- γ production, which suppresses Th2 polarization. A role for IFN- γ in allergy is suggested by the finding that, compared to T cells in control subjects, pulmonary T cells in asthmatic patients show reduced expression of T-bet. In addition, T-bet^{-/-} mice have been found to spontaneously exhibit AHR [34]. In a study by Durrant *et al.*, the production of Th2 cytokines in T-bet^{-/-} mice did not appear to be significantly higher than in WT mice, while a marked increase in IL-17 levels was observed in T-bet^{-/-} mice, indicating that T-Bet also inhibits Th17 development. Neutralization of pulmonary IL-17 in T-bet^{-/-} mice by anti-IL-17 antibody treatment during OVA challenge resulted in decreased levels of neutrophilic infiltration into the air-

Figure 1



Th17 and Th22 cells in allergic asthma and atopic dermatitis. Both allergies are characterized by a Th2-dominated cytokine milieu and evolve from an initial acute phase to a more severe/chronic phase. In allergic asthma, IL-17 and neutrophilia arise with increasing severity of disease, while IL-17 is absent in chronic lesions of AD. Otherwise, both chronic allergic asthma and chronic AD inflammation are characterized by elevated amounts of IL-22.

ways and decreased airway inflammation, essentially reversing the development of allergic asthma [35]. Together, these data may imply that IL-17-dependent severe asthma is due to a reduced amount of (T-Bet expressing) Th1 cells in the lungs of asthmatic patients.

The role of IL-23 in allergic airway inflammation is not well understood. Peng *et al.* showed that transgenic mice overexpressing IL-23R in T cells exhibited increased airway infiltration of eosinophils and Th2 cytokine production after OVA challenge, whereas those deficient in IL-23 displayed reduced airway inflammation. Furthermore, *in vitro* experiments showed that under Th17 promoting conditions, more IL-17 producing T cells were induced from IL-23R transgenic naive T cells after addition of IL-23, while IL-23 deficiency inhibited Th2 differentiation [36^{••}]. Therefore, these data unex-

pectedly suggest that, next to a role for IL-23 in the stabilization and expansion of Th17 cells, IL-23 may play a similar role in the development and function of Th2 cells.

Steroid-resistant asthma comprises an important source of morbidity in severe allergic asthma. Corticosteroids have been the gold standard for treatment of eosinophilic asthma because of their ability to downregulate Th2 genes, such as IL-5 and IL-13. However, some patients treated with inhalation glucocorticoids are insensitive and still have elevated levels of Th2 and Th17 cells compared to healthy controls [28]. A recent study indicated that Th17 cells are resistant to steroids *in vitro* and that AHR induced by transferred Th17 cells in a mouse model is steroid-resistant [37^{••}]. Among others, this finding raises the intriguing possibility that treatment of a selected

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group of asthma patients with corticosteroids creates IL-17 dependent neutrophil dominated inflammation associated with severe asthma.

Paradoxically, although some mouse model studies on airway hypersensitivity suggest that IL-17 is essential for antigen-specific responses in the lung to establish allergic asthma, one mouse model study showed that IL-17 may actually be protective by showing that administration of IL-17 in the chronic phase decreased ongoing Th2 cytokine production, reduced eosinophilia and bronchial hyperreactivity [29]. Recently, IL-22 was shown to negatively regulate the allergic response because neutralization of IL-22 augmented eosinophil recruitment to the lung. However, neutrophil recruitment was not affected by IL-22 neutralization [38]. When reviewing the currently available mouse model studies, it is difficult to draw firm conclusions on the role of IL-17 and IL-22 in allergic asthma, whereas more studies are required to evaluate the implications of the results for human asthma.

Atopic dermatitis

Atopic dermatitis (AD) is a chronic inflammatory skin disease associated with elevated IgE serum levels and tissue eosinophilia, characterized by epidermal hyperplasia and red, scaly, itchy patches of the skin. Neutrophils are largely absent in AD skin biopsies, possibly due to reduced production of neutrophil-chemoattractants [39]. While the acute phase of AD is clearly characterized by Th2-polarization, the exact contribution of different T cell subsets to the pathogenesis of chronic AD is still unclear. Originally it was thought that chronic inflammation results from a Th2-Th1 switch under influence of local production of Th1-inducing cytokine IL-12, that emerges into this Th2-dominant cytokine milieu [40,41]. However, recent data suggest a more complex picture in which absence of IL-17 and upregulation of IL-22 coincides with ongoing Th2 domination in chronic AD (Figure 1).

