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Th17 response and its regulation in inflammatory upper airway diseases

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Running Head: Th17 response in AR and CRS

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Summary

Allergic rhinitis (AR) and chronic rhinosinusitis (CRS) are two widely prevalent inflammatory diseases in the upper airways. T-cell immunity has been suggested to play an important pathogenic role in many chronic inflammatory diseases including inflammatory upper airway diseases. Inappropriate CD4⁺ T cell responses, especially the dysregulation of the Th1/Th2 balance leading to excessive Th1 or Th2 cell activation, have been associated with allergic rhinitis and chronic rhinosinusitis. Nevertheless, recent studies suggest that IL-17A and IL-17A-producing Th17 cell subset, a distinct pro-inflammatory CD4⁺T cell lineage, may also play an important role in the pathophysiology of inflammatory upper airway diseases. Th17 cells may promote both eosinophilic and neutrophilic inflammation in AR and CRS. In addition, a few, but accumulating evidence shows that the Th17 responses can be tightly regulated by endogenous and exogenous substances in the context of AR and CRS. This review discusses recent advances in our understanding of the expression and

function of the Th17 response and its regulation in inflammatory upper airway diseases, and the perspective for future investigation and clinical utility.

Introduction

Allergic rhinitis (AR) and chronic rhinosinusitis (CRS) are two widely prevalent inflammatory diseases in the upper airways. They are characterized by exaggerated and/or prolonged inflammation and immune responses in local mucosa. CD4⁺ T helper (Th) cells play a critical role in orchestrating local mucosal immune responses. Our understanding of the immunopathology of many chronic inflammatory diseases has been transformed by advances in basic studies of Th cell biology, especially the propositions of distinct subsets [1]. Over the past 20 years, the role of Th1 and Th2 cells in the inflammatory upper airway diseases has been extensively studied. For example, dysregulation of the Th1/Th2 balance may lead to excessive Th2 cell activation, subsequently resulting in induction of AR [2-4]. However, the interplay of different immune cells, cytokines, chemokines, and further mediators in inflammatory upper airway diseases is much more complex than a simple Th1/Th2 imbalance would explain. In recent years, the classic paradigm of Th1/Th2 cell-mediated immunity has been evolved to include a novel Th cell subset expressing IL-17, named as Th17 cell, which appears to be involved in a number of immune-mediated diseases, including inflammatory bowel diseases, asthma, and also AR and CRS [1]. In addition, a few, but accumulating, evidence suggest that the Th17 responses in upper airways can be tightly regulated by various endogenous and exogenous substances. In this review, we summarize current knowledge regarding the role of Th17 response and its regulation in inflammatory

upper airway diseases, and the perspective for future investigation and clinical utility.

The biology of Th17 cells

CD4⁺Th cells can be categorized into different subsets based on the cytokine profiles that they produce and the immune responses that they orchestrate. Initially, two Th cell subsets, Th1 and Th2 cell, have been described. Under the instruction of polarizing cytokine IL-12, naïve CD4⁺T cells differentiate into Th1 cells that are governed by transcription factor T-bet and are able to produce IFN- γ as the signature cytokine. Th1 cells have a significant role in promoting immune responses that are critical in defense against intracellular pathogens [5]. In contrast, Th2 cells controlled by transcription factor GATA-3 produce cytokines typically including IL-4, IL-5, and IL-13 and stir humoral immune responses that are important in driving resistance to extracellular parasites, such as helminths [6, 7]. The Th1/Th2 balance has been considered to be important for homeostatic maintenance of immune system. Dysregulation of Th1/Th2 balance leads to excessive Th1 cell or Th2 cell activation, resulting in the development of autoimmune or allergic diseases, respectively [8]. Nevertheless, in recent years, the identification of CD4⁺CD25⁺ regulatory T cells (Tregs) and Th17 cell lineage provides new insight into the cellular and molecular mechanisms involved in immune responses and related diseases, and leads to the revision of the classic Th1/Th2 paradigm in such settings [8, 9]. Tregs have high expression of CD25 and low surface level of CD127 in addition to high level of transcriptional factor forkhead box P3 (Foxp3) [9]. Tregs are considered key regulators to prevent or limit effector immune responses against inner and external insults [9, 10]. The peripheral Treg pool is composed of naturally arising

