Review Article

Role and Function of Regulatory T Cell in Chronic Rhinosinusitis with Nasal Polyposis

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Chronic rhinosinusitis with nasal polyps (CRSwNP) is a subtype of chronic rhinosinusitis characterized by high edema in the stroma, albumin deposition, and formation of pseudocysts [6]. At present, it is believed that the colonization of some pathogenic bacteria (such as Staphylococcus aureus) and fungi (such as Aspergillus fumigatus) induces the development of nasal polyps in CRSwNP [7–9] which is associated with T helper 2 (Th2) inflammation. Moreover, previous studies have reported that the expression of interleukin (IL)-4, -5, -6, and -13 mediated the inflammatory process [10, 11]. In addition, a low frequency of CD4+ T cells and a high frequency of CD8+ T cells were observed in patients with nasal polyposis [12].

During the recruitment of CD4+ T cells into the nasal mucosa, regulatory T (Treg) cells are considered to play a key role in the formation of nasal polyps by modulating the balance of Th1 and Th2 immunity [13, 14]. Studies have been conducted to investigate the function of Tregs. Some of the findings have shown that Tregs are associated with the tolerance to autoantigens and antigens of food and commensal microflora [15–17]. In addition, the reduction in the number or function of peripheral Tregs leads to chronic immunopathological processes, such as cancers and autoimmune disorders [16, 18–20]. This review was aimed at introducing the classification of Tregs, their mechanisms, and functions in the etiology of CRSwNP and Treg as a recent therapeutic target in CRSwNP treatment.

1. Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a subtype of chronic rhinosinusitis (CRS), which is characterized by persistent inflammation of the paranasal sinus mucosa [1]. It is one of the most common nasal diseases that affects a large proportion of the world’s population and is reported to be associated with some lower airway diseases, such as asthma [2]. CRSwNP not only causes nasal discomfort such as nasal congestion and purulent discharge but also causes extranasal symptoms such as headache, ear tightness, and sleep disorder [3]. Aside from physical symptoms, CRSwNP can also cause mental symptoms, such as anxiety and depression, which may seriously affect the efficiency of people’s lives and work [4, 5].

CRSwNP is characterized by high edema in the stroma, accompanied by albumin deposition and the formation of pseudocysts [6]. At present, it is believed that the colonization of some pathogenic bacteria (such as Staphylococcus aureus) and fungi (such as Aspergillus fumigatus) induces the development of nasal polyps in CRSwNP [7–9] which is associated with T helper 2 (Th2) inflammation. Moreover, previous studies have reported that the expression of interleukin (IL)-4, -5, -6, and -13 mediated the inflammatory process [10, 11]. In addition, a low frequency of CD4+ T cells and a high frequency of CD8+ T cells were observed in patients with nasal polyposis [12].

During the recruitment of CD4+ T cells into the nasal mucosa, regulatory T (Treg) cells are considered to play a key role in the formation of nasal polyps by modulating the balance of Th1 and Th2 immunity [13, 14]. Studies have been conducted to investigate the function of Tregs. Some of the findings have shown that Tregs are associated with the tolerance to autoantigens and antigens of food and commensal microflora [15–17]. In addition, the reduction in the number or function of peripheral Tregs leads to chronic immunopathological processes, such as cancers and autoimmune disorders [16, 18–20]. This review was aimed at introducing the classification of Tregs, their mechanisms, and functions in the etiology of CRSwNP and Treg as a recent therapeutic target in CRSwNP treatment.

2. Subtypes of Treg

Tregs are identified by surface markers (such as CD4 and CD25), intracellular markers (such as Forkhead-Box-Protein P3 (FOXP3)), and cytokines (such as TGF-β and IL-10). FOXP3, which is the most important transcription factor, is
associated with Treg and CD25 expressions [21, 22]. In addition, the different FOXP3 expression stabilities are an indication to distinguish different types of Treg [23, 24]. The phenotype of Tregs is commonly CD4+CD25+FOXP3+ T cells. However, studies have found that CD8+ T cells have immunosuppressive effects in some diseases and organ transplantsations [25]. A recent study showed that CD8+CD25+ T cells with immune regulatory activity can also express FOXP3, which is later referred to as CD8 Treg [26, 27]. A study by Pant et al. [28] showed that the reduction of CD8 Treg is associated with the process of CRSwNP.

