

Mechanism of Th17 and Treg in Allergic Rhinitis

Leqin Shu^{1*} and Ziyuan Wang²

¹The High School Affiliated to Renmin University of China, Beijing, 100000, China

²Department of Immunology, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences; School of Basic Medicine, Peking Union Medical College, Beijing 100730, China

Abstract. Allergic rhinitis (AR) influenced over half billion people around the globe, and its mechanism had been studied for long. While the role of Th1 and Th2 in AR was supported by substantial evidence, the relationship between Th17, Tregs, and AR was less researched. The role of Th17 and Tregs was less understood and sometimes downplayed. However, Recent studies suggested a close relationship between Th17, Tregs, and AR. Th17 and Treg secreted cytokines that could promote or attenuate inflammation and other AR symptoms via interaction with other molecules, cells, and pathways. This essay summarized these studies, and might provide a more thorough insight on AR mechanism and potential AR treatments. Th17 enhanced AR through the release of pro-inflammatory cytokines, including IL-17 that induced other immune cell response through multiple pathways, increased IgE production via interaction with other interleukins and cells, and promoted the release of other pro-inflammatory mediators. Tregs inhibited inflammation of via the release of anti-inflammatory cytokines including IL-10 and TGF- β , which suppressed the response of other immune cells such as T cell, B cell, eosinophil, and mast cell, inhibited IgE function via regulated immune cell response, and decreased pro-inflammatory factor release through involvement in the STAT3 related pathway. Based on these studies, several potential AR treatments emerged, as anti-IL-17-neutralizing antibodies, anti-IL-33 antibodies, and CC10 effectively inhibited inflammation, and probiotic NVP-1703 reduced rhinorrhea, nasal congestion, watery eyes, and sleep disturbance, though further research was necessary in order to comprehensively examine and compare the efficacy of these treatments. Understanding the role of Th17 and Treg could help researchers develop new drug that target specific messenger in signalling transduction pathways of Th17 and Treg cytokines that might augment or attenuate AR symptoms or immune response, giving rise to a probability of AR treatments with less adverse effects and stronger efficacy in the future.

1. Introduction

Allergic rhinitis (AR) affects over half billion people around the globe and about one half of population in developed countries. Some countries even have 50% of population with AR [9]. AR's symptoms, including sneezing, runny nose, sore throat, etc., can interfere with daily routines, and about 10%-40% of AR patients possess asthma, which has high mortality, as one of AR's severe complications. Pollen allergy is one major factor that triggers AR, others include air pollution, dust mite fecal particles, animal dander, etc. During spring and early summer, anemophilous flower and tree pollen could be easily inhaled. These pollens could stimulate antigen presenting cells (APCs) to directly cell-to-cell contact with T cells. The interactions of antigen-specific pMHC-TCR in the immune synapse might promote or suppress T cell differentiation. If T cell differentiates, mast cells bind to the IgE bodies, and when the same allergen is inhaled again, it will be able to cross-link to the allergen, releasing

pro-inflammatory mediators including histamine, prostaglandins, leukotrienes, and cytokines, giving rise to inflammatory symptoms [25].

T helper 17 cells (Th17) and Regulatory T cells (Treg) are important subsets of CD4+ T cells (Th0), also involved in acute respiratory distress, chronic obstructive pulmonary disease, etc. Interleukin 17 (IL-17) expressing Th17 is formed through Th0 differentiation under stimulation of Interleukin 6 (IL-6) and/or Interleukin 1 β (IL-1 β), along with Transforming Growth Factor Beta (TGF- β). In the absence of proinflammatory factors, when transcription factor forkhead box P3 (Foxp3) is further activated by SMAD2 and SMAD3, Th0 cells differentiate into Treg cells. Th17 cells mainly fight fungi and bacterial infections, and are related to inflammatory response. Th17 cells release IL-17 that modulates proinflammatory cytokines such as TNF- α and IL-1 β , induces other chemokines and prostaglandins, and recruits eosinophil, neutrophil and mast cell [20]. In contrast, Tregs promotes tolerogenic dendritic cell (DC) phenotypes, inhibiting the inflammatory phenotypes, and suppress Th2, Th17, and

*Corresponding author's e-mail: Linda13311207892@outlook.com

other cells contributing to inflammation. Tregs restricted inflammation mediated by Th1 and Th2, and regulate allergic inflammation by synthesizing IL-10 and TGF- β [8]. Other studies have indicated Treg's inhibition on other effective T cell, B cell, eosinophil, and mast cell response, and increased Treg population post administration of mesenchymal stem cell, which secretes IL-10 and TGF- β to inhibiting inflammation.