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Tregs that develop in the thymus and inducible Tregs that are converted from conventional CD4⁺ T cells in the periphery [10, 11]. Tregs may exert their suppressor/regulatory activity through the mechanism of immunosuppressive cytokine (TGF- β , IL-10) induction or cell contact although the definitive mechanisms remain to be characterized [10, 11]. In contrast, Th17 cells have a crucial role in the induction of immune-related tissue injury and are characterized by the predominant production of IL-17A, IL-17F, IL-6, TNF- α , and IL-22 [12]. In murine models, IL-1 and TGF- β , in combination with IL-6, have been identified to drive the differentiation of Th17 cells and IL-23 has been found to amplify and stabilize Th17 cells [13]. Although the exact roles of these cytokines in the differentiation of human Th17 cells remain debated, they, alone or in combination, are capable of inducing differentiation of human Th17 cells [13, 14]. In addition, it is found that STAT3 and ROR γ t are key transcription factors for the generation of Th17 cells [13, 14]. Th17 cells and Tregs seem to be dichotomously related in that TGF- β induces Foxp3 expression in naïve T cells, but TGF- β and IL-6 together drive the generation of pathogenic Th17 cells from naïve T cells [15]. Moreover, Th17 cells are relatively unstable with regarding to their cytokine producing phenotypes compared to Th1 and Th2 cells. Cells polarized in Th17 cell conditions for as long as 3 weeks can produce INF- γ and IL-4 in the presence of IL-12 or IL-4, respectively [16]. Under homeostatic or inflammatory conditions, IL-17⁺INF- γ ⁺ double-producer cells are easily detected *in vivo* [17]. Th17 to Th1 conversions have been reported in animal model of colitis, ocular inflammation, and diabetes, indicating considerable plasticity of Th17 cells [18]. Although IL-17 can also be produced by other immune cells such as macrophages, B cells, NKT cells, innate lymphoid cells, and CD8⁺ T cells, IL-17A and IL-17F are expressed

most abundantly by Th17 cells [13, 14]. IL-17A and IL-17F have critical roles in various immune responses such as host defense against pathogens and autoimmune conditions. IL-17A is more frequently involved in the development of autoimmunity, inflammation and tumors, and in host defense against bacterial and fungal infections, whereas IL-17F has a predominant role in mucosal host defense [14]. IL-17RA is the first to be described as the receptor for IL-17A, and subsequently, another receptor subunit, IL-17RC, has been identified [13, 14]. Both receptor subunits can mediate the response to IL-17A [13, 14]. The IL-17RA/IL-17RC complex also functions as a signaling receptor for IL-17F. The activation of IL-17RA/IL-17RC complex in response to IL-17A and IL-17F may lead to the activation of the downstream signaling pathways involving the adaptor protein, Act1, mitogen-activated protein kinase (MAPK) including extracellular signal-regulated kinases (ERK) and the p38 kinase, and transcriptional factor NF- κ B [13, 14]. In addition, other transcription factors, such as activator protein 1 and CCAAT/enhancer binding protein δ may also be involved in IL-17/IL-17RA/IL-17RC signaling pathway [14]. The activation of these pathways finally result in secretion of a number of cytokines and mediators, such as IL-6, TGF- β , TNF- α , CXCL1, and CXCL8, thus promoting pro-inflammatory and remodeling events [13,14].

When it comes to the role of Th17 cells in the specific diseases, it takes a long way for them to come to the spotlight of the researchers. Limitations of the Th1/Th2 paradigm in the setting of the experimental autoimmune encephalomyelitis model of multiple sclerosis has provided the first clue to the possibility that novel Th17 cells, beyond Th1 and Th2 subsets, could be contributing to the onset and progression of autoimmune disorders [19]. In the past few years, dysregulated Th17 responses have been implicated in the pathophysiology of a

number of immune and inflammatory disorders, including rheumatoid arthritis, inflammatory bowel diseases, psoriasis, asthma, and chronic obstructive pulmonary disease (COPD) [20-23]. The first line of evidence of the involvement of Th17 cells in airway diseases comes from the study of asthma and COPD. The elevated IL-17A expression in asthma and COPD can enhance recruitment of neutrophils to the site of airway inflammation through the induction of CXCL1, CXCL2, and CXCL8 production from human epithelial cells, fibroblasts, and vascular endothelial cells [24]. In addition, IL-17A can induce the expression of mucin genes in human bronchial epithelial cells and promote the migration of human airway smooth muscle cells, thus facilitate the airway remodeling [25, 26]. As with other immunological responses, there must be a regulation network set in place in order to ensure the immune homeostasis and prevent aberrant Th17 responses. A growing number of regulators have been implicated in the modulation of Th17 responses in the context of specific inflammatory conditions [27-29]. For example, osteopontin and thymic stromal lymphopoietin have been shown to regulate the differentiation of Th17 cells in inflammatory bowel diseases and rheumatoid arthritis [27, 29]. In the inflammatory lower airway diseases, resolving E1, simvastatin, dopamine, complement factor C5a, and peptidoglycan recognition protein 1 have been identified as regulators of Th17 responses [30-34]. The inflammatory upper and lower airway diseases are intimately connected with each other and share a lot of cellular and molecular pathogenic pathways [35]. As the studies on Th17 cells spur out for asthma and COPD, more and more attentions have also been paid on the involvement of Th17 cells in inflammatory upper airway diseases. Emerging evidence underscores an important role of Th17 cell subset and its regulation in the inflammatory upper airway

diseases including AR and CRS.