For Treg subtypes, Tregs can be divided into two categories according to their origin. Tregs derived from the thymus are called thymus-derived Tregs (tTregs), and Tregs that differentiate in peripheral tissues are called peripherally derived Tregs (pTregs) [29]. tTregs express FOXP3 and have high self-affinity for T cell receptors [24]. They are associated with tolerance to autoantigens [16]. pTregs, which are derived from peripheral naive Th cells, are most commonly found in peripheral barrier tissue and act as suppressors of local inflammation when faced with exogenous antigens [16, 30]. The decrease in pTregs may lead to a series of chronic T cell-related immune diseases [30].

Based on differentiation, Tregs can be divided into naive Tregs (nTregs), central memory Tregs (cmTregs), effector memory Tregs (emTregs), and effector Tregs (eTregs) [24]. Each has different actions in the lymphoid or lymphoid organs. Their differentiation and homing direction require specific receptors and cytokines [31, 32]. Moreover, CCR7 and CD62L molecules play a key role during migration to secondary lymphoid organs [33]. When they act in lymphoid organs, Tregs are identified by the expression of inducible costimulatory (ICOS) or CD44 [34].

Different subtypes of Tregs show different states and varying functions. However, the conversion of Treg between different subtypes (activation) and the suppressive effect of Treg are dependent on cytokine transmission.

3. Activation and Suppressive Mechanism of Treg

3.1. Activation of Treg. On the surface, Tregs express the following: CD25, ITIM domain protein (TIGIT), lymphocyte activation gene 3 (LAG-3), ICOS [35–37], cytotoxic T lymphocyte antigen 4 (CTLA-4), tumor necrosis factor receptor (TNFR) family-related protein (GITR), programmed death-1 (PD-1), and its ligand (PD-L1) [38]. Tregs regulate the secretion of cytokines and the expression of surface biomarkers by expressing a variety of intracellular transcription factors, such as FOXP3 and IRF-4 [39]. They are responsible for Treg activation, function, and interaction with antigen-presenting cells (APCs) and other immune cells (summarized in Figure 1).

With antigens as an inflammatory stimuli, naive CD4+ T cells can be induced and differentiated into Tregs [40]. Tregs usually act by regulating the recruitment of effector T cells to sites of inflammation and impairing the capacity of APCs that induce adaptive immune responses [41, 42]. Based on the expression of CD45RA or RO, Tregs can be divided into three subgroups: resting Tregs (rTregs, CD4+CD25+FOXP3+CD45RO−RA−), activated Tregs (aTregs, CD4+CD25+FOXP3−CD45RA RO+), and cytokine-secreting nonsuppressive T cells (CD4+FOXP3−CD45RA RO− T cells) [43, 44]. Tumor necrosis factor receptor 2 (TNFR2) is highly expressed by aTregs and converts rTregs into an activated state [45, 46]. aTregs, which express elevated levels of TNFR2, appear to be highly immunosuppressive, and an excessive and uncontrolled expression of it may lead to cancer [47–49]. Meanwhile, cytokine-secreting nonsuppressive T cells produce proinflammatory cytokines, such as IL-17 [43].

The initiation and regulation of Tregs is modulated by APCs, such as dendritic cells (DCs) and macrophages. DCs are composed of conventional DCs (cDCs) and plasmacytoid DCs (pDC) [50]. The capacities of cDCs and pDCs to activate Tregs differ. pDCs usually have a poor capacity to induce Tregs but act as strong activators of effector T cells (Teff), which function differently from Tregs. Activated cDCs, which express higher levels of Toll-like receptor (TLR)-2,6,8 and self-peptide/MHC have the capacity to stimulate the proliferation and expansion of Tregs [51, 52]. CTLA-4 of Tregs can bind to ligands CD80 and CD86 on the surface of DCs to limit costimulatory signals [53]; PD-1 on Tregs can bind to PD-L1 and PD-L2, which are expressed on the surface of DCs to suppress the function of Teff [54].

