



The role of Th17 lymphocytes in the pathogenesis of chronic rhinosinusitis

Review

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Abstract

Chronic rhinosinusitis (CRS) encompasses inflammatory conditions affecting the nasal and paranasal sinus mucosa. Two major subtypes are distinguished by the presence (CRSwNP) or absence (CRSsNP) of nasal polyps. This review examines the role of T helper 17 (Th17) cells and interleukin-17 (IL-17) cytokines in CRS immunopathology. Th17 lymphocytes produce inflammatory mediators, including IL-17A and IL-17F, which can disrupt sinonasal epithelial barrier function. Multiple studies correlate IL-17 levels and Th17 signaling with mucosal inflammation in CRS patients. However, significant endotypic and phenotypic variability modifies IL-17 involvement. CRSwNP often presents hallmark Th2-linked eosinophilic inflammation, while CRSsNP and subsets of Asian CRSwNP display Th17-associated neutrophilia. Overall, the literature implicates Th17 and IL-17 activity in CRS, but the heterogeneity of immunological subtypes mediates variable cytokine profiles. Further research into precise immunopathogenic mechanisms is needed to elucidate the contribution of Th17/IL-17 to disease and personalized therapeutic development.

Keywords

chronic rhinosinusitis • Th17 cells • IL-17

1. Introduction

Chronic inflammation of the nasal mucosa and sinuses is also called chronic rhinosinusitis (CRS) [1]. It is estimated that this heterogeneous group of inflammatory diseases in European countries can affect from 7 to 21% of the adult population. In the United States, this represents about 14%, while in China, this represents between 2.1 and 8% of the population [2]. It should be emphasized that in Poland, published epidemiological data estimates the prevalence of this disease to be between 4 and 6 million cases among the adult population [3].

Sinus inflammation can be classified according to the duration of ailments: acute (up to 4 weeks), subacute (4–12 weeks), recurrent, and chronic (lasting over 12 weeks) [1]. CRS is a complex inflammatory disease with pathogenesis involving genetic and environmental factors. Based on family studies, it has been estimated that CRS exhibits heritability ranging from 13 to 53%, with the highest correlation observed in people with coexisting asthma, aspirin intolerance, and nasal polyps [4]. In addition, it is suggested that asthma occurs in 20–31.9% of CRS patients [5]. The standard features of nasal polyps and cystic fibrosis, a common genetic disease caused by a mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, provide additional evidence that genetically determined immunological changes in the nasal mucosa contribute to CRS development. Interestingly, the results of twin studies

on CRS have been inconsistent, suggesting that genetic and environmental factors may play a role in CRS pathogenesis [6].

Regarding CRS, two subgroups can be distinguished: one in which nasal polyps are present (chronic rhinosinusitis with nasal polyps, CRSwNP) and another in which nasal polyps are absent (chronic rhinosinusitis without nasal polyps, CRSsNP) [7]. CRSwNP is a multifactorial and highly heterogeneous disease characterized by persistent mucosal inflammation and tissue remodeling [8]. Nearly 60% of polyp patients are diagnosed with lower airway comorbidities, including bronchial asthma [9]. On the other hand, CRSsNP may be idiopathic, odontogenic, or caused by immunodeficiency, vasculitis, or other autoimmune conditions [10].

Studies conducted in several independent centers indicate that among patients with CRSwNP and CRSsNP, there are differences in the immunological mechanisms leading to the disease. In addition, differences are also observed between populations, e.g., in terms of the prevalence of comorbidities. Considering the general risk factors for CRS, the following are distinguished: anatomical obstruction of the ostiomeatal complex, impaired mucociliary clearance, impaired epithelial defense, superantigen action, immune system dysfunctions, genetic factors, and environmental exposures such as inhaled allergens and irritants as well as microorganisms and biofilms [11].

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Various microorganisms have been identified in the biofilms of CRS patients, including bacteria such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Staphylococcus epidermidis*, as well as fungi like *Candida albicans* and *Aspergillus niger*. Among these, *S. aureus* is frequently associated with CRS, particularly in the most severe cases and in patients with comorbid asthma. *S. aureus* can secrete superantigens that modulate the host's immune response. Additionally, biofilms formed by *S. aureus* or *P. aeruginosa* have been linked to unfavorable postoperative outcomes and disease recurrence in CRS patients [12].

This review summarizes emerging evidence on the involvement of T helper 17 (Th17) cells and their signature effector cytokines, including interleukin-17A (IL-17A) and IL-17F, in CRS pathogenesis.