When stimulated by allergen, IL-17 producing Th17 cells release IL-17 A, IL-17 F, IL-21, and IL-22, which stimulate airway structural cells via regulating the expression of vascular endothelial growth factor (VEGF), in turn producing chemokines that attract neutrophils, resulting in an inflammatory immune response. IL-17 A and/or IL-17 F induces the release of TNF- α , IL-1 β , IL-6, and other proinflammatory factors by venous endothelial cell, airway and epithelial smooth muscle cell, and human bronchial fibroblast *in vitro*, and IL-17A led to increased VEGF transcription. Other studies have shown that IL-17A participated in eosinophil's recruitment into the mucosa by potentiating Th2 driven STAT6 activation. IL-22 could influence IFN- γ -induced expression of chemokine CXCL10 and in turn impact lymphocyte recruitment in AR. Though IL-21's role in AR has been controversial, recent studies have shown that IL-21 enhanced B cell differentiation into plasma cells which increased IgE production, contributing to AR. Therefore, IL-17 A, IL-17 F, and IL-22 are involved in AR pathology through multiple pathways and could influence other interleukins and cells that enhance AR symptoms. As illustrated in previous studies that Tregs produce anti-inflammatory cytokines and activate Foxp3 that could inhibit Th17 differentiation, most Tregs' role is to inhibit AR [18]. Tregs were important in airway immune homeostasis maintenance, and beside regulating Th17 cell and its interleukins, they control allergic inflammation by synthesizing IL-10, IL-35, and TGF- β , inhibiting Th2 polarization and IgE synthesis. Tregs also continuously express CTLA-4, which causes downregulation of APCs by interacting with their CD80/CD86. However, not all Tregs inhibit AR. Though most Tregs established and maintained tolerance to aeroallergens, limited CD4⁺ or CD8⁺ cell, ILC2s, and granulocyte proliferation, ST2⁺ Tregs increased GATA3, IL-5, and IL-13 production, elevating upper airway inflammation [16]. This article will examine the proinflammatory pathways of IL-17 and IL-22, including how they interact with other interleukins that could lead to upper airway cell response; potential Th17 inhibitors; and the anti-inflammatory pathways of Tregs that regulate Th17 cell response in AR.

2. Th17 cells and AR

Abundant evidences suggest the involvement of Th17 cell and its cytokines IL-17A, IL-17F, IL-21, IL-22 in AR pathology [2]. Examination of immature AR mouse model and 50 children cases confirmed that IL-17A, IL-17F and IL-33 level in nasal mucus were significantly higher in AR group, as compared with the control group. A correlation study of 88 AR patients shows a higher serum IL-17 level in AR patients than in the control group. Baumann and

others' study have shown an elevated eotaxin-3 and IL-17 level in late phase nasal allergic change, which might contribute to the enhanced AR severity [7]. Other research shows a remarkably higher serum IL-17 level and peripheral Th17 cell level in AR group compared with the control group, and the plasma protein production of Th17 associated cytokines IL-17, IL-6, and IL-23 is significantly increased in AR patients, which leads to enhanced inflammation and severity of AR [24]. Further studies suggest a significantly increased production of IL-17A and IL-22 in moderate/severe persistent AR patients, and the serum level of nasal mucosa IL-17A + and IL-22+ correlates with the nasal eosinophil count, suggesting increased eosinophil infiltration into nasal mucosa, limiting chronic inflammation and stimulating priming effect, in turn intensifying nasal hypersensitivity. These results demonstrate a positive relationship between Th17 and AR severity.

IL-17 induces neutrophil, macrophage production, basophil, mast cell, and eosinophil production and degranulation and B cell differentiation, leading to neutrophil and eosinophil recruitment in airway [14]. AR mechanism included a sensitization process where allergen-specific T cells were activated to stimulate allergen-specific IgE production, and a recent study found that IL-17A increased IgE plasma cell level and IgE production by directly acting on B cells. During the process, IL-17A effect via IL-17RA and IL-17RC subunits, and molecules in the process include signalling intermediates such as coordinating NF- κ B, Act1/TAK1/TRAF6, and JAK1-associated phosphatidylinositol-3-kinase signalling. It stimulates B cells and causes I κ B α degradation, followed by p50 translocation to B cell nucleus, and then NF- κ B binding to the promoter of AID, IFN regulatory factor 4, and ϵ GLT, and, eventually, NF- κ B and STAT6 were activated concurrently, and through cascade initiation, led to AID and ϵ GLT transcription, which is responsible for IgE class switch recombination. What's more, IL-17 induces CD34 human progenitors growth and differentiation into neutrophils, and activated airway smooth muscle cells to release eotaxin, an eosinophil-specific CC chemokine associated with eosinophil recruitment to inflammation site. Meng and others argued that IL-17A/F increased CXCL1, a neutrophil chemoattractant, and IL-8, which induces leukocyte migration. Amin and others suggest that IL-17 promoted eosinophils survival and degranulation in a Th2 skewed environment by inducing granulocyte-macrophage colony-stimulating factor (GM-CSF) production to prolong eosinophil survival, and in atopy IL-17 and eosinophil cationic protein (ECP) may augment nasal inflammation in AR patients. Shi and others' research shows IL-17 can recruit macrophages and is a survival factor for airway macrophages. IL-17 might also enhance fibroblasts' production of vascular endothelial growth factor (VEGF), and IL-17 and VEGF interaction is related to neutrophil infiltration [4].

