Dual Role of Th17 Cytokines, IL-17A,F, and IL-22 in Allergic Asthma

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Abstract The proinflammatory role of T helper (Th) 17 cells and therefore of its cytokines, IL-17 (IL-17A), IL-17F, and IL-22, in autoimmune disorders has been favored, although there is evidence that not only IL-17A but also IL-17F and IL-22 have a dual role as negative regulators. Here we review the concept of the dual function of IL-17A, IL-17F, and IL-22 in the light of recent strategies to use neutralization of these cytokines as potential alternative to neutralizing TNF and IL-1 treatments in chronic inflammatory disorders. Expectedly, in allergic lung inflammation, neutralization of IL-17A inhibited neutrophil recruitment. However, this IL-17A antibody treatment concomitantly increased eosinophil recruitment by neutralizing IL-17A's dual role as negative regulator. IL-17A negatively regulated dendritic cell function and activation of T helper cell (Th)2 cytokine production. Furthermore, IL-17A inhibited Th2-characteristic chemokine and adhesion molecule expression. On a mechanistic level, IL-17A acted on IκB-β by preventing degradation and in turn leading to reduced NF-κB activation or IL-17A inhibited transcription factor IRF-1. Therefore, anti-IL-17A therapy, although presenting a promising lead in chronic inflammatory disorders, bears a potential risk of exacerbating allergic asthma.

1 IL-17A, IL-17F, and IL-22 Production by Antigen-Specific T Helper Th17 Cells Inhibits Th2 Response

Interleukin-17A (IL-17A, aka IL-17) is the founding member of a multimember cytokine family consisting of IL-17A to IL-17F [1]. It forms homodimers containing five highly conserved cysteine residues forming a cysteine knot.

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IL-17A and IL-17F homodimers and IL-17F/IL-17A heterodimer transduce their signals through the receptor composed of IL-17RA and IL-17RC [2, 3].

IL-17A and IL-17F are produced by the memory T cells termed Th17, a T helper cell lineage distinct from Th1 and Th2 cells, which is negatively regulated by interferon-γ and IL-4 [4, 5]. Unchecked activation of Th17 cells by IL-23 is linked to chronic inflammation in experimental autoimmune encephalomyelitis (EAE) and type II collagen-induced arthritis, two heretofore prototypical "Th1" disease models [6, 7].

The IL-23-Th17 cell axis has been implicated to contribute to the allergic Th2 response [8]; for review, see [9]. IL-23 as well as the co-expressed Th17 cells cytokines IL-17A and IL-22 [10] is found in the lung of allergic patients [11–13] and in lung homogenates of ovalbumin (OVA)-sensitized and challenged mice [8, 14]. In vitro production of IL-17A and IL-22 was triggered with IL-23 and even further enhanced in the presence of OVA, in cultures of mediastinal lymph node (MLN) cells isolated from antigen OVA-sensitized and challenged mice [8, 14]. Therefore, the role of IL-17A and IL-22 was addressed in the allergic response.

IL-17A was indeed required during antigen sensitization to develop a Th2 response in allergic asthma, as shown in IL-17R-deficient mice [8]. Neutralization of IL-17A, however in this model, augmented the allergic response, while recombinant IL-17A administration reduced pulmonary eosinophil recruitment and bronchial hyperreactivity. Recombinant IL-17A reduced eosinophil-chemokine eotaxin (CCL11) and thymus- and activation-regulated chemokine (TARC/CCL17) in lungs in vivo, and antigen uptake by dendritic cells and IL-5 and IL-13 production in regional lymph nodes were also reduced by recombinant IL-17A [8]. These findings demonstrated a novel negative regulatory role of IL-17A. A beneficial role of IL-17A has been confirmed in the model of chronic fungal-induced asthma. In this model, the protective role of TLR6 was dependent on IL-23 and the production of IL-17A. TLR6 deficient mice showed reduced IL-23 and IL-17A expression and an exacerbated Th2 response, which was normalized by addition of recombinant IL-23 which recovered the IL-17A production [15]. Furthermore, Murdoch and Lloyd provide evidence in the model of acute allergen-induced response that the γδT cell-dependent normalization of lung function and resolution of inflammation was dependent on the production of IL-17 [16]. Therefore, endogenous IL-17A has a dual role. While it is essential during antigen sensitization to establish allergic Th2 response, in sensitized mice IL-17A attenuates the Th2 response.

A new role as negative regulator of antigen-driven Th2 response was ascribed for IL-17F. IL-17F dampened antigen activation of DCs resulting in a reduced Th2 response and reduced inflammation [14]. These findings may provide a possible explanation why Yang and colleagues found an increased allergic response in IL-17F-deficient mice [17].