2. The role of Th17 lymphocytes in the human body

Available literature data distinguishes the following subpopulations of helper T lymphocytes: Th0 (naive cells), Th1, Th2, Th9, Th22, and the relatively recently discovered Th17 lymphocytes [13, 14]. It is worth noting that research on the differentiation of Th17 lymphocytes into IL-17-producing cells has been carried out mainly in mouse models, which demonstrate some differences compared to humans. In mouse models, it has been shown that Th17 cells originate from Th0 CD4+ cells under the influence of factors obtained from the microenvironment. However, in humans, Th17 lymphocytes may derive from a distinct CD4+CD161+ subset with constitutive expression of the RAR-related orphan receptor- γ transcription factor (ROR γ t) characteristic of the Th17 phenotype [15-17].

Th17 lymphocytes were first described by Aggarwala et al. in the early 2000s as the primary source of the IL-17 cytokine, hence the name [13]. It has been proven that in the differentiation of naive Th0 cells into Th17 lymphocytes, transforming growth factor beta (TGF- β) plays an important role, although to a lesser extent than in mouse models, along with IL-6 and IL-21 and IL-23, which exhibit the strongest effects. In the process of Th17 lymphocyte differentiation, the IL-23 receptor plays a significant role in response to the combined activity of IL-1 β and IL-23. Additionally, it is believed that alongside the aforementioned factors, IL-1 β and IL-2, which have auxiliary functions, as well as the ROR γ t transcription factor and signal transducer and activator of transcription 3 (STAT3), may play important roles [15, 18].

Notable in the context of Th17 biology is the C-C motif chemokine receptor 6 (CCR6), which is present on the surface of Th17 lymphocytes. Studies show that CCR6 engagement elicits an almost 100-fold increase in IL-17 secretion compared to CCR6-negative cells. This may indicate an important role of this chemokine receptor in the Th17 phenotype differentiation process. Notably, the ligand for this receptor is the CC motif chemokine ligand 20 (CCL20), which has chemotactic properties

for T and B lymphocytes and dendritic cells. This chemokine plays a key role in forming and migrating Th17 lymphocytes to inflammatory sites while also affecting IL-17 expression [15, 19]. Aside from IL-17A and IL-17F, Th17 lymphocytes can produce tumor necrosis factor- α (TNF α), IL-6, IL-21, IL-22, IL-23, and granulocyte-macrophage colony-stimulating factor (GM-CSF) [20]. Additionally, the Th17-derived cytokine IL-21 acts in an autocrine manner to promote lymphocyte differentiation towards the Th17 phenotype [21]. However, Th17 cells are not the only source of IL-17, as this cytokine can also be produced by monocytes, neutrophils, natural killer cells, CD8+ cytotoxic T lymphocytes, and $\gamma\delta$ T lymphocytes. Additionally, research has shown that regulatory T lymphocytes (Tregs) can produce IL-17 under inflammatory conditions [15].

On the other hand, multiple factors have been discovered that can negatively regulate Th17 cells, including the cytokines: IL-4, IL-5, IL-12, IL-27, and interferon γ (IFN- γ). These are produced by other Th subsets such as Th1, Th2, and Tregs [18, 22]. For instance, IL-12 signaling causes Th17 lymphocytes to acquire IFN- γ production while decreasing IL-17 expression [15]. Conversely, IL-5 was shown to inhibit the differentiation of both Th17 and Th1 subsets [23]. Moreover, Liu et al. demonstrated that IL-27 inhibits IL-17 secretion from Th17 cells, representing a potential therapeutic approach for Th17-mediated diseases [24]. Available literature indicates that IL-4 inhibits both Th17 differentiation and IL-17 expression. However, the precise molecular mechanisms underlying this suppression remain unknown, as does the effect of IL-4 on other Th17-associated genes like ROR γ t and IL-22 [25]. Additionally, IFN- γ exhibits suppressive effects on Th17 cells [15].

Numerous studies have aimed to elucidate the role of Th17 lymphocytes in humans, but the findings are often ambiguous. Chen et al. suggested that while IL-6 and TGF- β increase ROR γ t expression, they do not independently induce Th17 differentiation from naive human T cells. Additionally, they found that IL-23 strongly promoted Th17 production but also elicited other proinflammatory cytokines [26]. Alternatively, Wilson et al. discovered either IL-1 β or IL-23 alone sufficiently induced IL-17+ cell development [27]. Interestingly, van Beelen et al. demonstrated human Th17 derivation solely from memory T cells rather than naive lymphocytes due to muramyl peptide enhancement of IL-23 and IL-1 secretion by dendritic cells [28]. In summary, unlike mouse models, human Th17 cells do not require TGF- β for differentiation and this cytokine does not exert inhibitory effects [29] (Figure 1).

