International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 10, No. 1, 2025

IL-4/IL-13 Signaling Regulation and Monoclonal Antibody Therapy in Chronic Rhinosinusitis with Nasal Polyps

Tao Lin *, Yingying Zhang, Dongling Lian, Zhiqing Ma

Department of Otorhinolaryngology-Head and Neck Surgery, Guangzhou Red Cross Hospital (Guangzhou Red Cross Hospital of Jinan University), Guangzhou Guangdong, 510000. China

*** Corresponding author:** Tao Lin

Abstract: Chronic rhinosinusitis with nasal polyps (CRSwNP) is a prevalent inflammatory disorder characterized by nasal obstruction, rhinorrhea, hyposmia/anosmia, and facial pain. It is driven by type 2 (T2) inflammation, primarily mediated by IL-4, IL-13, and IL-5. Current treatments, including corticosteroids and surgery, often fail to address the underlying T2 inflammation and have limitations in efficacy and safety. Recent advances in monoclonal antibody therapies targeting IL-4/IL-13 signaling, such as dupilumab, have shown significant efficacy in reducing nasal polyp burden, improving olfactory function, and enhancing quality of life. However, challenges remain due to disease heterogeneity and the need for personalized treatment strategies. Future research should focus on leveraging multidimensional technologies to dissect disease heterogeneity, developing novel therapeutic agents, and conducting head-to-head clinical trials to refine treatment selection.

Keywords: Chronic Rhinosinusitis with Nasal Polyps (CRSwNP); Type 2 Inflammation; IL-4/IL-13 Signaling; Monoclonal Antibodies; Dupilumab; Personalized Treatment.

1. Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a chronic inflammatory disorder of the nasal and paranasal sinus mucosa, affecting 4%–10% of the global population[1] . Clinically characterized by persistent nasal obstruction, rhinorrhea, hyposmia/anosmia, and facial pain or pressure, CRSwNP frequently presents with comorbid conditions such as asthma and aspirin-exacerbated respiratory disease (AERD), which collectively exacerbate disease burden. The condition profoundly impairs quality of life, with over 60% of patients experiencing depression or anxiety secondary to sleep disturbances, chronic fatigue, and social dysfunction. Annual healthcare expenditures and indirect productivity losses attributable to CRSwNP are estimated to exceed billions of US dollars.

Pathologically, CRSwNP is defined by type 2 (T2) inflammation driven by Th2 lymphocytes and group 2 innate lymphoid cells (ILC2s) [2]. Central to this process are the proinflammatory cytokines IL-4, IL-13, and IL-5[3]. IL-4 and IL-13 disrupt nasal epithelial barrier integrity via IL-4 receptor alpha (IL-4Rα) signaling, leading to aberrant mucin secretion and ciliary dyskinesia[4]. Concurrently, IL-5 promotes eosinophil differentiation, recruitment, and survival, perpetuating eosinophil-dominant inflammation. Notably, IL-4/IL-13 signaling directly impairs olfactory epithelium (OE) regeneration and downregulates olfactory receptor expression [5], mechanistically explaining the prevalent olfactory dysfunction in CRSwNP. Clinical studies have demonstrated positive correlations between IL-4/IL-13 levels in nasal polyp tissues and disease severity or recurrence risk.

Current standard therapies for CRSwNP include intranasal corticosteroids, systemic corticosteroids, and functional endoscopic sinus surgery (FESS). However, 30%–60% of patients exhibit suboptimal responses to corticosteroids, with long-term use associated with adverse effects such as metabolic disturbances and osteoporosis. While FESS provides rapid mechanical decompression, postoperative recurrence rates reach 40%–70% within five years. Crucially, conventional therapies fail to address the T2 inflammation-mediated epithelial barrier disruption and irreversible olfactory damage[1]. These limitations have driven intensive research into novel biologics targeting IL-4/IL-13/IL-5 signaling pathways, aiming to achieve precise and sustained disease control[6].

2. Molecular Mechanisms of IL-4/IL-13 Signaling and Their Roles in CRSwNP

2.1. Molecular Mechanisms

IL-4 and IL-13 exert their biological functions through distinct receptor complexes. IL-4 primarily binds to the Type I IL-4 receptor, a heterodimer composed of IL-4Rα and the common γ-chain (γC), while IL-13 signals via the Type II IL-4 receptor, formed by IL-4Rα and IL-13Rα1. Both cytokines activate the JAK-STAT6 pathway: IL-4 binding to IL-4Rα recruits JAK1 and JAK3 kinases, leading to phosphorylation of IL-4Rα and subsequent STAT6 activation. In contrast, IL-13 signaling through IL-13Rα1 and IL-4Rα activates JAK2 and TYK2, which phosphorylate STAT6 [7]. Phosphorylated STAT6 dimerizes and translocates to the nucleus, driving transcription of target genes such as *CCL11*, *CCL26*, and *MUC5AC*. These genes mediate goblet cell hyperplasia, mucus hypersecretion, and eosinophil chemotaxis .