Tregs can also proliferate by direct recognition of self-antigens and commensal microbes [55]. They can also clone and expand in vivo and in vitro after antigen stimulation and maintain their inhibitory function after expansion [56].

3.2. Cytokines Related to Treg. The activation of Tregs depends not only on surface biomarkers but also on cytokines. Further, Tregs are regulated by various networks of cytokines, such as IL-2, IL-7, IL-15, and TGF-β, to exert their immunosuppressive effects on T cells, B cells, NK cells, DCs, and macrophages.

IL-2 is important in regulating the development, function, and stability of Tregs [57]. IL-2 binds to CD25 of conventional T cells (Tconv) and activates three intracellular signaling pathways: mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase, and signal transducer and activator of transcription 5 [58]. These pathways regulate the proliferation and memory formation of Tconv as well as the immunosuppressive function of Tregs [58]. IL-2 directly upregulates FOXP3 and CD25, and when it binds to CD25, it lowers the threshold of effect on the development and homeostasis of Tregs [59–61]. Studies have also found that IL-7 can maintain the expression of CD25 and potentially enhance the responses of Tregs to IL-2, especially during cutaneous immunosuppression [32, 62, 63].

TGF-β is associated with the direction of differentiation of CD4+ T cells toward Tregs or Th 17 [57, 64]. TGF-β secreted by APCs or Treg itself can promote FOXP3 gene expression and lead to the differentiation of CD4+ T cells toward Tregs [57]. The downstream targets of TGF-β are mainly Smad family transcription factors, which interact with one another to form different types of DNA-binding complexes [65]. When exposed to lower concentrations of TGF-β, T cells can be induced to differentiate toward Th17 [40]. Despite the dual ability of TGF-β, some other cytokines (such as IL-2 and IL-6) are
needed to further induce either FOXP3 or the transcription factor RORγt [66–68]. For example, FOXP3 expression can be activated in the presence of TGF-β and IL-2 with TCR affinity and APC interaction [57].

IL-15 contributes to antigen presentation and the production of type I cytokines (IL-12 and IFN-γ) in APCs [69]. It is also involved in the stability and memory formation of CD4+ T cells [70]. In addition, IL-15 can promote FOXP3 expression via the STAT5 pathway [71]. Moreover, IL-15 acts as a supplement to IL-2 during the development of Tregs, but it cannot rescue the function of Treg in the absence of IL-2 [16]. Marshall et al. reported that IL-5 may provide an alternative pathway for CD4+ T cells to differentiate into Tregs, but this requires clarification [72].

In addition to the cytokines mentioned above, many other cytokines also regulate the function and behavior of Tregs. Tumor necrosis factor (TNF) can promote the proliferation of Tregs and regulate their suppressive function [73, 74]. IL-33, which promotes Th2-polarized immune responses, mediates the proliferation of Tregs and enhances their immune regulatory functions [75, 76]. IL-6 regulates the balance between Tregs and Th 17 by inhibiting the differentiation of Tregs and promoting Th 17 generation [77, 78].

4. Tregs in CRSwNP

CRSwNP, the most common type of CRS, is thought to be associated with the Th2 immune response. It is usually characterized by the accumulation of eosinophils, T cells, neutrophils, and increased levels of IL-5 and IgE and decreased TGF-β1, which is in contrast to those of chronic rhinosinusitis without nasal polyps (CRSSNP) with elevated TGF-β1 and IFN-γ [79–81] (interactions between cells are shown in Figure 2; changes in cytokine levels from different studies are shown in Table 1). Studies have compared the differences between tissues from nasal polyps and the nasal sinus mucosa. The results showed that there was no significant difference in Tregs and CD4+ T cells between the two groups; however, elevated levels of pDCs and activated CD8+ T helper cells were observed in the nasal polyp tissue [82, 83]. Ickrath et al. [12] demonstrated that there was a significantly higher proportion of aTregs and memory T cells (CD3+ CD4+ CD45RA- FOXP3low) in polyp tissues than in peripheral blood. Sharma et al. [30] conducted an immunohistochemical analysis of Tregs in the affected sinonasal tissues and found a large number of both CD25+ FOXP3+ and CD4+ FOXP3+ cells in the CRSwNP group than in the CRSSNP group (p < 0.05). Mann
et al. reported that although there was a large proportion of Tregs in the polyp tissues, a lower proportion of aTregs was also observed in the CRSwNP group [84]. This explains why a larger number of Tregs result in a decreased immunosuppressive effect.