3. Characteristics of interleukin 17

The IL-17 family includes interleukins IL-17A (denoted as IL-17), B, C, D, E (denoted as IL-25), and IL-17F. The first reports on this family of interleukins date back to the early 1990s, when, in 1993, Rouvier et al. cloned and described IL-17A for the first time, which was initially called CTLA 8 [30]. It is believed that interleukins IL-

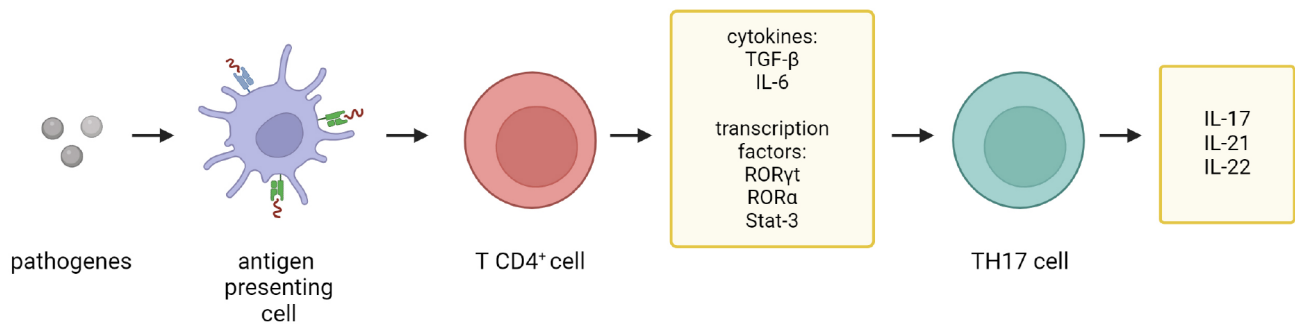


Figure 1. The differentiation of Th17 cells

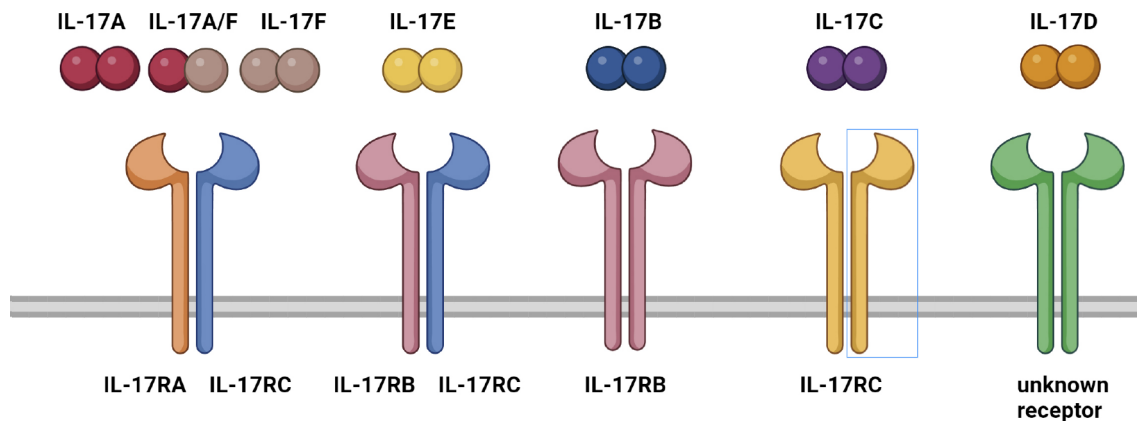


Figure 2. IL-17 receptor family

17A and IL-17F are produced by a variety of immunocompetent cells, i.e., memory T CD4⁺, CD8⁺, γδ, natural killers (NK) lymphocytes, and neutrophils. In addition, it has been proven that each member of the IL-17 interleukin family has a certain degree of homology in the amino acid sequence in relation to IL-17A, ranging from just below 20% to about 55% [31]. IL-17F has the highest degree of homology in relation to IL-17A, and depending on the IL-17 isoform, it is from 40 to 55% [32]. It is worth noting that these two interleukins are located next to each other on human chromosome 6; however, their transcription proceeds independently. IL-17 mRNA transcripts are detected in neutrophils and eosinophils. IL-17F is synthesized by activated T cells and monocytes [33].