IL-17 interact with other interleukins and Th cells to stimulate proinflammatory cytokine release, thus enhancing inflammation in AR [14]. And IL-17A enhanced IL-13's activation of intracellular signal transduction and STAT6 that upregulates GATA3 and

induces CD4+ cells differentiation to Th2 cells, and IL-17A/F can promote IL-1 β production, which might be associated with T lymphocyte and endothelial cell activation. Lv and others suggest that under AR condition, IL-6 and prostaglandin E2 (PGE2) production was induced by IL-17. IL-6 is a proinflammatory factor and PGE2 promotes Th2 development by inhibiting Th4 cytokines and increasing Th2 cytokines, and PGE2-EP4-cAMP signalling is speculated to inhibit Treg differentiation. Not only can IL-17 induce other interleukins and cells, other cells and biological molecules can also regulate IL-17 expression. In other allergic diseases such as asthma, competing endogenous RNA LncRNA-MEG3 inhibited miRNA-17 expression that directly targeted ROR γ t to suppress Th17 cells, leading to a higher Th17 level and contributing to Treg/Th17 axis imbalance [3]. Other studies show that inflammatory ILC2s could express IL-17 and ROR γ t high levels, which in turn promotes IL-17 production.

IL-17 increases IgE production and the release of inflammatory mediators such as prostaglandins, histamine, proinflammatory cytokines, and leukotrienes by its self or associated axis in AR. As shown by a positive correlation between sIgE and IL-17/23 serum levels, IL-17/23 axis may promote production of sIgE, in turn increasing sIgE binding with Fc receptor on mast cells and basophils, leading to basophils and mast cell degranulation upon re-exposure to the allergen, which results in the release of leukotriene, histamine, and neutrophil chemotactic factor acting on the nasal mucosa and causing airway smooth muscle tightening, vascular permeability increase, and enriched mucus secretion, which corresponds to AR features such as telangiectasias, enhanced vascular permeability, and elevated gland secretion [24]. What's more, IL-17A/F were able to trigger chemokine release from innate effector eosinophils, such as the proinflammatory chemokine CCL4 production of eosinophils, and IL-17F/23 combination could further stimulate eosinophil production of IL-1 β and TNF- α . Another way IL-17A/F contribute to inflammatory response is that they activate IL-33 transcription through IL17RC and activated ILC2 and Th2 cells to participate in allergic inflammation, which provided certain preventive pathological basis for allergic rhinitis in children. Wise and others' study have shown that in AR, IL-17 receptors induced, TNF- α , matrix metalloproteinase, IL-1, IL-8, and IL-6 in different cell types.

Beside IL-17, studies have shown an increased IL-23 level in AR patients, suggesting a relationship between IL-

23 and the severity of AR. More specifically, IL-23 is able to promote eosinophil infiltration in the airway. It can also enhance IL-17 production in ovalbumin (OVA) -induced AR [19]. Also, IL-23 can induce IL-36, which can in turn promote the Peripheral blood mononuclear cells differentiating Th17 cells and regulate P13K/AKT and ERK pathway to enhance Th17 inflammation, forming a positive feedback loop. According to M. EL-Aidy and others, the upregulation of Th2 cell-mediated airway inflammation happens in two phases, in which Th2 activation in the airways was promoted by IL-23. Based on these studies, IL-23 has a crucial role in AR inflammation response by enhancing neutrophil infiltration and Th2 mediated-airway inflammation, and forming positive feedback loop with Th17 cells. Thus, IL-23 enhances inflammatory response in AR through upregulation of Th2 and Th 17 inflammatory pathway and promotion of eosinophil infiltration. IL-23's effect on serum IgE level is unclear due to controversial results of experiments on serum IL-23 and IgE association. According to Manti and others, a positive correlation was observed between serum levels of IL-23 and IgE, while another study suggested non-significant negative correlation and no significant association [26].