Impaired Treg function and differentiation play an important role in the onset and deterioration of CRSwNP. Treg exerts its suppressive effect mainly through its surface molecules, as well as the proteins (such as CD25 and CTLA-4) and cytokines it secretes (such as IL-10 and TGF-β). Treg dysfunction leads to the imbalance of Th1/Th2 and Treg/Th17 [85]. The hyperimmune response of Th2 results in IgE-mediated eosinophil infiltration and cellular edema, which promotes remodeling of the nasal sinus mucosa. Further, Treg/Th17 imbalance results in the imbalance between matrix metalloproteinases and tissue inhibitors of metalloproteinases via TGF-β1, and this causes the deposition of albumin, collagen, and other extracellular matrix proteins [86, 87]. Moreover, the decrease in Treg and downregulation of FOXP3 expression weaken the inhibition of Th17 differentiation, lead to the aggregation of neutrophils in the nasal sinus mucosa, and aggravate the inflammation characteristic of CRSwNP [88, 89].

However, there were geographical differences in the immune processes of CRSwNP. Studies from different regions have suggested that different races and geographical environments have an impact on the immune process of CRSwNP [93–96]. Some studies found that patients with CRSwNP from Western countries show more Th2-skewing inflammation, while patients from Southeast Asia tend to show Th1/Th17 inflammation [91, 97]. Cao et al. claimed that Chinese patients with CRSwNP showed reduced Tregs and decreased TGF-β production compared to healthy controls [79]. Similar conclusions were also observed by Li et al. [98] and Wang et al. [99].

The pathogenesis of CRSwNP is usually due to an imbalance of microbial flora (dysbacteriosis) in the nasal sinuses or the invasion of pathogenic microorganisms [100, 101], caused by many bacteria, such as Corynebacterium tuberculostearicum, Staphylococcus aureus, and Haemophilus influenzae [102–104]. Studies have reported that colonization by Staphylococcus aureus or Haemophilus influenzae potentially contributes to the development of nasal polyps [105, 106]. Studies have demonstrated that leukocidin ED, which is secreted by Staphylococcus aureus and acts as a cytolytic toxin, can result in the depletion of most effector memory T cells, leading to the impairment of Th1 and Th17 immune responses.

Table 1: Changes of cytokines in patients with CRSwNP in different studies.

| Reference | Upregulated | Downregulated |
|-----------|-------------|---------------|
| Cho et al. | IL-2, IL-4, IL-6, IL-10, IL-17, and IFN-γ | nm | [90] |
| Ba et al. | IL-1β, IL-6, and IL-8 | IL-5 | [91] |
| Cao et al. | IFN-γ, IL-5, IL-17A, IL-22, and IL-23 | nm | [79] |
| Li et al. | TGF-β, IL-10, and IL-18 | IFN-γ | [92] |
| König et al. | IL-5, IL-17 | IL-10, IL-12, IL-13, and IFN-γ | [81] |

nm: not mentioned.
responses and disruption of balance between Th17 and Treg [107–109]. Staphylococcal enterotoxin B can trigger the significant elevation of IFNγ, IL-2, IL-13, etc. [110], which can also affect the differentiation and function of Tregs. In a study by Cho et al. [90], T cells that expressed retinoic acid receptor-related orphan receptor c (RORc) in peripheral blood mononuclear cells (PBMCs) significantly increased after treatment with Staphylococcal enterotoxin B in patients with eosinophilic polyps. Upregulation of RORc+ T cells can also downregulate Tregs [111]. Yang et al. also revealed the negative regulation of Tregs by Haemophilus influenzae after a long-term and low-dose exposure [112]. Rai et al. [113] investigated the changes in Th17, Treg, and various cytokines in patients with Aspergillus flavus-infected CRSwNP and found an immune imbalance with increased Th17, reduced Tregs, elevated levels of IL-10 and IL-17, decreased levels of TGF-β in PBMCs, and an elevated expression of TLR-2 in patients.