IL-22, similar to IL-17A [7, 18–20], has been found in diseased tissues from patients with different chronic inflammatory diseases, involving infiltrating activated T cells, such as rheumatoid arthritis, psoriasis, inflammatory bowel disease, and COPD [21–25]. IL-22 is expressed by IL-9-activated mast cell and by Th17 cells initiated by TGF-β in the context of IL-6 and other proinflammatory

cytokines [10]. IL-22 is increased in lung homogenates of OVA-sensitized and challenged mice [14]. Neutralization of endogenous IL-22 in OVA-sensitized mice increased the eosinophilic response [14], whereas administration of recombinant IL-22 attenuated the acute allergic response [26, 27].

These data provide evidence that IL-17A,F and IL-22 besides their inflammatory role have a negative regulatory function in allergic lung inflammation.

2 Increasing Evidence Supports This Novel Role of IL-17A and IL-22 as Down Modulators of a Committed Immune Response

It has in the past abundantly been described that full acquisition of pathogenic function in experimental autoimmune encephalomyelitis (EAE) by effector Th17 cells is mediated by IL-23. However, as shown most recently, stimulation of the myelin-reactive T cells with TGFβ plus IL-6, instead of IL-23, completely abrogated their pathogenic function despite upregulation of IL-17A production [28]. These regulatory Th17 cells failed to upregulate the proinflammatory chemokines crucial for central nervous system inflammation. In contrast, the regulatory Th17 cells produced IL-10, which had potent anti-inflammatory activities. This study by Cua's group [28] did not show whether IL-17A directly conveyed negative regulation of inflammation, which was rather due to co-expressed IL-10 in EAE. Several experimental approaches listed below have indeed demonstrated direct inhibitory functions of recombinant and endogenously produced IL-17A in vitro and in vivo. Furthermore, an IL-17A-induced expression of the anti-inflammatory IL-10 has been demonstrated in macrophages, yet IL-17A has moderate effects on monocytes and macrophages [29].

First, expression of recombinant murine IL-17A in *Vaccinia* virus increased viral virulence significantly in mice [30], suggesting that IL-17A negatively regulated the antiviral host defense. Second, administration of recombinant IL-17A ameliorated and negatively regulated the late phase of experimental autoimmune neuritis (EAN), a model of peripheral nerve demyelination [31]. Third, in vitro studies provided possible mechanisms of how IL-17A acts as a suppressor. IL-17A inhibited the chemokines RANTES (CCL5), Fractalkine (CX3CL1), and CTACK (CCL27) [32–34] and the mononuclear leukocyte adhesion molecule VCAM-1 in TNF-activated mesenchymal cells [35]. Fractalkine, CTACK, RANTES, and VCAM-1 are involved in inflammatory responses of both Th1 and Th2 types. RANTES and VCAM-1 are essential in the recruitment of mononuclear cells, and VCAM-1 is involved in the formation of germinal centers (present in autoimmunity). Therefore, existence of the novel negative regulatory role of IL-17A needs to be revisited in multiple inflammatory and immune disorders.

Revisiting the role of IL-17A in multiple immune responses would help address the question as to whether IL-17A acts like a regulatory T cell (Treg) cytokine such as TGFβ or IL-10, which reduces allergic pulmonary challenges as well as vast T

cell responses [36–38]. Indeed, in initial experiments IL-17A was described as a Treg cytokine in cell cultures, inhibiting vast T cell responses [36, 39]. Furthermore, Treg cells and TGFβ promote under proinflammatory conditions the development of Th17 cells and production of IL-17A [40]. Therefore, IL-17A as a downmodulator of the dendritic cells and Th2 response provides evidence for a novel feedback mechanism by which Treg cells may control a Th2 response in the effector phase of allergic asthma.

Protective role of IL-22 has also been ascribed in other models than allergic lung inflammation. IL-22 provided protection to hepatocytes during acute liver inflammation [41] and protected against ConA- or tetrachloride-induced liver injury [42]. Second, delivery of IL-22-Ig fusion gene ameliorated experimental autoimmune myocarditis (EAM) in rats [43]. Third, local IL-22 gene delivery led to rapid amelioration of intestinal inflammation in a mouse model of ulcerative colitis, and conversely, inhibition of IL-22 activity by local overexpression of its antagonist, IL-22 binding protein, prevented recovery and goblet cell restitution in acute colitis (DSS) [44]. Therefore, even though IL-22 is an upregulator of proinflammatory gene expression and has proinflammatory function, there is growing evidence that IL-22 has, similar to IL-17A, a protective role in inflammatory diseases such as colitis, EAE, and allergic lung inflammation.