Though clinical studies regarding IL-22 in AR is highly controversial, all illustrated a IL-22 level increase in patients with allergic airway diseases, and a clinical study of house dust mite induced AR mice model suggests that in nasal lavage and serum, higher level of IL-22 is positively related to IL-10 level, leading them to conclude an anti-inflammatory function of IL-22 that is supported by Al-Saeedi and others [1]. However, another study shows that serum IL-22 is positively associated with IL-10 yet negatively associated with nasal lavage IL-22, which might be explained by the immunosuppressive effect of IL-22 only in early stages of immune response. Furthermore, IL-17 and IL-22 increase with CCL20, resulting in neutrophilic inflammation in acute neutrophilic asthma mice model. And in inflammatory skin diseases, IL-22 leads to pro-inflammatory gene expression, and IL-22 and IL-22R α interaction induced T cell migration into skin lesions and the production of activation-regulated chemokine and thymus. Based on these studies, IL-22 could be a proinflammatory cytokine that also has anti-inflammatory effects, and there is speculation that its function depends on stages of immune response.

Figure 1 summarizes the relationship of Th17 and its cytokines IL-17, IL-23, and IL-22 to AR.

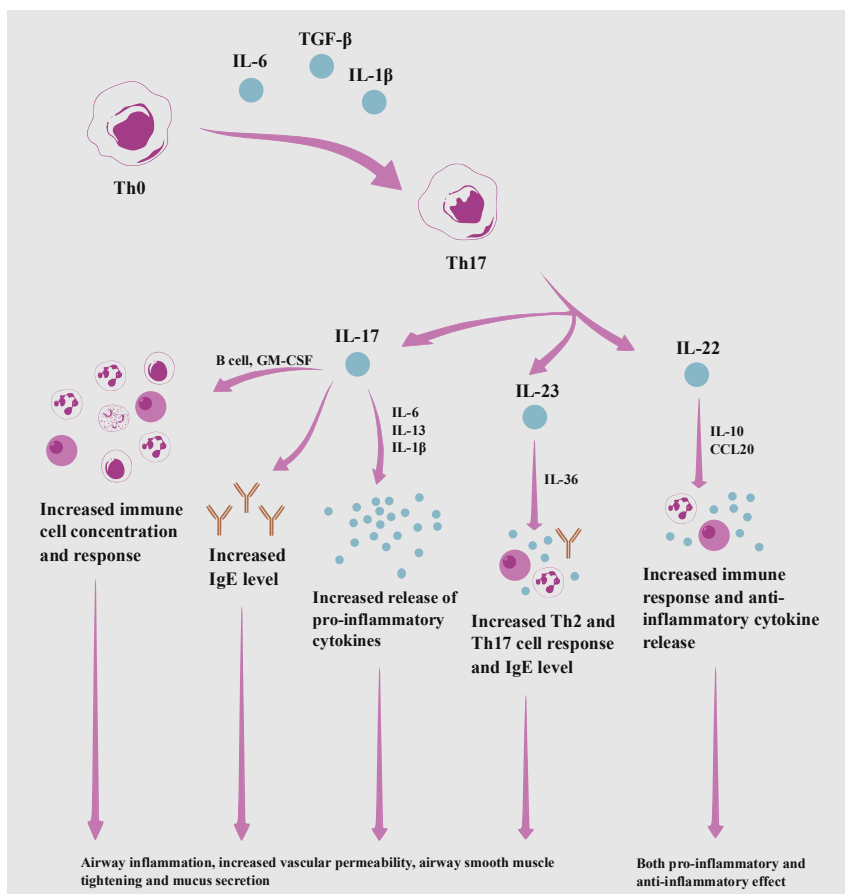


Fig. 1. Simplified graph showing the mechanism of Th17 in AR

3. Tregs and AR

Substantial studies suggested that Treg inhibits anti-inflammatory response and AR syndrome by producing anti-inflammatory cytokines such as IL-10, TGF-β, and IL-35 [12]. Compared with the control group, snoring, sneezing, and nasal itching scores were significantly higher in AR mice, while the IL-10 intervention group exhibited lower score compared with the AR group. Other studies suggested a lower peripheral CD4+CD25+Foxp3+Tregs level in AR patients than normal controls. In OVA induced recombinant AR mice model, the elevated eosinophils and mast cell level was remarkably reduced by recombinant mouse IL-10 treatment. Gu and others' study in OVA induced mice shown a reduced Treg proportion and Foxp3 mRNA level compared to the controls. Furthermore, a study on 25 AR children and 20 healthy children illustrated a lower Treg percentage and TGF-β and IL-10 expression in the AR group than the control group, suggesting a decrease in both Treg number and function in AR. A study including 20 AR patients illustrated reduced blood stream CD4+CD25+FoxP3+ Tregs and a strong correlation between Treg level and the release of IL-35, which in turn promoted IL-35 and IL-10 secretion by increasing Treg and Breg conversion. IL-35 is a newly identified anti-inflammatory cytokine that inhibits eosinophil infiltration.