Th17 responses in AR

AR has been considered to be initiated by the skewed Th2 responses classically. Nevertheless, recent studies have demonstrated up-regulated Th17 responses in both peripheral blood and local mucosa in AR patients. Increased IL-17A level and Th17 cell number in peripheral blood have been found in patients with AR and IL-17 levels in serum correlated with severities of symptoms and peripheral eosinophilic counts in AR patients [4, 36]. IL-17A and IL-22 mRNA expression levels have been shown to be increased in peripheral blood mononuclear cells from allergic rhinitic and asthmatic pediatric patients [37]. The IL-17 levels in serum increased markedly in AR patients after inhaled antigen challenge [38]. We showed enhanced infiltration of Th17 cells accompanied by up-regulated expression of IL-23, the Th17 cell expansion cytokine, and CCL20, the Th17 cell chemoattractant, in diseased nasal mucosa in AR patients compared with those seen in controls [39]. In addition, single nucleotide polymorphisms (SNPs) of IL-17A and IL-17F have been demonstrated to be associated with AR and comorbid asthma in Chinese population [40].

Animal studies suggest that Th17 pathway can contribute to the development of allergic inflammation via promoting the production of pro-inflammatory and Th2 cytokines and facilitating eosinophil recruitment into local mucosa in the setting of AR [36, 39]. Increased IL-17A levels and Th17 cell frequencies have been found in nasal lavage fluid in AR murine model induced by ovalbumin or house dust mite [36, 39]. After establishment of AR with ovalbumin challenge, IL-17A-deficient mice presented a significant suppression in symptom

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severity, serum IgE level, local eosinophil count, mast cell function, and IL-5 level in nasal lavage fluid compared with those seen in wild-type mice [36]. Similarly, exogenous anti-IL-17 and anti-IL-23 antibodies were able to reduce the symptom severity, Th2 response, and serum IgE level in AR mice induced by ovalbumin [41]. Primarily, IL-17A is suggested to contribute to asthma through its capacity to enhance recruitment of neutrophils to the site of airway inflammation [42]. Taking the advantage of adoptive transfer experiment with Th17 cells, we demonstrated that Th17 cells can promote not only neutrophil but also eosinophil recruitment into nasal mucosa in an AR murine model induced by ovalbumin [39]. The enhanced recruitment of eosinophils may result from the up-regulated expression of eotaxin-1 and eotaxin-2 expression in nasal mucosa after Th17 cell transfer [39]. These findings are consistent with those found in allergic lower airway inflammation and highlight the importance of Th17 cells in both neutrophilic and eosinophilic inflammation in airway diseases [39]. However, the mechanisms underlying the induction of eotaxin in airways by Th17 cells remain to be explored.

Glucocorticoids are effective in inhibiting Th2-driven diseases, whereas they may not be able to abrogate Th17 cell-driven inflammation. IL-17A has been suggested to play a role in glucocorticoids resistance [42]. In AR patients, increased MUC5AC expression is associated with IL-17 levels [43]. Glucocorticoids have been found to be able to inhibit MUC5AC mRNA expression in human nasal epithelial cells induced by IL-13 but not for that induced by IL-17A [43]. Moreover, IL-17A but not IL-13 promoted glucocorticoid receptor beta mRNA expression in human nasal epithelial cells, indicating that IL-17A may contribute to glucocorticoid resistance through a mechanism involving the up-regulation of glucocorticoid

receptor beta expression [43]. Therefore, beyond Th1/Th2 paradigm, these studies in humans and animals highlight an involvement of novel Th17 responses in the pathogenesis of AR.

Regulation of Th17 responses in AR

Despite the progress in our understanding of the pathophysiological functions of Th17 cells in inflammatory diseases, the regulation of Th17 responses remains relatively poorly understood [44]. The researches on the regulation of Th17 responses in AR are quite limited and the underlying mechanisms have not been thoroughly studied. However, these limited studies indicate that the Th17 responses may be regulated by endogenous molecules, drugs, steroids, and bacterial products in the setting of AR (Fig. 1).