2.2. Role in CRSwNP Pathogenesis

In chronic rhinosinusitis with nasal polyps (CRSwNP), IL-4/IL-13 signaling via heterodimeric receptors activates the JAK-STAT6 cascade, driving epithelial barrier dysfunction, Th2 inflammation, and eosinophil-mediated pathology[3] .

Olfactory Epithelial Dysfunction: IL-4/IL-13 signaling

directly disrupts olfactory epithelial (OE) neuronal function. Intranasal IL-4 (but not IL-13) administration in mice reduces olfactory sensitivity independently of structural OE integrity, suggesting IL-4-mediated neuroimmune crosstalk. Additionally, IL-4/IL-13 suppresses tight junction proteins (e.g., claudin-1), compromising epithelial barrier integrity and facilitating pathogen/allergen penetration [8].

Th2 Polarization and Eosinophil Recruitment: IL-4 drives Th2 differentiation via STAT6-dependent transcriptional activation of *GATA3*, amplifying IL-5 and IL-13 production[9] . IL-5 enhances eosinophilopoiesis, survival, and tissue infiltration, synergizing with IL-4/IL-13 to amplify type 2 inflammation. Clinically, IL-5 levels in nasal polyps correlate with eosinophil density, and anti-IL-5/IL-5Rα therapies significantly reduce eosinophilic inflammation .

Mucus Hypersecretion and Chemokine Induction: IL-13 dominates goblet cell metaplasia, upregulating *MUC5AC* via STAT6-dependent mechanisms . Concurrently, IL-4/IL-13 induces epithelial production of CCL11 and CCL26, chemokines that recruit eosinophils to sustain inflammation . This creates a pathological loop: mucus stasis promotes microbial colonization, further activating type 2 immunity[10] .

3. Advances in Monoclonal Antibody Therapies and Predictors of Therapeutic Efficacy

3.1. Core Therapeutic Target

Interleukin-4 (IL-4) and IL-13 drive Type 2 (T2) inflammatory responses via the shared IL-4 receptor alpha subunit (IL-4Rα), establishing this pathway as a core therapeutic target for chronic rhinosinusitis with nasal polyps (CRSwNP), asthma, and atopic dermatitis (AD). Biologics targeting IL-4/IL-13 signaling[11] , such as the anti-IL-4Rα monoclonal antibody dupilumab, have demonstrated significant clinical efficacy. As the first approved fully humanized IgG4 monoclonal antibody, dupilumab binds IL-4Rα to simultaneously inhibit IL-4 and IL-13 signaling, thereby improving nasal polyp size, olfactory function, and quality of life in CRSwNP[12]. In CRSwNP, dupilumab reduces nasal polyp scores (NPS), restores olfactory function, and alleviates disease burden by suppressing epithelial barrier disruption and eosinophilic infiltration[13]. For severe asthma, dupilumab lowers annualized exacerbation rates (AER) by 60%, reduces dependence on oral corticosteroids (OCS), and improves lung function (FEV1) and fractional exhaled nitric oxide (FeNO) levels. In AD, it mitigates skin inflammation and pruritus by inhibiting IL-4/IL-13-driven B cell activation and IgE production[14]. Novel humanized anti-IL-4Rα agents like CM310 have shown comparable efficacy in Phase II trials for severe eosinophilic CRSwNP (ECRSwNP), with mechanisms overlapping those of dupilumab. However, differences in antibody affinity or pharmacokinetics may confer advantages in specific patient subgroups.

3.2. Divergent Outcomes of IL-13-Specific vs. Broad IL-4/IL-13 Inhibition

Therapeutic outcomes vary across alternative targeting strategies. Anti-IL-13 monoclonal antibodies, such as tralokinumab, specifically neutralize IL-13 to suppress its signaling. While tralokinumab improves skin barrier function and reduces inflammatory biomarkers (e.g., TARC/CCL17) in AD, its limited efficacy in CRSwNP may reflect the secondary role of IL-13 in nasal polyp pathogenesis.