Moreover, the IL-17 cytokine family consists of homodimeric glycoproteins except for IL-17A/F cytokines, which can also occur as heterodimers [15, 30, 34–36]. The IL-17 receptor family comprises five conserved IL-17 receptors (IL-17Rs) (Figure 2). Each IL-17R contains two extracellular fibronectin type III-like domains and an intracellular Similar Expression to Fibroblast Growth Factor (SEFIR) domain [36] (Figure 2).

The IL-17A/F receptor acts as a heterodimer consisting of an IL-17RA subunit and a ligand-recognizing subunit, e.g., IL-

17RC interacting with IL-17A and IL-17F [37, 38]. The binding of IL-17A and/or IL-17F leads to the recruitment of the adaptor protein NF-κB activator 1 (Act1) via SEFIR domain interactions. Act1 then mediates downstream signaling through two main pathways. In the canonical pathway, Act1 ubiquitinates TRAF6, leading to activation of NF-κB, CCAAT/enhancer-binding protein (C/EBP), and MAPK pathways and subsequent transcriptional activation of pro-inflammatory cytokines, chemokines, and antimicrobial peptides [ref]. The non-canonical pathway involves Act1 phosphorylation, which recruits TRAF2/5 to stabilize target mRNAs. Both pathways work in concert to propagate IL-17-mediated inflammation [39]. (Figure 3)

Evidence suggests that IL-17Rs are located on many cells, including monocytes, endothelial cells, respiratory epithelial cells, and fibroblasts. Stimulation of these cells causes the release of TNF-α, IL-1β, IL-6, the chemokine (C-X-C motif) ligand 1 (CXCL1), CXCL2, CXCL5, CXCL8, and IL-8, which act as chemoattractants for granulocytes [36, 37, 38, 40–42]. Importantly, there is a feedback loop in this system. Cytokines such as IL-1β and IL-23 can enhance the expression of IL-17A and IL-17F. Moreover, the combination of IL-6, IL-1β, and IL-23 can induce the production of IL-17A and IL-17F in Th cells [43]. IL-23 is also responsible for the pathogenicity