3 Excess Endogenous IL-17A and IL-22 Production in the Absence of IL-4 Signals In Vitro and In Vivo

IL-17A production is induced by TGFβ in a proinflammatory milieu, including presence of IL-6, IL-1, or TNF, and its production is sustained by IL-23. In contrast, IL-17A production is inhibited by IL-4, IFNγ, IL-25 (IL-17E), or IL-27. In lungs, IL-17A has been shown to originate from antigen-specific Th17 cells as well as from an iNKT subpopulation, which is NK1.1 negative [45]. In an allergic lung response, IL-17A production was induced by IL-23 and controlled by IL-4 receptor signaling [8]. In mice lacking IL-4 responsiveness, IL-17A was overproduced correlating with reduced effector functions of allergic asthma. The inhibition of the Th2 response was indeed ascribed to endogenous IL-17A, as assessed using IL-17A neutralizing antibody treatment in vivo.

In the absence of IL-4 responsiveness, not only IL-17A but also IL-22 production was significantly increased upon allergen challenge, and similar to IL-17A, inhibition of endogenous IL-22 by neutralizing antibodies increased the allergic response, indicating that both IL-17A and IL-22 contribute to the inhibition of the Th2 response.

This increase in IL-17A and IL-22 in the absence of IL-4 responsiveness was not due to differences in IL-23 concentrations since pulmonary OVA-induced IL-23 concentrations are equal in IL-4Rα KO and WT mice [8]. Therefore, the IL-4 signals affect directly IL-22 and IL-17 production and do not act on IL-23

production [8]. However, the molecular mechanism of IL-22 expression, being either IL-23 dependent or independent, in allergic lung inflammation needs to be investigated in future experiments.

Neutrophil involvement has been ascribed to both infectious disease and allergic inflammation [46–48]. In allergy, neutrophil recruitment is in part due to endogenous IL-17 [8, 49], but not due to IL-22, since neutralization of IL-22 did not diminish neutrophil but increase recruitment in the allergic response. This is in line with a previous report, which demonstrated that IL-22 alone and in synergy with IL-10 decreased IL-8 production by human alveolar epithelial cell lines [50].

Therefore, a novel mechanism of how IL-4 promotes a Th2 response was proposed, by suppression of the novel suppressor molecules IL-17A and IL-22. This added a novel function of IL-4 to the list of its proallergic effects, including differentiation of Th2 lymphocytes, inhibition of T lymphocyte apoptosis, induction of IgE production, promotion of eosinophil transmigration into the lungs, mucus hypersecretion, and bronchoconstriction [8, 51–53].

4 Molecular Mechanism of Negative Regulatory IL-17A and IL-22 Effects

On a mechanistic level, IL-17A elicits dual effects and reportedly promotes expression of proinflammatory (hemopoietic, CXC-chemokines, acute phase) factors [54, 55], whereas it inhibits the production of mononuclear cell recruiting molecules like TNF-induced VCAM-1 and CC-chemokine RANTES [35]. This dual effect of IL-17A in human cell cultures predicted a reduced mechanism of mononuclear cell recruitment in vivo. CC-type chemokines RANTES (CCL5), TARC (CCL17) and eotaxin (CCL11) were induced by antigen OVA in vivo. TARC primarily attracts CCR4-positive Th2 cells. IL-17A reduced TARC production, which correlated with reduced lymphocyte counts and Th2-derived IL-5 concentrations in lung tissues. The expression of the major eosinophil attractant, eotaxin, was also reduced by IL-17A and accompanied by reduced eosinophil infiltration in the airways. Indeed, reductions or absence of these CC chemokines reportedly ablates allergic asthma [56–58]. Therefore, diminished cell attraction seems to be the pivotal mechanism of how IL-17A attenuates the allergic inflammation.

Further IL-17A effects like acute phase IL-6 and prostaglandin (PG)E2 elevations may also have corroborated to reduce locally the allergic inflammation in the lungs. IL-6 elevations inhibited aeroallergen-induced Th2 inflammation [59, 60]. PGE2 elevations reduced pulmonary allergy specifically via the E3 receptor [61]. Therefore, while IL-17A may upregulate negative regulators IL-6 and PGE2, it has a direct inhibitory effect on the local production of Th2 cytokines IL-4, IL-13, and IL-5 in the lung and regional lymph nodes [8]. Mechanistically, IL-17A inhibits dendritic cell activation and antigen uptake, which leads to reduced activation of T cells and reduced IL-4, IL-13, and IL-5 production, resulting in reduced allergic response.