3.3. Predictors of Treatment Response and Mechanisms of Resistance

Predictors of treatment response and mechanisms of resistance are critical for optimizing therapy. Patients with elevated baseline IL-5 levels or tissue eosinophilia exhibit enhanced responses to IL-4Rα-targeted therapies[15], whereas IL-13 inhibitor efficacy correlates with IL-13Rα1 expression. The Q576R polymorphism in IL-4Rα, which amplifies IL-4 signaling, may sensitize carriers to dupilumab[16]. Resistance mechanisms include STAT6 pathway alterations (e.g., activating mutations or epigenetic dysregulation), which enable signal bypass, and non-T2 inflammatory endotypes (e.g., neutrophil-dominant CRSwNP or asthma), which respond poorly to IL-4/IL-13 blockade. Such cases may require combination therapies targeting IL-17 or TSLP pathways to address refractory inflammation.

4. Clinical Applications and Safety Considerations

4.1. Clinical Application Expansion

The clinical application of monoclonal antibodies in chronic rhinosinusitis with nasal polyps (CRSwNP) has expanded from patients with conventional treatment failure to include recurrent/refractory cases, particularly in subgroups with comorbid asthma or nonsteroidal anti-inflammatory drug (NSAID) intolerance. Anti-IL-4Rα monoclonal antibodies (e.g., dupilumab), by inhibiting IL-4/IL-13 signaling pathways, not only reduce polyp recurrence but also concurrently improve asthma symptoms, offering dual benefits for CRSwNP patients with comorbid asthma[17]. Optimization of combination therapeutic strategies remains a current clinical priority. Co-administration of biologics with intranasal corticosteroids enhances mucosal repair through synergistic mechanisms: topical steroids suppress epithelial barrier-disrupting factors (e.g., IL-4/IL-13), while biologics target upstream inflammatory signals, accelerating mucosal healing and reducing fibrosis. For instance, in postoperative mucosal defects involving ≥75% of the sinus cavity, combined intralesional steroid injections and biologic therapy reduced stenosis incidence from 40% to 8% (P=0.039)[18].

4.2. Clinical Application Expansion

Despite marked efficacy, safety profiles require cautious evaluation. Local injection-related reactions (e.g., pain and fatigue following subcutaneous/intramuscular administration) and nasal application-associated conjunctivitis/epistaxis are frequently reported. While biologics demonstrate favorable long-term safety overall, sustained suppression of type 2 inflammatory pathways may elevate risks of opportunistic infections (e.g., sinonasal fungal colonization). Furthermore, combination therapies with anti-PD-1/CTLA-4 monoclonal antibodies (e.g., CS1002 + CS1003) could enhance antitumor efficacy but may also trigger immune-related adverse events (e.g., pneumonitis, colitis). The potential impact of IL-4Rα inhibitors on Th1/Th17 pathways warrants vigilance, necessitating validation through multicenter prospective studies[19].

4.3. Challenges in Management

In CRSwNP management, IL-4/IL-13-targeted biologics (e.g., dupilumab) face significant challenges despite proven efficacy. First, reliance on injectable administration may limit patient adherence, driving exploration of non-invasive delivery systems such as inhaled formulations or transmucosal nanoparticle-based antibodies. These small-molecule biologics could enhance local drug concentrations while minimizing systemic exposure. Second, the lack of predictive biomarkers hampers personalized treatment strategies[20]. Additionally, insufficient head-to-head comparative data among different biologics complicates optimal treatment selection.

4.4. Emerging Small-Molecule Inhibitors

Emerging small-molecule inhibitors targeting downstream effectors (e.g., CCL11/CCL26 inhibitors) show therapeutic promise. Preclinical studies demonstrate that blocking IL-4/IL-13-mediated chemokines reduces eosinophilic infiltration and mucus hypersecretion[21]. Compound IR, which modulates CCL11 expression and upregulates anti-inflammatory cytokines (IL-10, TGF-β), exhibits immunoregulatory potential. Single-cell RNA sequencing has revealed disease heterogeneity, identifying TSLP-mediated recruitment of specific T-cell subsets (IL-4/IL-13-secreting) and IL-13-driven fibrotic mechanisms linked to distinct plasma cell populations.