CC10 and Th17 responses

Clara cell 10-kDa protein (CC10) is an anti-inflammatory and immunomodulatory protein secreted by the epithelial lining of the lung and nose [45]. CC10 has been shown to antagonize the activity of secretory phospholipase A2 and diminish inflammatory cell chemotaxis [45]. CC10 expression is downregulated locally in patients with allergic airway diseases, including AR and asthma [45]. Although CC10 has previously been demonstrated to suppress Th2 responses, our recent study has shown that CC10 can also attenuate Th17 responses in the context of AR. CC10 had no direct effect on in vitro Th17 cell differentiation, but it was able to inhibit Th17 cell polarization through modulation of dendritic cell (DC) function in terms of costimulatory molecule and Th cell polarizing cytokine expression [39]. CC10 could also inhibit the local expression of Th17 cell chemokine, CCL20 [39].

Nevertheless, currently, the putative surface receptor of CC10 remains enigmatic; therefore the biological signaling pathway underlying the effect of CC10 on DCs waits for further investigation. CC10 is relatively small, resistant to proteases, and stable to extremes of heat and pH and can be produced by recombinant methods. These characteristics make CC10 an excellent candidate for clinical development to target Th2 and Th17 pathway for the treatment of allergic airway diseases.

Inhaled corticosteroids and Th17 responses

In vitro study showed that steroid could not affect the production of IL-17A and IL-22 by Th17 cells [46]. Qu et al found that one-year intranasal glucocorticoid treatment could not decrease the ratio of Th17 cells and the mRNA expression of ROR γ t in peripheral blood mononuclear cells, and the serum levels of IL-6, IL-17, and IL-23 [47]. Interestingly, a recent report found that although budesonide or formoterol alone did not affect the intracellular levels of IL-17A, ROR γ t, and Foxp3 expression in cultured T cells from children with moderate asthma and AR, the combination of budesonide and formoterol could significantly reduce the intracellular levels of IL-17A and ROR γ t, whereas increase the intracellular levels of Foxp3, in cultured T cells [48]. Moreover, IL-17A levels and Th17 cell frequencies in plasma and sputum supernatants were significantly reduced in children with moderate asthma and AR after 12-week combination treatment of budesonide and formoterol [48], suggesting that combination of budesonide and formoterol may restore the balance of Tregs/Th17 cells in asthma and AR [48]. Glucocorticoids have been shown to increase β 2 receptor expression in epithelial cells, mast cells and smooth muscle cells [48], therefore, it is possible that

glucocorticoids may promote the anti-inflammatory activity of long-acting β -agonist and lead to the suppression of Th17 response. However, this hypothesis needs further validation.

β -1, 4-mannobiose and Th17 responses

The β -1,4-mannobiose (MNB) is a rare sugar in nature and its biological function has not been completely revealed [49]. MNB possesses prebiotic activity. It has been shown that prebiotics are able to stimulate the growth of particular bacterial species and improve host health. Oligosaccharides with prebiotic activity have been demonstrated to suppress cow milk allergy in mice through inducing Tregs [49, 50]. MNB can directly stimulate innate immune system as a TLR4 agonist and induce tolerance to TLR2 and TLR4 agonists, reducing TNF- α production [49]. In a dextran sodium sulfate-induced porcine model of intestinal inflammation, it has been demonstrated that mannanase-hydrolyzed copra meal containing 67.8% MNB could decrease the IL-17 mRNA expression in ileal mucosa [51]. Yang C et al have discovered that MNB oral administration could significantly decrease sneezing frequency in a mouse model of intranasally-induced pollen allergy [50]. Moreover, MNB oral administration could inhibit IL-4 and IL-17A secretion, whereas promote TGF- β and IL-10 secretion from spleen cells [50]. In addition, MNB could inhibit the activation of a rat mast cell line, RBL-2H3 cells, as reflected by a decrease in histamine secretion, intracellular Ca^{2+} concentration, and Fc ϵ RI mRNA expression [50]. These results demonstrated that MNB is a potential therapeutic nutritional supplement candidate for the treatment of nasal pollen allergy through targeting Th2/Th17/Treg responses; however, the effect of MNB on Th17 responses needs to be confirmed in AR patients in future.

Antidepressants and Th17 responses

AR commonly progresses to chronic and persistent condition, with depression as one of its comorbidities [52, 53]. The importance of treating the depression in AR patients has been increasingly recognized [52, 53]. Desipramine is a representative of tricyclic antidepressants [53]. Interestingly, a recent study found that desipramine also had an anti-allergic action. It was found that oral administration of desipramine could relieve the nasal symptoms of AR mice induced by ovalbumin [53]. Desipramine could suppress ovalbumin specific IgE levels and IL-4 levels in serum and nasal lavage fluids, but had no effect on IFN- γ level. Importantly, desipramine could up-regulate Tregs, whereas down-regulate Th17 cells, in spleen cells, suggesting that desipramine can restore the balance between Tregs and Th17 cells in the murine model of AR [53]. Whether desipramine or other antidepressants have the similar effect on Treg/Th17 balance in humans needs further investigation.