However, the inhibition of the Th2 response by IL-17A represented a reduction rather than a complete blockade. Intact anti-allergen IgE concentrations in the circulation may explain why IL-17A did not completely block but rather reduced pulmonary allergy and asthma. Elevated IgE concentrations reportedly correlate with and contribute to allergic reactions [62], although it is not sufficient for the development of allergy. Therefore, IL-17A acts as negative regulator of established Th2 response locally in lungs.

In the experimental models of allergic lung inflammation, IL-22 dampened the hallmarks of an allergic Th2 response in vivo, by inhibition of DCs and their expression of co-stimulatory molecules upon antigen treatment [14]. IL-22 attenuates further the allergic response by inhibiting the induction of TARC (CCL17), IL-13 and IL-25 as shown in vivo [26, 27]. In vitro, IL-22 prevented TNF-α/IL-13-induced TARC and IL-13 production in murine Clara cells [26] and IL-25 production in the lung epithelial cell line MLE-15 induced by IL-1β or LPS [27]. Therefore, these data corroborate that IL-22 not only has a negative regulatory function in experimental models of autoimmunity, and inflamed liver and colon but also in established Th2 response in the lung.

5 High Efficiency of Inhibitory Function of IL-17A In Vivo and In Vitro

Intranasal administration of recombinant IL-17A reduced eosinophil recruitment and a Th2 response, while neutrophil recruitment was not induced when applied locally at low doses of 2.5 μg/kg IL-17A to allergen-treated mice [8]. These findings were supported by the following cell culture data [35]. IL-17A inhibited TNF-induced chemokine RANTES expression in human synovial fibroblasts and mouse lung fibroblasts. This inhibitory activity of IL-17A was sixfold more potent than its stimulatory activity on TNF-α-induced IL-6 or IL-8 secretion (IC50 = 0.2 ng/ml vs. ED50 = 1.2 ng/ml), measured in the same cells. Furthermore, neutralization of the human IL-17A receptor (IL-17R) by antibodies competitively reversed the IL-17A-induced IL-6 upregulation. However, anti-IL-17R antibody only partially neutralized the inhibitions of RANTES production by IL-17A. Yet, IL-17R was essential for the RANTES inhibition, as assessed in IL-17R-deficient cells. Therefore, inhibitory and stimulatory functions of IL-17A involve receptor IL-17R but show distinct dose responses and in turn different sensitivities to an IL-17R antagonizing antibody. These findings suggest a higher efficiency of the inhibitory over the stimulatory IL-17A functions and may explain why a net negative regulatory effect of IL-17A manifests in chronic inflammation in vivo where IL-17A production is low.

6 Molecular Signaling of Inhibitory Effects of IL-17A and IL-22

IL-17A interferes at TNF-activated NF-κB signaling in human synoviocytes [35]. This inhibition is immediate, within 20 min, and proposes a direct effect of IL-17A rather than via expression of secondary mediators. The reduced degradation of specifically IκB-β, but not IκB-α, provides a late inflammatory phase control mechanism by IL-17A for the following reason. It has been shown that inhibitor IκB-α is of importance for the transient inactivation of NF-κB, whereas IκB-β as part of a multimeric complex is involved in the persistent inactivation of NF-κB [63, 64]. The fact that IκB-β but not IκB-α is affected by IL-17A further supports the possibility that IL-17A is implicated in the regulation of the chronic phase of inflammation and immunity.

However, interferences of IL-17A on TNF-induced NF-κB activity virtually depend on the cell type and promoter targeted by TNF. For example, unlike the synoviocytes described above [35], TNF-induced NF-κB binding was only moderately and not statistically significantly reduced by IL-17A in colonic myofibroblasts [32]. In those cells, it was proposed that IL-17A interfered at the TNF-induced RANTES production mainly through inhibition of IRF-1. This in turn prevented the cooperation of IRF-1 with the NF-κB activity.

Furthermore, in macrophages it has been shown that IL-17A inhibited TNF expression transiently, the effect of IL-17A being biphasic with an early decrease of TNF release (at less than 30 min) and a marked stimulation later on (by 6 h) [29]. After 60 min and later, IL-17A also inhibited cAMP production and the transcription factor activities of CREB, AP-1, as well as NF-κB in the macrophages [29].