4.5. Combination Therapeutic Strategies

Combination therapeutic strategies (e.g., biologics + mucosal repair-targeted agents) may optimize clinical outcomes through synergistic multi-pathway interventions. Disrupting type 2 inflammatory feedback loops—particularly the TSLP/IL-25-ILC2-IL-4/IL-13 axis—is critical. Experimental models indicate redundant roles of IL-25 and IL-33 in promoting ILC2 expansion, while TSLP exacerbates inflammation through basophil-derived IL-4/IL-13 release. Dual targeting of TSLP and IL-25 signaling (e.g., anti-TSLP monoclonal antibodies + IL-17RB inhibitors) may more effectively suppress inflammatory cascades[22]. Mechanistic studies further suggest that IL-3 modulates cytokine microenvironments by inhibiting TSLP-induced CXCL1/CXCL2 secretion, highlighting the therapeutic value of multi-cytokine network interventions.

5. Conclusion and Prospect

Conclusions and Perspectives The IL-4/IL-13 signaling pathway has been identified as a central driver in the pathogenesis of chronic rhinosinusitis with nasal polyps (CRSwNP)[4]. Targeted monoclonal antibody therapies, such as IL-4Rα inhibitors (e.g., dupilumab), which block IL-4/IL-13 signaling, have transitioned from mechanistic studies to clinical application. These biologics demonstrate significant efficacy in reducing nasal polyp burden, restoring olfactory function, and improving quality of life, marking a transformative advancement in CRSwNP management[12]. However, the high heterogeneity of the disease—manifested through diverse inflammatory endotypes and molecular subtypes—remains a critical barrier to precision medicine [24].

Future research should leverage multidimensional technologies, including single-cell sequencing and spatial transcriptomics, to dissect the molecular heterogeneity of CRSwNP. Such approaches will clarify the dependence of distinct subtypes on IL-4/IL-13 signaling, enabling tailored therapeutic strategies[24]. Drug development should prioritize bispecific antibodies (e.g., targeting IL-4Rα/IL-13Rα1) and small-molecule inhibitors (e.g., CCL11/CCL26 antagonists) to enhance efficacy while minimizing systemic adverse effects[6]. Furthermore, real-world evidence (RWE) and head-to-head clinical trials (e.g., comparing dupilumab with omalizumab) are essential to refine treatment selection, addressing current limitations such as biomarker scarcity and cost-effectiveness concerns[26].

By integrating foundational research, clinical translation, and technological innovation, IL-4/IL-13-targeted therapies hold promise for delivering safer and more effective solutions not only for CRSwNP but also for broader type 2 inflammatory diseases. This paradigm shift may ultimately transition treatment goals from symptom alleviation to disease modification, revolutionizing long-term patient outcomes.

References

[1] Peters AT, Tan BK, Stevens WW. Consultation for Chronic Rhinosinusitis With Nasal Polyps and Asthma: Clinical Presentation, Diagnostic Workup, and Treatment Options. J Allergy Clin Immunol Pract. 2024;12(11):2898-2905. doi:10. 1016/j.jaip.2024.07.019.

[2] Stevens WW, Kato A. Group 2 innate lymphoid cells in nasal polyposis. Ann Allergy Asthma Immunol. 2021;126(2):110-117. doi: 10.1016/j.anai.2020.08.001.

[3] Bachert C, Hicks A, Gane S, et al. The interleukin-4/interleukin-13 pathway in type 2 inflammation in chronic rhinosinusitis with nasal polyps. Front Immunol. 2024;15:1356298. Published 2024 Apr 16. doi:10. 3389/ fimmu.2024.1356298.

[4] Fieux M, Carsuzaa F, Bellanger Y, et al. Dupilumab prevents nasal epithelial function alteration by IL-4 in vitro: Evidence for its efficacy. Int Forum Allergy Rhinol. 2024;14(8):1337-1349. doi:10.1002/alr.23343.

[5] Saraswathula A, Liu MM, Kulaga H, Lane AP. Chronic interleukin-13 expression in mouse olfactory mucosa results in regional aneuronal epithelium. Int Forum Allergy Rhinol. 2023;13(3):230-241. doi:10.1002/alr.23073.

[6] Haloob N, Karamali K, Hopkins C. The Role of Biologics in the Treatment of Chronic Rhinosinusitis. BioDrugs. 2023;37 (4):477-487. doi:10.1007/s40259-023-00602-9.

[7] Minskaia E, Maimaris J, Jenkins P, et al. Autosomal Dominant STAT6 Gain of Function Causes Severe Atopy Associated with Lymphoma. J Clin Immunol. 2023;43(7):1611-1622. doi:10. 1007/s10875-023-01530-7.

[8] Akdis CA, Arkwright PD, Brüggen MC, et al. Type 2 immunity in the skin and lungs. Allergy. 2020;75(7):1582-1605. doi: 10.1 111/ all.14318.