Bacteria and Th17 responses

Given their important role in maintaining mucosal immunity, it is not surprising that recent investigations demonstrate the involvement of Gram-negative and Gram-positive bacteria in Th17 response induction in the gut and lung [54, 55]. One paper also showed an association between bacteria and Th17 responses in the upper airway diseases [56]. In that study, authors found that besides several Gram-negative bacteria and moulds, a high number of Gram-positive bacteria could also colonize the surfaces of pollen grains, especially *Bacillus* type [56]. Culture immature DCs isolated from grass pollen allergic donors with supernatants of homogenized Gram-positive bacteria (e.g. *Bacillus cereus* and *Bacillus*

subtilis) was able to induce maturation of DCs as reflected by the up-regulation of CD80, CD83 and CD86 expression and by the enhanced production of IL-6, IL-12p40 and TNF- α , although a more pronounced effect could be found if DCs were cultured with LPS [56]. Consequently, stimulation of autologous CD4⁺ T cells with DCs pulsed by supernatants of homogenized Gram-positive bacteria and grass pollen could lead to an enhanced proliferation of T cells and production of IL-4, IL-13, IL-10, IL-17, IL-22, and IFN- γ by T cells compared with T cells that were stimulated with DCs pulsed only with allergen [56]. Therefore, not only LPS from Gram-negative bacteria, but also the products from Gram-positive bacteria may serve as immune adjuvants to augment DC maturation and promote inflammatory Th1, Th2 and Th17 responses in a non-specific pattern that facilitating the initiation of allergic immune responses in upper airways. Interestingly, recent studies showed that extracellular vesicles, the bacteria-secreted-nanometer-sized vesicles, in indoor dust can induce neutrophilic lung inflammation accompanied by infiltration of Th1 and Th17 cells in mice [57]. It is worthy to investigate whether bacteria-derived extracellular vesicles have a role in pollen-induced allergic responses and in AR in future.

Immunotherapy and Th17 responses

Currently, allergen specific immunotherapy (SIT) is the only etiological treatment for AR and has a long-term efficacy on improvement of clinical symptoms, although the mechanisms underlying its efficacy have not been completely clarified [58]. Li et al sought to investigate the effect of subcutaneous SIT on Th17 cell-mediated inflammatory responses in AR patients who were monosensitized to house dust mite [59]. They found that 2-year SIT

could significantly suppress mRNA expression of IL-17 and ROR γ t in peripheral blood mononuclear cells and the levels of IL-17, IL-6 and IL-23 in plasma [59]. In addition, Th2/Th1 ratio and proportions of Th17 cells were suppressed while IL-10 producing CD4⁺ T cell were elevated after SIT [59]. Most importantly, a positive correlation between IL-17 mRNA/protein levels and clinical symptom scores was observed [59]. This study indicates that SIT may restore the Th1/Th2/Th17/Treg balance in AR patients and IL-17 may be a useful biomarker for both AR severity and SIT therapeutic effect.

Th17 responses in CRS

CRS is an inflammation of the sinonasal mucosa and many inflammatory cells and cytokines are involved in its pathologic process [60]. Primarily on the basis of the absence and presence of nasal polyps, CRS is divided into two types: CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP). CRSsNP and CRSwNP express distinct inflammation and remodeling patterns [61]. CRSsNP is characterized by a Th1 predominated neutrophilic milieu; whereas CRSwNP is featured by a Th2-biased eosinophilic inflammation [60, 61]. Although the enhanced expression of Th17 response has not been found in sinonasal mucosa in Caucasian CRS patients without cystic fibrosis [60], an upregulated Th17 response has been demonstrated in Asian patients with either CRSsNP or CRSwNP [62]. In Caucasian patients with cystic fibrosis, Derycke L et al found a significant upregulation of IL-17A and myeloperoxidase expression in nasal polyps and the cellular sources of IL-17A were mainly T-lymphocytes [63]. Furthermore, they found that IL-17A was able to modulate the survival of neutrophils in nasal polyps from non-cystic fibrosis patients directly, highlighting a role of