IL-17 expression is enhanced in acute lesions in atopic dermatitis skin compared with uninvolved skin [42] and a correlation between the number of Th17 cells in peripheral blood and acute AD severity has been reported [43]. Surprisingly however, in chronic skin lesions IL-17 levels are not enhanced [42]. In addition, comparison of skin biopsies from chronic AD and lesional psoriasis confirmed that the IL-23/Th17 axis is largely absent in chronic AD [16,18^{••}]. It is known that an impaired IL-17 response underlies diseases which are associated with recurrent and persistent infections of the skin such as hyper IgE syndrome [44]. The diminished presence of IL-17 in chronic AD may also contribute to the observed absence of neutrophils in biopsies of chronic AD skin.

Genetic mutations in filaggrin have recently been reported in 8–48% of AD patients [45,46] and this has emphasized the role of the skin barrier function disorder

in the maintenance of AD. Filaggrin is an important protein in the maintenance of epidermal integrity, and abnormal filaggrin may lead to impaired skin barrier function. Recently, filaggrin-deficient mice were shown to possess increased IL-17 mRNA levels in skin lesions shortly after epicutaneous application of OVA [47[•]]. Because AD patients without mutations in filaggrin also show reduced expression of filaggrin, possibly due to the presence of IL-4 and IL-13 [48], loss of epidermal integrity may favor Th17 mediated inflammation in acute lesions.

A recent study shows that, next to a Th2 polarization, AD skin had upregulated expression of IL-22 [18^{••}], suggesting that a Th2/Th22 polarization dominates chronic AD. CCL27, the ligand for CCR10, is highly expressed in skin lesions from AD patients [49] and combined with the recent finding that Th22 cells particularly express CCR10 might be an explanation for the increased Th22 presence in chronic AD skin. However, due to a partial inhibition of antimicrobial peptide production by the Th2 microenvironment [50], the IL-22-dependent upregulation of antimicrobial peptides such as human β -defensin 2 and S100 proteins [11] in patients with AD is ineffective. Together with the absence of IL-17, this may in part explain the skin colonization with *Staphylococcus aureus* observed in 85% of chronic AD patients.

On the other hand, IL-22 has been shown to induce acanthosis and hypogranulosis in skin by downregulation of genes involved in terminal differentiation of the skin [8,22]. This regenerative and wound healing function of IL-22 might contribute to the epidermal hyperplasia observed in AD. Further research on the role of Th22 and Th17 is justified to elucidate the interplay between these Th cell subsets in acute and chronic AD.

Conclusion

In this review we addressed the role of IL-17 and IL-22 in allergic asthma and AD. Although both allergies evolve from an initial acute phase to a more severe/chronic phase, IL-17 as pathogenic cytokine seems to act differently. In allergic asthma, IL-17 and neutrophilia only come up with increasing severity of disease. At present, mouse models of allergic asthma do not uniformly support a functional significance of Th17 cells in allergic airway inflammation, nor do these models address the question why these cells do emerge in patients when asthma becomes severe. In this respect, an attractive possibility is that Th2-dependent allergic asthma symptoms essentially do not require Th17 cells, but that these highly pathogenic cells arise as a result of insults that are different from allergic reactions, for example due to underlying bacterial infection.

Whereas IL-17 in allergic asthma is most strongly expressed at the more severe stages, IL-17 in AD is

absent in chronic lesions. The reason of this contrasting presence of IL-17 in these different allergic inflammations is enigmatic. Otherwise, both chronic allergic asthma and chronic AD inflammation are characterized by elevated amounts of IL-22. IL-22 is less pro-inflammatory compared to IL-17, probably because IL-22 does not attract immune cells, and will mainly have a role in protective and regenerative epithelial cell responses. More research is needed to more precisely understand the underlying mechanisms of the contrasting presence of IL-17, as well the functional significance of both IL-17 and IL-22 in the different allergic phenotypes.

Conflict of interest

The authors declare no financial conflict of interest.

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