Tregs regulate effective T cell activity, and TGF-β and IL-10 play major role in AR. One way is through

regulating other immune cells. Tregs inhibited effective T cell, mast cell, B cell, and eosinophil response, and increased Treg population posted administration of mesenchymal stem cell, which secretes TGF-β and IL-10 to inhibiting inflammation. IL-10 also reduces IL-12, INF-γ, and IL-2 production, thus directly inhibiting Th1 cell differentiation. Other studies suggest a suppressive function of TGF-β and IL-10 on Group 2 Innate lymphoid cells, which induced Th2 cytokine release, and epidermal growth factor Amphiregulin (AREG) that participated in the reprogramming of eosinophils to the inflammatory site [10]. TGF-β and IL-10 downregulates eotaxin production to suppress OVA-induced airway eosinophil recruitment [15]. TGF-β stimulates Foxp3 expression in a paracrine feedback loop to promote Th0 conversion to Tregs including CD4CD25 Tregs that inhibit allergic airway disease, and inhibits macrophage proliferation and function, antibody secretion by B cells, and FcεRI expression in mast cells. The crosslink of FcεRI with multivalent antigen is an essential step in the induction of immediate hypersensitivity reactions and is associated with prolonged inflammation [17]. In conclusion, TGF-β and IL-10 release through Tregs inhibit eosinophil recruitment, function of macrophage, mast cell, and B cell, Th2 cytokine production, and Th1 cell differentiation.

TGF-β and IL-10 inhibit IgE function. Expression of IL-10 inhibits the expression of IgE receptor in mast cells, therefore inhibiting IgE function. IL-10 producing Tregs promote plasma cell development and induce peripheral blood mononuclear cells, including B cells, to produce

IgG4, which is competitive with IgE in binding allergen. Also, IL-10 is shown to downregulate IgE induced by IL-4, and CD8+ Tregs suppress CD4+ T lymphocyte proliferation and IL-4, which induce IgE class switch. According to Park and others, TGF- β directly diminish serum IgE function by disrupting B cell maturation in atopic dermatitis, and indirectly reduce IgE expression by inhibiting mast cell response induced by IL-33 and STAT3 and ERK signalling pathways, which suppressed TNF- α production, and suppressing mast cell responses to IgE. Enhanced TGF- β signalling is associated with the anti-allergen effect of CpG-ODN, which induce Id2/E2A complexes in LPS/IL-4-stimulated B cells to down regulate IgE production and inhibit IgE class switch recombination [22]. Based on these studies, Treg cytokines inhibit inflammation in AR by regulating other interleukins and via signal transduction pathways, or by acting on T lymphocytes and B cells.

Moreover, the release of proinflammatory factors was inhibited by TGF- β , IL-35, and IL-10. The junction ligand-receptor of IL-10R1 and IL-10R2 triggers signal transduction by phosphorylating with proteins that induced signal transducer and STAT3, which further

activated the suppressor transcription of cytokine signalling 3 and some pre-apoptotic genes, and suppressed pro-inflammatory cytokines TNF- α , IL-6, and IL-1 β expression. Other studies identified IL-10 as a functional proliferator in mast cells, which expressed IL-10R, and IL-10R-dependent signalling results in STAT3-mediated expression of anti-inflammatory genes through JAK-STAT pathway activation. TGF- β /SMAD pathway promoted IL-4 release and decreases IFN- γ expression, thus inhibiting inflammatory response. Tregs also functioned to inhibit CD8+ T cell response by interacting with dendritic cells and depleting effector T cell function consequently. Based on Yokota and others' study, IL-35 notably increased IL-10, IL-2, and IL-27 production, and reduced pro-inflammatory cytokines TNF- α , IL-17, IL-4, IL-5, and IL-13 release. IL-35 was also inhibited IL-17 release and IL-4 secretion in asthma patients. Therefore, Treg cytokines TGF- β , IL-10, and IL-35 directly or indirectly suppressed pro-inflammatory cytokine release and increased anti-inflammatory cytokine production.

Figure 2 represents the association of IL-10 and TGF- β release from Treg with AR symptoms.