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Th17 cells in neutrophilic inflammation in CRSwNP [63]. However, in Japanese patients with CRS, Makiyama et al found that the number of IL-17A⁺ cells was positively associated with computer tomography scan cores and the number of EG2⁺ eosinophils in sinonasal mucosa [64]. Jiang et al found that the expression levels of IL-17 and ROR γ t did not differ between Chinese eosinophilic and non-eosinophilic CRSwNP [65]. Saito T discovered that the localization of IL-17A expression predominantly coincided with eosinophils and CD4⁺ lymphocytes and IL-17A-positive cells correlated with tissue eosinophilic, but not with neutrophils in Japanese patients with CRSwNP associated with asthma [66]. These studies indicate an association between Th17 responses and eosinophilic inflammation in Asian CRS patients. However, it remains elusive as to how IL-17A drives eosinophilic inflammation in Asian CRS patients. Makiyama et al. found that IL-17A was able to induce GM-CSF and IL-6 production by dispersed nasal polyp cells; however, no significant effect has been found on IL-5, IL-13, RANTES, or eotaxin production [64]. GM-CSF is involved in priming, chemotaxis, cytokine production, and apoptosis inhibition of eosinophils [64]. IL-6 can promote Th2 cell differentiation and disruption of IL-6 signaling in lung can decrease antigen-induced eosinophilic inflammation [64]. However, whether IL-6 and GM-CSF play a truly important role in Th17 cell-mediated eosinophilic inflammation in the context of CRS and whether there is any other underlying mechanism need to be explored *in vivo* either in animal models or in human beings.

Regulation of Th17 responses in CRS

Similar to the study of regulation of Th17 responses in AR, the researches regarding the regulation of Th17 responses in the setting of CRS are very limited (Fig. 1). Moreover, the lack of a suitable and widely accepted animal model for CRS makes the study of cellular and molecular mechanisms underlying Th17 cell functions and the regulation of Th17 responses in CRS more difficult, since in vitro models utilizing human tissue have some inherent limitations.

Staphylococcus aureus enterotoxins and Th17 responses

Staphylococcus aureus enterotoxins, acting as both antigens and superantigens, have been implicated in the pathogenesis of nasal polyposis, particularly in Caucasians [67, 68]. Staphylococcus aureus enterotoxin B (SEB) stimulation of dispersed nasal polyp cells induced significant IL-17A production [64]. Neutralization of IL-10 or IL-18 did not affect the SEB-induced IL-17A synthesis; in contrast, neutralization of IL-12/IL-23 p40 significantly, albeit partially, suppressed IL-17A synthesis [64]. IFN- γ neutralization also significantly improved IL-17A synthesis [64]. These results suggest that SEB can induce the production of IL-17A in CRSwNP through inducing the expression of IL-23, the cytokine responsible for the proliferation and stabilization of Th17 cells. It should be noted that, although IL-17 is mainly produced by Th17 cells, other immune cells in nasal polyps may also be the cellular sources of IL-17 [64, 65], therefore, that study did not provide a definite result about the regulation of Th17 responses by SEB. Moreover, whether Staphylococcus aureus enterotoxins can modulate the differentiation of Th17 cells directly or indirectly also

requires further study. Yu et al found that when mice epicutaneously sensitized with ovalbumin, the addition of SEB could augment not only Th2, but also Th17 responses systemically [69]. Epicutaneous sensitization with combination of ovalbumin and SEB might markedly enhance ovalbumin-induced neutrophilic and eosinophilic inflammation in murine lung through IL-17A dependent mechanism [69]. This animal study also highlights a role of SEB in augmentation of Th17 responses.

Cyclooxygenase pathway and Th17 responses

Eicosanoids are generated via arachidonic acid cascade. The activation of phospholipase A2 results in release of arachidonic acid from membrane phospholipids in mammalian cells [70]. Arachidonic acid is in turn transformed by cyclooxygenase (COX) and lipoxygenase pathways. There are at least 2 different COX isozymes, COX-1, the constitutive isoform, and COX-2, the inducible one. COX-2 activation leads to synthesis of several prostaglandins (PG), including PGE2 [70]. COX-1 and COX-2 may play important role in regulating Th1/Th2 balance [71]. Recently, COX2/PGE2 pathway has also been implicated in the induction of Th17 pathogenicity [19]. PGE2 favors Th17 cell expansion and IL-17 production directly through increasing IL-17 and reducing INF- γ production by freshly isolated memory T cells or indirectly through increasing IL-23 and blocking IL-12 release from dendritic cells [72, 73]. Alteration in the COX pathway has been implicated in the pathogenesis of CRSwNP [70]. Diclofenac is COX-1/COX-2 inhibitors [74]. Treatment with diclofenac caused a significant decrease in IL-17A production in dispersed nasal polyp cells [64]. On the contrary, PGE2 significantly increased IL-17A production [64]. Treatment with

EP2 and EP4 receptor-selective agonists, but not with EP1 receptor-selective agonists, significantly augmented SEB-induced IL-17A production in dispersed nasal polyp cells [64]. In contrast, treatment with EP3 receptor-selective agonist modestly inhibited IL-17A production in dispersed nasal polyp cells [64]. This study showed the involvement of PGE2-EP2/EP4 pathway in the induction of IL-17A in CRSwNP. However, as mentioned above, since nasal polyp cells consist of many cell types other than T cells, the precise effect of COX pathway on Th17 cells needs to be study at cellular level in future.