IL-22, on the molecular and cellular level, acts by activating STAT3. In vitro stimulation of epithelial cell with IL-22 resulted in the phosphorylation of STAT3, and diminished TNF/IL-13 induced TARC and IL-13 production [26]. Beneficial effect of IL-22 through STAT3 activation has previously been published. So IL-22 enhanced hepatocyte survival, by enhancing expression of transcription factor STAT3, Bcl-2, and Bcl-xL in inflamed liver and colon [41, 42]. STAT3 activation in intestinal epithelial cells and IL-22 was linked to mucosal wound healing [65]. IL-22 activated STAT3 and induced IL-10 by colon epithelial cells [66]. Prevention of DC activation and antigen (OVA) sensitization induced by transfer of ex vivo OVA-loaded DC has previously been ascribed to the prototype immune regulator IL-10 [25] and newly for IL-22 [14]. Whether the negative regulatory effects of IL-22 in allergic lung inflammation are due to IL-22 or indirectly induced needs further investigation.

7 IL-17 and IL-22 Have Similar Effects in Allergic Lung Inflammation but Are Still Distinct

The Th17-derived IL-22 and IL-17A negatively regulated allergy and DC functions. Its expressions were further induced by allergic stimulation together with IL-23 and were controlled by IL-4Rα signals. While neutralizing IL-22 or

IL-17 antibodies augmented the allergic response, IL-22, IL-17A, and IL-17F reduced the response by inhibiting DC functions. Therefore, the data demonstrate that IL-22 and IL-17 are novel endogenous negative regulators of allergy, and IL-22, IL-17, or Th17 cells may represent an interesting therapeutic target in lung allergy.

IL-17A and IL-22 are both co-expressed in Th17 cells [10], yet they are induced through independent pathways. Recent studies showed that IL-22 but not IL-17A and IL-17F production strongly depends on aryl hydrocarbon receptor signals [67].

Furthermore, IL-22 production is induced in absence of IL-6, while IL-17A production depends on the presence of IL-6 [22]. Additional IL-22 production is ascribed to IL-9 activated mast cells [68]. We found that IL-17A, but not IL-22 production, was markedly dependent on the intracellular signaling of the IL-1 receptor and its adaptor MyD88 pathway in lymph node cell cultures originating from OVA-treated mice [14]. A review by Eyerich and colleagues provides an overview on overlaps and differences between IL-17 and IL-22 [69]. Together this suggests collaborative and nonredundant pathways leading to Th17 cytokines and allergy.

8 Anti-IL-17 and Anti-IL-22 Therapies: A Risk or Advantage?

The pathological role of IL-17A, IL-17F, and IL-22 in autoimmune disorders has convincingly been documented and hence favored so far, although there is emerging evidence that IL-17A, IL-17F, and IL-22 also have a beneficial role as negative modulator in antigen-specific immune processes and allergic asthma [8, 14, 26–28, 31].

Increased IL-17A concentrations in allergic asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, and acute respiratory distress syndrome (ARDS) (for review, see [11]), but also rheumatoid arthritis (RA), were linked to the pathology of the diseases [20]. IL-17A neutralization inhibits experimental murine arthritis [20] and is a potential alternative therapy to TNF neutralization in rheumatoid arthritis. The novel negative regulatory function of IL-17A indicates, however, that such a therapy bears the potential risk of exacerbating allergic asthma. Therefore, an anti-IL-17A treatment in chronic inflammatory disorders seems very promising, inhibiting neutrophil recruitment in inflamed lungs and joints, while the exacerbating Th2 response in experimental allergic response by anti-IL-17A antibodies may exclude respective groups at risk from such a therapeutic anti-IL-17A treatment.

Because of the proinflammatory function of IL-17A and IL-22, neutralizing therapies targeting either IL-17 or IL-22 are considered in allergic asthma [70, 71]. However, inhibiting IL-17A or IL-22 may bear the potential risk of opportunistic infections. IL-22 together with TNF-α was found to be important to keep the epidermal integrity during infection with *Candida albicans* [72]. Mutations in STAT3 in animal models and humans confer a defect in IL-17 function, resulting

in increased susceptibility to respiratory infections with bacteria and fungi [70, 73, 74]. Neutralization of IL-22 resulted in exacerbation of bacterial infections, suggesting a protective role in mucosal/epithelial host defense [75]. And IL-22 was protective during the development of lung fibrosis induced by chronic exposure to *Bacillus subtilis* [76].

Still, because of the novel function of IL-22 and IL-17 as endogenous negative regulators of allergy, IL-22, IL-17, or Th17 cells may represent an interesting therapeutic target in lung allergy.

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