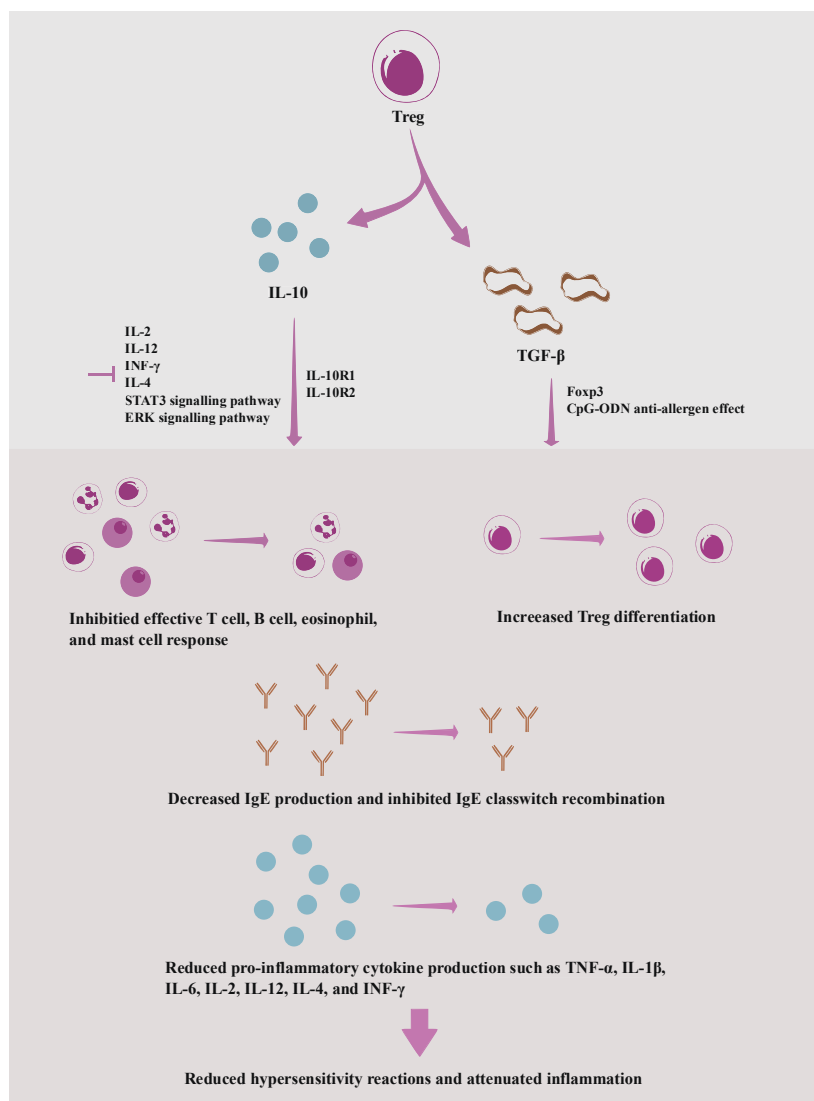


Fig. 2. Simplified graph showing the mechanism of Treg in AR

4. Treatments

Persistent research led to pharmacotherapy development of AR. Common drug treatments include intranasal, oral, and injectable corticosteroids, intranasal decongestants, intranasal or oral antihistamines, intranasal and oral cromolyn, intranasal anticholinergics, biologics such as omalizumab, and leukotriene receptor antagonist. These drugs target IgE, mast cell, eosinophils, and other immune cells. However, adverse effects were still existed.

Oral Corticosteroid could moderate sneezing. The second-generation anti-histamine drugs could address sneezing, g, rhinorrhea, nasal obstruction and itching, and eye symptoms, while its adverse effects included adrenocortical insufficiency, infection, diabetes, peptic ulcer, glaucoma, and moon face nasal blockage, and watery rhinorrhea, but would cause gastrointestinal and hepatic disorders, dry mouth, sleepiness, myocardopathy, and anticholinergic effects. Intranasal decongestants were effective in nasal obstruction treatments, but could cause agitation, sleeplessness, headache, and palpitations. Cromolyn could inhibit histamine release and mast cell degranulation, but could cause epistaxis, nasal irritation, and sneezing, and required three to four times of injection a day. Anticholinergics were effective in treating rhinorrhea, congestion, and sneezing, but could brought up adverse effects such as nasal mucosa dryness, epistaxis, and headache. Some ubiquitous biologics targeted the high-affinity IgE Fc receptor, epithelial cell-derived cytokine pathway, IL-4/IL-13, and IL-5, and several side effects of biologics were increased blood creatine phosphokinase, localized injection site reactions, anaphylaxis, myalgia, and oropharyngeal pain. Leukotriene receptor antagonists inhibit leukotrienes, thereby inhibiting bronchoconstriction, mucus formation, nasal congestion, and eosinophil influx, but could cause headaches, influenza infection, abdominal pain, depression, cough, and dyspepsia [21]. Based on these study results, the recent, or most often used AR treatment still possessed many adverse effects, new studies upon Th17 and Tregs might assist in future development of drugs with less adverse effects and more efficiency.