Glucocorticoids and Th17 responses

With regard to the role of glucocorticoids in the regulation of Th17 responses in CRS, reports have been varied. Kou et al. have found that a predominant Th17 cell population and impaired Treg function characterized Chinese CRSwNP [75]. The protein levels of Smad7 and IL-17A, and the mRNA levels of ROR γ t were higher in polyp tissues in CRSwNP patients without fluticasone propionate nasal spray treatment than those seen in CRSwNP patients with intranasal fluticasone propionate treatment for 6 weeks [75], suggesting that intranasal steroid treatment may attenuate Th17 responses in CRSwNP. Molet et al also found an obvious, but insignificant, decrease of the number of IL-17 immunoreactive cells in CRSwNP patients after 4-week intranasal fluticasone propionate treatment [76]. On the contrary, Wen et al. have demonstrated that levels of IL-17 was not significantly reduced in nasal secretions after oral steroid treatment (30 mg of prednisone once daily for 7 days) in Chinese CRSwNP patients, despite that a significant suppression of INF- γ , IL-4 and IL-5 has been demonstrated [77]. The discrepancy between these studies may be related to difference

in the administration route of the drugs. However, the change of Th17 responses under the influence of glucocorticoid need to be evaluated at cellular level in order to get more precise information of Th17 cells.

Th17 pathway as potential therapeutic or drug targets in patients with inflammatory upper airway diseases

Many agents for targeting IL-17A itself or IL-17A signaling or factors upstream of IL-17A that regulate IL-17A production are being investigated at the clinic or preclinic in various Th17-related inflammatory diseases (Fig.2) [78-80]. These studies shed light on the possibility of use of Th17 pathway as potential therapeutic or drug targets in patients with inflammatory upper airway diseases.

IL-6 and IL-1 β target: IL-6 and IL-1 β are key regulators and inducers of Th17 cells. Type II interleukin-1 receptor (IL-1RII) is a non-signaling decoy receptor that blocks the activity of interleukin-1 (IL-1). It has been shown that IL-1RII ameliorated experimental autoimmune myocarditis by blocking IL-1 and inhibiting production of the cytokines important for the polarization of T cells toward a Th17 phenotype, such as IL-6 and TGF- β [81]. Tocilizumab is a therapeutic blocking antibody targeting the IL-6 receptor (IL-6R), which has been found to be therapeutically effective for rheumatoid arthritis, systemic juvenile idiopathic arthritis, and Castleman's disease, is already available for clinical use [82]. It has been demonstrated that tocilizumab was able to reestablish the balance between Th17 cells and Tregs towards a more protective status in treating idiopathic arthritis [83]. Therefore, IL-6 and IL-1 β blocker can be considered as potentially novel therapeutic options for upper

airway diseases regarding its inhibitory effect on Th17 responses.

IL-23 target: Monoclonal antibody against the p40 subunit of IL-23/IL-12 was effective in controlling gut and skin inflammation in mouse models and was able to inhibit the biological activity of IL-23 and IL-12 and the respective Th17 and Th1 pathway [78]. Clinical studies of a humanized anti-p40 monoclonal antibody, Ustekinumab, conducted in patients with Crohn's disease and psoriasis demonstrated a noticeable clinical improvement [78, 79]. Although clinical trials of agents that block IL-23 have not been conducted in patients with upper airway diseases, it is worth testing the efficacy of IL-23 blocking for the treatment of upper airway diseases.

ROR γ t target: It has been shown that small molecule ROR γ t inhibitors including digoxin and ursolic acid are able to inhibit Th17 cell differentiation and function [84, 85]. SR1001, a first-in-class, high-affinity synthetic ligand specific to both ROR α and ROR γ t can also inhibit Th17 cell differentiation and function [86]. SR1001 binds specifically to the ligand binding domains of ROR α and ROR γ t and induce a conformational change, leading to diminished affinity for coactivators and increased affinity for corepressors [86]. Treatment of animals with digoxin, SR1001, or ursolic acid was shown not only to delay the onset, but also to reduce the severity of multiple sclerosis in mouse models [84]. In addition, a recent study showed that digoxin treatment led to a beneficial outcome in the rat model of collagen-induced arthritis and attenuated acute cardiac allograft rejection by antagonizing ROR γ t activity [84, 85]. Thus, these promising results make ROR γ t inhibitors as good therapeutic candidates for controlling Th17 upper airway diseases.