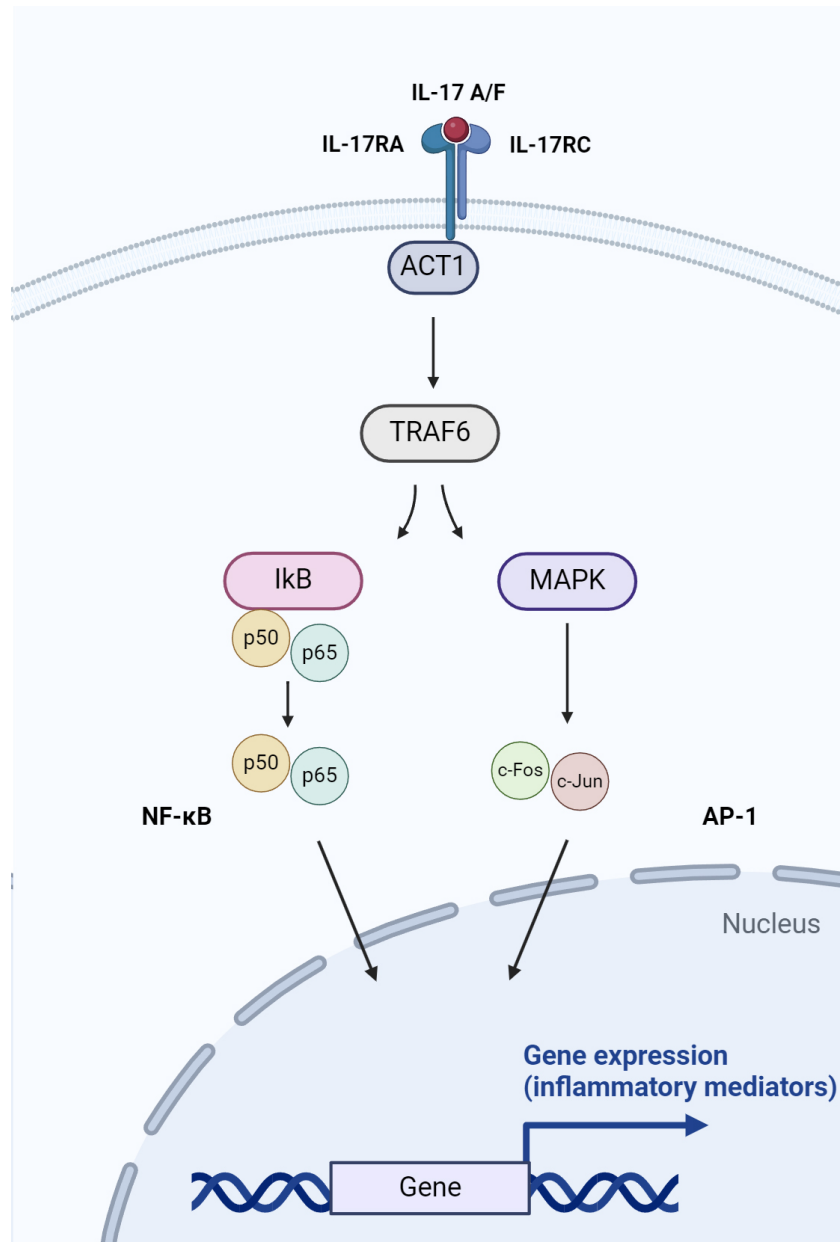


Figure 3. IL 17 A/F signaling pathway

of autoreactive Th17 cells and promotes IL-17 production in various types of lymphoid cells, including CD3+CD4-CD8- populations and natural lymphoid cells [44–46].

Available research suggests that cytokines from the IL-17 family (IL-17A and IL-17F) play a key role in defending the host organism against bacterial and fungal infections. However, increased IL-17A cytokine synthesis is also associated with allergic, immunoinflammatory, and autoimmune diseases such as psoriasis, rheumatoid arthritis, systemic lupus erythematosus, and others [47, 48].

4. The role of Th17 lymphocytes in the pathogenesis of chronic rhinosinusitis

Currently, several types of Th lymphocytes are recognized to participate in the development of CRS, with Th1, Th2, and Th17 cells playing the most prominent roles. Pilot studies in upper respiratory mucosa tissue indicated that Th1 cells producing IFN- γ are characteristic of CRSsNP, while Th2 cells producing IL-5 are usually observed in CRSwNP. Moreover, it has been proven that the involvement of types of helper lymphocytes in the pathogenesis of CRS differs between continents [49]. Derycke et

al. suggest that in the Caucasian race, over 80% of polyps express a Th2 profile, while in China, polyps express a dominant Th17 cell profile [50, 51].

Caucasian CRSwNP is characterized by a predominant eosinophilic Th2-type inflammation with high levels of IL-5, extracorporeal photopheresis, and local IgE, while Asian CRSwNP shows polarization towards Th1/Th17. Typical features of nasal polyp remodeling in both ethnic groups are albumin accumulation and edema formation in the extracellular matrix. Interestingly, no significant differences in IL-17A mRNA levels were found between CRSsNP, CRSwNP, and the control group [46, 55]. However, it has been shown that in the Caucasian population, patients with cystic fibrosis exhibit a predominant Th17 profile [50].

Wang et al. examined the mutual regulation of Th2 and Th17 in Chinese patients with CRSwNP. They showed that cytokines secreted by Th2, IL-4, and IL-13 inhibited the expression of factors associated with Th17, while cytokines secreted by Th17, IL-17, and TGF- β increased the expression of factors associated with Th2. In turn, dexamethasone treatment inhibited both Th2 and Th17 pathways. These results demonstrate that Th2 and Th17 signaling pathways antagonize one another while concurrently mediating mutual regulatory effects [51].

The above research demonstrates that CRSwNP cytokine profiles exhibit differentiation dependent on endotype, comorbidities, geographical region, and race [8]. Zhang et al. conducted further studies confirming these observations, showing that Chinese CRS patients' polyp tissue displayed neutrophilic inflammation with increased Th17 levels, whereas no such relationship emerged in Belgian patients [49, 52].

Additionally, Ramezani et al. investigated how Th1, Th2, and Th17 cytokines and interferons influence upper airway epithelial barrier function in CRSwNP cases. While Th1/Th2 signaling and interferons showed no impact on mucosal integrity, the Th17 products IL-17, IL-22, and IL-26 provoked significant damage. Hence, Th17 cytokines may facilitate a leaky mucosal barrier that enables CRSwNP progression [53].