Recent decades, there were increasing experimental results suggesting potential treatment focusing on Th17 and Tregs. Gu and others experimented anti-IL-17-neutralizing antibodies in AR mice model, showing a reduced sneezing, eosinophil count, and neutrophil percentage, decreased inflammatory mediator in nasal mucosa, inhibited Th2, Th17 production, and increase Treg response. Kim and others examined the role of anti-IL-33 monoclonal antibody in AR murine model. They injected the anti-IL 33 antibody into OVA mice, and found reduced serum levels of IgE, eosinophilic infiltration into nasal mucosa, skin denudation and nose scratching, and IL-13, IL-4, and IL-5 in the bronchoalveolar lavage fluid than the controls. CC10 suppressed Th17 cell depolarization by expressing Th cell polarizing cytokines and costimulatory molecules to regulate DC function, inhibited the local expression of CCL20, a chemokine of Th17, thus suppressing inflammation, and relived nasal

mucosa injuries. A study done on C57 AR mice model illustrates that Notch2 directly promoted CD4+ T cell differentiation into Tregs, and Notch2 overexpression can reduce allergic inflammation in nasal mucosa. In addition, Androgen Receptor signalling can limit epithelial cells' allergen-induced IL-33 production and Tregs' ST2 expression, therefore increasing Tregs' inhibitive function on airway inflammation. α -Lipoic acid treatment of OVA mouse model up-regulated IL-10 and Foxp-3, and down-regulated IL-17, TGF- β , ROR γ t, STAT3, and p-STAT3 production in nasal lavage fluid compared to the naïve group. Gallic acid (GA) and Chlorogenic acid (CGA) could down-regulate IL-17 and ROR γ t level in nasal lavage fluid of AR mice model [13]. And in AR mice, water-extracted *Lonicera japonica* polysaccharide (WLJP) could improve rubbing and sneezing by regulating the NLRP3-IL-17 signalling axis between nasal mucosa and gut [6]. Other studies on asthma patients' IL-22 and IL-17 positive T cells suggested that miR-323-3p suppressed IL-22 production and TGF- β pathway in T cells through a negative feedback loop, which might be a target for anti-inflammatory treatment. Quercetin attenuated OVA-induced rubbing and sneezing, and quercetin treatment increased the serum percentage of Tregs, IL-10, and Foxp3, and suppressed the serum level of Th17, IL-17, and TGF- β . Kang and others' study on AR patients illustrated that probiotic NVP-1703, mixture of *Bifidobacterium longum* and *Lactobacillus plantarum*, could increase serum IL-10 level, IL-10/IL-13 ratio, and IL-10/IL-4 ratio, and therefore effectively reduce nasal congestion, rhinorrhea, sleep disturbance, and watery eyes of perennial AR. What's more, in comparison with the AR group, nasal rubs and sneezes were significantly decreased via *Lonicera japonica* polysaccharide (LJP) treatment, which significantly reduced serum TNF- α , IL-1 β , IL-17, and IgE concentration, and though not significantly, reduced serum IL-23 level in AR mice model [5]. With increasing understanding and research on Th17 and Treg's role in AR, treatment targeting Th17 and Treg cytokines were likely to develop and improve.

However, most of these treatments still remained preliminary. The anti-IL-17-neutralizing antibody treatment's influence on Th1 and T-bet mRNA level was not significant. Though compelling evidence suggested the possibility for anti-IL-33 treatment, its exact mechanism is not thoroughly examined. Treatment with CC10 also required further study on its putative surface receptor and interaction with DC. Notch2 overexpression treatment had controversial results, since another study illustrated Notch signal pathway promoting Th2 response in allergic airway inflammation via lymph node egress, and the effect of Notch required careful examination. Besides the several complex pathways Androgen Receptor involved, its mechanism to attenuate IL-33 production was not fully understood. And the effect of α -Lipoic acid treatment was controversial, in that it might elevate OVA-specific IgE at the same time of countering inflammation. Though down-regulating several pro-inflammatory cytokines, GA may up-regulate Th1 immune response, and whether high dose of CGA administration results in greater effect or becomes toxic to human needed further research [11]. The mechanism for

WLJP, a macromolecule of 23 kDa, to enter cells could be complex, and the assembly and activation of NLRP3 inflammasome and interaction between WLJP and NLRP3 required further research [23]. What's more, in the case that IL-22's effect was controversial and less studied in AR, targeting miR-323-3p to regulate IL-22 expression and AR symptoms could be ambiguous and difficult. The probiotic NVP-1703 treatment also needed further study

to determine whether its effect surpassed current treatments, or has long-term effects for AR. In addition, the complex signalling pathways of quercetin required further study. And the LJP needed to be isolated from flowers and then separate and purified to clarify the main active ingredients or study their structure-activity relationships in order to be developed as AR treatment.