IL-17A receptors and signaling target: The main function of Th17 cells depends on

specific IL-17A receptors and downstream signalling pathways, many of which involve protein tyrosine kinases, such as MAPK including ERK and the p38 MAPK, etc. Treatment of human bronchial epithelial cells with anti-IL-17R antibodies decreases activity of the IL-17 cytokine [87]. Inhibition of the p38 MAPK by SB202190 as well as ERK by PD98059, has been found to attenuate IL-17A-induced release of neutrophil migrating factors including IL-8 *in vitro* [88]. Therefore, targeting IL-17A receptors and signaling also provides alternative therapeutic potentials in Th17-mediated upper airway diseases.

IL-17A target: Inhibition of IL-17A was effective in mouse models of multiple sclerosis and rheumatoid arthritis [89-90]. Anti-IL-17A antibodies treatment decreased Th2-related cytokine production and suppressed eosinophilic inflammation in an asthma mouse model [91]. Furthermore, soluble IL-17A receptor-immunoglobulin fusion protein has been shown to inhibit IL-17A production and prolong cardiac allograft survival in a rat model [92]. Phase I and III trials evaluating the efficacy and safety of anti-IL-17A antibodies used for the treatment of rheumatoid arthritis and psoriasis are undergoing [80].

Conclusive remarks:

Considerable progress has been made in our understanding of Th17 cells since their initial discovery. Our knowledge of Th17 cell differentiation, regulation, and its role in airway diseases as well as other inflammatory diseases have expanded rapidly. In this review, we discussed the recent reports on the function and the regulation of Th17 responses in the inflammatory upper airway diseases including AR and CRS. Despite that an important role of Th17 cells has been revealed in the pathogenesis of AR and CRS and a number of

endogenous or exogenous substances have been demonstrated to tightly regulate the Th17 responses in AR and CRS, it is critical to address several challenges in future researches: (1) to define the regulation of Th17 responses at cellular level in upper airway diseases, particularly in CRS; (2) to better understand the molecular mechanisms regulating Th17 responses in AR and CRS; (3) to clarify the potential interaction between Th17 cells and other subsets of T cells in the upper airway diseases; and (4) to translate the finding regarding Th17 cell and its regulation into the treatment of AR and CRS in clinic.

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Figure legends:

Figure 1. The regulation of Th17 response in inflammatory upper airway diseases. Th17 response may promote both eosinophil and neutrophil recruitment to nasal mucosa through inducing the expression of eotaxin-1 and eotaxin-2, and CXCL1, CXCL2 and CXCL8, respectively. Bacteria can enhance Th17 response by up-regulating the CD80, CD86, CD83, IL-6, and TNF- α expression by dendritic cells, whereas epithelial cell-derived Clara cell

10-kDa protein (CC10) may inhibit Th17 response via down-regulating IL-23 and IL-6 production and enhancing TGF- β production by dendritic cells. Staphylococcus aureus enterotoxin B (SEB) promotes Th17 response by stimulating IL-23 production. Budesonide and formoterol, β -1,4-mannobiose (MNB), antidepressants, and allergen specific immunotherapy (SIT) can restore the balance of T regulatory cells (Tregs)/Th17 cells.

Figure 2. Th17 pathway as potential therapeutic or drug targets. In lymphoid organs, dendritic cells present antigens to naïve CD4⁺T cells and drive the differentiation of Th17 cell subtype through secreting IL-1 β , IL-6, and IL-23. IL-6R blocking antibody (Tocilizumab), non-signaling decoy receptor for IL-1 (type II interleukin-1 receptor, IL-1RII), and anti-IL-12/23p40 antibody (Ustekinumab) can block these Th17 cell-inducing cytokines and suppress the differentiation of Th17 cells. The activation of transcription factor, ROR γ t, is critical to Th17 cell differentiation. Digoxin, ursolic acid and SR1001 can inhibit the function of ROR γ t, thus suppressing the differentiation of Th17 cells. Differentiated Th17 cells migrate to the local airway and secrete IL-17A that binds to specific IL-17 receptors (IL-17R) on fibroblasts and epithelial cells and leads to subsequent inflammation. IL-17A can be blocked by anti-IL-17A antibody or soluble IL-17R-immunoglobulin fusion protein. IL-17A/IL-17R signaling may be suppressed by anti-IL-17R antibody, p38 mitogen-activated protein kinase (MAPK) inhibitor (SB202190), and extracellular-signal-regulated kinase (ERK) inhibitor (PD98059).