In patients with CRSwNP, the expression of FOXP3 is significantly lower than that in healthy controls [114]. FOXP3 acts as a biomarker of CD4+ Tregs and is important in regulating its function and development [115, 116]. In a study by Roongrotwattanasiri et al. [88], there was a decrease in the number of CD4+ Tregs; however, no difference was detected between the epithelia and lamina propria of nasal polyps. Upregulation of RORc+ T cells can also downregulate Tregs [111]. Yang et al. also revealed the negative regulation of Tregs by Haemophilus influenzae after a long-term and low-dose exposure [112]. Rai et al. [113] investigated the changes in Th17, Treg, and various cytokines in patients with Aspergillus flavus-infected CRSwNP and found an immune imbalance with increased Th17, reduced Tregs, elevated levels of IL-10 and IL-17, decreased levels of TGF-β in PBMCs, and an elevated expression of TLR-2 in patients.

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5. Treg as Therapeutic Target in CRSwNP

Since the role of Treg in the pathogenesis of CRSwNP has been extensively studied, the study of Treg as a therapeutic target has also been widely investigated. Here, we list three nonsurgical treatments targeting Treg.

5.1. Steroid Therapy. In the treatment of CRSwNP, systemic or local administration of glucocorticoids (GCs), such as prednisone, which can suppress NF-κB and MAPK pathways and alleviate tissue edema and nasal polyp size, was thought to be effective [139–141]. GCs have strong anti-inflammatory and immunomodulatory effects on immune cells and nonlymphoid tissues [142–145]. However, the effects of GCs on Tregs remain controversial. In terms of the impact on the number of Tregs, previous studies found that nonactivated Treg cells underwent apoptosis after administration of GCs [146]. Meanwhile, others reported of the relatively lower sensitivity of nonactivated Tregs to GC treatment that induced less apoptosis than other non-Treg cells [147, 148]. In addition, GC treatment can increase CTLA-4 cells and decrease CD69+ cells in the CD25+ cell population, which results in the expansion of Treg cells [149, 150]. Lin et al. investigated the effect of budesonide nasal spray treatment on CD8+ Tregs in patients with CRSwNP and found no increase in the percentage of CD8+ Treg cells in polyp tissues, although TGF-β and its mRNA were upregulated [151]. Edward et al. treated CRSwNP patients with oral prednisone and found an expansion of overlapped Treg cells in nasal polyp tissues via CCL4 chemotaxis without a significant increase in adjacent ethmoid sinus mucosa and PBMCs [152]. This conclusion confirms the results of earlier studies that Treg cells expanded locally in polytissues [153, 154]. However, in terms of the impact on the function of Tregs, some in vitro studies found that although the number of Treg cells significantly increased, their
suppressive properties were not enhanced accordingly [155]. Nevertheless, it is still debatable whether the same results can be obtained in in vivo experiments. In the study by Kou et al., the nasal administration of GCs promoted the function of Tregs via the TGF-β1-Smad2 signaling pathway [154].

In terms of the impact on the differentiation of Tregs, the nasal administration of GCs was found to enhance TGF-β1 production to activate FOXP3 expression, which promoted the differentiation of T cells toward Tregs [154]. Moreover, TGF-β1 can drive IL-10 production, which can also maintain the expression of FOXP3, thus regulating the differentiation of Tregs [156].