Table 1. Summarization of Th17/Treg targeted AR treatments

Treatment	Mechanism	Effect	Reference
Anti-IL-17-neutralizing antibodies	Inhibited Th2, Th17 production, increase Treg response, decreased eosinophil count and neutrophil percentage, no significant influence on Th1 and T-bet mRNA level	Reduced sneezing and attenuated inflammation	Gu et al., 2017
Anti-IL-33 monoclonal antibody	Decreased total serum IgE level, eosinophilic infiltration, and IL-4, IL-5, and IL-13 in the bronchoalveolar lavage fluid, exact mechanism unclear	Reduced nose scratching and skin denudation	Kim et al., 2012
CC10	Inhibited Th17 cell depolarization and local expression, putative surface receptor and interaction with DC required further study	Attenuated inflammation and relived nasal mucosa injuries	Liu et al., 2015
Notch2 overexpression	Promoted CD4+ T cell differentiation into Tregs, had controversial results and required careful examination	Attenuated inflammation in nasal mucus	Jiao et al., 2021 Tindemans et al., 2020
Androgen Receptor signaling	Limited epithelial cell IL-33 production and Tregs' ST2 expression, mechanism to attenuate IL-33 production not fully understood	Attenuated inflammation	Gandhi et al., 2022
A-Lipoic acid	Up-regulated IL-10 and Foxp-3, down-regulated IL-17, TGF- β , ROR γ t, STAT3, and p-STAT3 production in nasal lavage fluid, controversial effect	Attenuated inflammation	Van Nguyen et al., 2020
GA and CGA	Down-regulated ROR γ t and IL-17 level, but GA may up-regulate Th1 immune response, toxicity of high dose CGA required further study	Attenuated inflammation	Fan et al., 2019 Shi et al., 2020 Dong et al., 2020
WLJP	Regulation of the NLRP3-IL-17 signaling axis, required further research in WLJP and NLRP3 interaction	Improved behavior of rubs and sneezes	Bai et al., 2022 Huang et al., 2020
miR-323-3p	Suppressed TGF- β pathway and IL-22 production in T cells through a negative feedback loop, effect could be ambiguous	Attenuated inflammation	Kärner et al., 2017
Quercetin	Increased Tregs, IL-10, and Foxp3 percentage, suppressed Th17, IL-17, and TGF- β level in serum, exact signaling pathway required further study	Reduced rubbing and sneezing	Ke et al., 2023
Probiotic NVP-1703	Increased serum IL-10 level, IL-10/IL-4 ratio, and IL-10/IL-13 ratio, efficacy and long-term effect required further study	Reduced rhinorrhea, nasal congestion, watery eyes, and sleep disturbances	Kang et al., 2020
LJP	Reduced serum IgE, TNF- α , IL-1 β , and IL-17 concentration, main active ingredients and structure-activity relationships unclear	Reduced nasal rubbing and sneezing	Bai et al., 2020

5. Conclusion and outlook

AR influenced a large portion of people worldwide and it could be triggered by multiple factors such as pollen and dust mites. For decades researchers examined the mechanism underlying AR, and Th1 and Th2 cells were believed to be involved, and, were thoroughly researched consequently. However, recent studies presented that Th17 and Treg also played crucial role in AR pathogenesis, yet they were sometimes ignored by scientists. For this reason, Th17 and Treg's association with AR were discussed in this passage, attempting to provide an overall understanding of AR mechanism. The relationship of Th17 and AR was first examined and expanded based on

different interleukins, and the discussion of IL-17 was separated based on its different means of effect. Basically, Th17 played a pro-inflammatory role through its release of pro-inflammatory cytokines, mainly IL-17, which interacted with other immune cells and cytokines to elevate pro-inflammatory cytokine production, immune cell response, and IgE level, contributing to airway inflammation, airway smooth muscle tightening, increased vascular permeability, and mucus secretion. Then the anti-inflammatory role of Tregs were analysed. Treg cytokine TGF- β and IL-10 participated in multiple signalling transduction pathways to inhibit pro-inflammatory cytokine release, attenuate immune cell response, and reduce IgE level, resulting in decreased hypersensitivity reactions and attenuated inflammation of AR. Though IL-17, IL-10, and TGF- β played the main

role in the pro-inflammatory and anti-inflammatory effect of Th17 or Tregs, other Th17 and Treg cytokines were also mentioned.

Understanding how Th17 and Treg participated in AR could promote AR treatment development. The last portion of this passage compared several prevailing AR treatments and offered insights into potential Th17 and Treg related AR drug development. The prevailing AR treatments exhibited adverse effects and could have been expensive or troublesome to continuously inject. The discovery of Th17 and Treg pathways in AR provided new targets for AR drug development, which might be inhibiting Th17 cell response or increasing Treg response through regulation of their transcription factors, suppressing IgE production via interaction with Th17 or Treg cytokines, or participating in Th17 or Treg signalling pathways to regulate other immune cell responses. Proposition of potential AR treatments were not rare, but little of these studies examined thoroughly the mechanism underlying the treatment's effect, which symptom of AR could be cured for how long or how many times of injection, or the efficacy and adverse effects of these treatments compared to the prevailing drugs. Therefore, this passage offered perspectives into future drug development to some extent, but were insufficient in pointing out the efficacy and competence of these potential AR treatment as compared with the prevailing treatments. Further research on Th17 and Treg pathways in AR and the practicality or efficacy of potential AR treatment was required to help scientists develop AR treatments with better efficacy and less adverse effects.

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