[9] Pelaia C, Pelaia G, Crimi C, et al. Biological Therapy of Severe Asthma with Dupilumab, a Dual Receptor Antagonist of Interleukins 4 and 13. Vaccines (Basel). 2022;10(6):974. Published 2022 Jun 19. doi:10.3390/vaccines10060974.

[10] Tay HL, Foster PS. Biologics or immunotherapeutics for asthma?. Pharmacol Res. 2020;158:104782. doi:10.1016/j. phrs. 2020.104782.

[11] Hoy SM. Dupilumab: A Review in Chronic Rhinosinusitis with Nasal Polyps. Drugs. 2020;80(7):711-717. doi:10.1007/ s402 65-020-01298-9.

[12] Hopkins C, Wagenmann M, Bachert C, et al. Efficacy of dupilumab in patients with a history of prior sinus surgery for chronic rhinosinusitis with nasal polyps. Int Forum Allergy Rhinol. 2021;11(7):1087-1101. doi:10.1002/alr.22780.

[13] Ferri S, Montagna C, Casini M, et al. Sleep quality burden in chronic rhinosinusitis with nasal polyps and its modulation by dupilumab. Ann Allergy Asthma Immunol. 2024;132(1):69-75. doi: 10.1016/j.anai.2023.08.594.

[14] Kychygina A, Cassagne M, Tauber M, et al. Dupilumab-Associated Adverse Events During Treatment of Allergic Diseases. Clin Rev Allergy Immunol. 2022;62(3):519-533. doi:10.1007/s12016-022-08934-0.

[15] Fujieda S, Matsune S, Takeno S, et al. Dupilumab efficacy in chronic rhinosinusitis with nasal polyps from SINUS-52 is unaffected by eosinophilic status. Allergy. 2022;77(1):186-196. doi:10.1111/all.14906.

[16] Yang B, Wilkie H, Das M, et al. The IL-4Rα Q576R polymorphism is associated with increased severity of atopic dermatitis and exaggerates allergic skin inflammation in mice. J Allergy Clin Immunol. 2023;151(5):1296-1306.e7. doi:10. 1016/ j.jaci.2023.01.011.

[17] Laidlaw TM, Bachert C, Amin N, et al. Dupilumab improves upper and lower airway disease control in chronic rhinosinusitis with nasal polyps and asthma. Ann Allergy Asthma Immunol. 2021;126(5):584-592.e1. doi:10.1016/j. anai.2021.01.012.

[18] Paoletti, G., Paoletti, G., Casini, M.,et al. Very rapid improvement of extended nitric oxide parameters, associated with clinical and functional betterment, in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) treated with Dupilumab. Journal of investigational allergology & clinical immunology.doi:10.18176/jiaci.0851.

[19] Ryser FS, Yalamanoglu A, Valaperti A, et al. Dupilumab-induced eosinophilia in patients with diffuse type 2 chronic rhinosinusitis. Allergy. 2023;78(10):2712-2723. doi:10. 1111/ all. 15844.

[20] Guo CL, Liu FF, Wang DY, Liu Z. Type 2 Biomarkers for the Indication and Response to Biologics in CRSwNP. Curr Allergy Asthma Rep.2023;23(12):703-713. doi:10.1007/ s11882-023-01114-w.

[21] Ren X, Wang Z. High chemokine ligand 11 levels in nasal lavage fluid: A potential predictor of and therapeutic target for murine eosinophilic chronic rhinosinusitis. Life Sci. 2021; 271: 119218. doi:10.1016/j.lfs.2021.119218.

[22] Abdu S, Xia J, Yuan H, et al. IL-25 Enhances B Cell Responses in Type 2 Inflammation Through IL-17RB Receptor. Allergy. Published online January 19, 2025. doi:10.1111/all.16472.

[23] Gayvert K, Desrosiers M, Laidlaw TM, et al. Nasal brushing molecular endotyping distinguishes patients with chronic rhinosinusitis with nasal polyps with better response to dupilumab. J Allergy Clin Immunol. 2024;154(3):619-630. doi: 10.1016/j.jaci.2024.05.030.

[24] Rodriguez-Iglesias M, Calvo-Henríquez C, Martin-Jimenez D, et al. Effect of Dupilumab in CRSwNP Sinonasal Outcomes from Real Life Studies: A Systematic Review with Meta-analysis. Curr Allergy Asthma Rep. 2025;25(1):13. Published 2025 Feb 5. doi:10.1007/s11882-025-01192-y.