In summary, the involvement of Th17 lymphocytes in the pathogenesis of CRS varies depending on geographical location, race, and comorbidities. Caucasian CRSwNP is characterized by a predominant Th2 profile, while Asian CRSwNP shows polarization towards Th1/Th17. The Th2 and Th17 signaling pathways appear to antagonize each other while also mediating mutual regulatory effects. Th17 cytokines may contribute to the progression of CRSwNP by facilitating a leaky mucosal barrier.

5. The role of IL-17 in the pathogenesis of chronic rhinosinusitis

Recently, attempts have been made to answer the question about the role of the IL-17 cytokine synthesized by Th cells in the pathogenesis of chronic rhinosinusitis. Despite ongoing research, there is no clear answer to the question asked.

Jiang et al. found that IL-17 expression levels did not differ between eosinophilic and non-eosinophilic sinusitis with nasal polyps among the Chinese population. However, they observed an elevated expression level of the IL-17RD receptor in non-eosinophilic CRSwNP compared to eosinophilic CRSwNP. Interestingly, IL-17 expression measured in the serum of CRSwNP patients did not differ from the control group [54].

In Japanese participants, Makihara et al. associated IL-17A presence in sinus and nasal tissues with both local eosinophilia and ostiomeatal obstruction [55]. Similarly, Saitoh et al. detected increased IL-17A immunoreactivity and mRNA in Japanese CRSwNP patients' nasal polyps compared to normal mucosa, predominantly localizing with eosinophils and CD4-positive lymphocytes. Notably, IL-17A-positive cell infiltration correlated with tissue eosinophilia but not neutrophilia while dictating the extent of epithelial damage and basement membrane thickening. These findings suggest that IL-17A plays an important role in the accumulation of eosinophils in nasal polyps and the remodeling of nasal polyps in chronic rhinosinusitis and coexisting asthma [56].

In contrast, Hu et al. found that IL-17A expression was higher among the Chinese population with CRSwNP and CRSsNP compared to controls. Additionally, they observed that IL-17 expression was higher in samples of neutrophilic chronic sinusitis than in eosinophilic chronic sinusitis, although the difference was not statistically significant [57].

Chapurin et al. associated predominant IL-17A cytokine profiles with an increased number of previous sinus surgeries, suggesting that type 3 inflammatory state markers may indicate a particularly difficult-to-treat CRS endotype [58].

In summary, while some studies suggest that IL-17A expression is associated with eosinophilia and remodeling in CRSwNP, others have found higher IL-17 levels in neutrophilic CRS. The role of IL-17 in CRS pathogenesis appears to vary depending on the population studied and the specific CRS endotype. Further research is needed to clarify the contribution of IL-17 and IL-17A/F heterodimers to the inflammatory response in CRS and to identify potential therapeutic targets.

6. Conclusions

In conclusion, current literature strongly supports the involvement of Th17 cells and their signature cytokines, particularly IL-17A and IL-17F, in the pathogenesis of chronic rhinosinusitis. The increased abundance of Th17 cells producing these cytokines in the nasal polyps and peripheral blood of CRSwNP patients highlights their potential role in driving the inflammatory response. However, the precise mechanisms by which Th17 cells and IL-17 cytokines contribute to CRS pathology remain incompletely understood. Future studies should focus on elucidating the specific signaling pathways and cellular interactions mediated by IL-17A, IL-17F, and their heterodimers in the context of CRS. Additionally, investigating the potential

interplay between Th17 cells and other immune cell populations, such as eosinophils and neutrophils, could provide valuable insights into the complex inflammatory milieu in CRS.

Furthermore, exploring the relationship between Th17 cytokines and other key mediators of inflammation, such as IL-21 and IL-22, may reveal novel therapeutic targets for CRS. Ultimately, a deeper understanding of the role of Th17 cells and IL-17 cytokines in CRS pathogenesis will inform the development of more targeted and effective treatment strategies for this chronic inflammatory condition.

Authors contribution

Authors contribution Writing - Original Draft Preparation - M.C-K and A.Z-N, Writing - Review and Editing - A.M-S, K.M, H.Z-B, M.P-Z, Visualization - A.M-S, Literature review - K.M, Final proofreading and approval of the version for publication - M.C-K, A.N-Z, K.M, H.Z-B, A.M-S

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Conflict of interest

The authors have no potential conflicts of interest to declare.

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