5.2. Biological Therapy. Biologic therapy is becoming a novel and promising treatment for CRSwNP [157, 158]. Biologic drugs (monoclonal antibodies) can precisely block the effect of specific chemokines that control the Th2 inflammatory endotype when conventional therapy fails [159, 160]. Recently, many monoclonal antibodies targeting various cytokines have been developed, including omalizumab [161] (anti-IgE), mepolizumab [162, 163], reslizumab [164] (anti-IL-5), and dupilumab [165] (anti-IL-4 and IL-13). These targeted chemokines play key roles in the differentiation, chemotaxis, activation, and survival of eosinophils, basophils, mast cells, etc. [158]. Monoclonal antibodies targeting these chemokines have the ability to block different receptor-binding actions in patients with CRSwNP [157, 166, 167], which may alleviate the type 1 or type 2 inflammation response.

In addition to the monoclonal antibodies mentioned above that have been tested in patients with CRSwNP, other monoclonal antibodies targeting the Treg/Th17 balance have also been studied [168]. Some target Th17-related cytokines and receptors (such as IL-17, IL-23, and IL-6) that affect the expression level of RORyt indirectly increase Tregs in order to correct the imbalance [169–174]. Although no clinical trials have been conducted in CRSwNP patients, these still have the potential to improve CRSwNP symptoms by correcting the Treg/Th17 balance.

5.3. Probiotic Therapy. Based on the hypothesis of dysbacteriosis, probiotics are also used in the treatment of CRSwNP. Studies have investigated the therapeutic mechanisms of various bacteria, such as Lactobacillus and Bifidobacterium, as probiotics [175]. Previous studies have shown that Lactobacillus could regulate the differentiation of Th17 and Treg cells in peripheral lymphoid organs by mediating the production of several cytokines (such as IL-4 and IL-17) [176, 177]. Although the mechanisms of action of probiotics in CRSwNP treatment are not fully understood, Treg should be further studied as a medium for probiotics to modulate the immune response in CRSwNP.

6. Conclusion
Treg cells, a suppressive immunoregulatory T cell subset, play a vital role in the process of CRSwNP. CRSwNP, which is thought to be associated with the Th2 immune response, is characterized by Treg/Th17imbalance (decreased level of Tregs and increased level of Th17) in polyp tissue. Dysbacteriosis in the nasal sinuses or invasion of pathogenic microorganisms also contributes to the onset of CRSwNP. For example, Staphylococcus aureus can break the balance between Th17 and Treg cells, and Staphylococcal enterotoxin B can trigger the upregulation of RORc expression and downregulation of FOXP3 expression. However, further studies are needed to investigate the specific mechanism of dysbacteriosis interaction with Treg and other immune cells in order to better understand the immune modulation and disease progression of CRSwNP.

Th17 and Treg cells have opposite effects; however, their development also shares reciprocal pathways. The number of Tregs is negatively associated with Th1- and Th2-related cytokines (such as INF-γ, IL-4, and IL-5) in polyp tissues in both atopic and nonatopic patients. Future efforts should be made to understand the influence of atopy on the Treg/Th17 and Th1/Th2 balance in CRSwNP and their cytokine communication.

In the treatment of CRSwNP, glucocorticoids are considered a traditional and effective therapeutic drug because they potentially promote the expansion and function of Tregs. However, its effects on Tregs in different kinds of CRS need to be further studied. Monoclonal antibodies are a promising therapeutic option because they can block specific chemokines. However, at present, this therapy is relatively expensive, and monoclonal antibodies against Treg-related cytokines have not been confirmed to be effective in the clinical setting, which is still the direction of future efforts. Probiotics, such as Lactobacillus, are also used in the treatment of CRSwNP, but their effects on Tregs are not fully understood. Moreover, little is known about the effect of other probiotics in regulating Treg in CRSwNP. In the future, we should further investigate the role of probiotics in Treg immune regulation and identify more probiotics for Treg for the treatment of CRS. Additionally, through a deeper understanding of Treg and its related immune cells, safer and more effective novel therapeutic strategies need to be explored.

Data Availability
All data generated or analyzed during this study are included in this article.

Conflicts of Interest
The authors declare that there is no conflict of interest regarding the publication of this paper.

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