The roles of eosinophils and interleukin-5 in the pathophysiology of chronic rhinosinusitis with nasal polyps

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Abstract (249/250 words)

Chronic rhinosinusitis with nasal polyps (CRSwNP) is generally associated with eosinophilic tissue infiltration linked to type 2 inflammation and characterized by elevated levels of interleukin (IL)-5 and other type 2 inflammatory mediators. Although distinct and overlapping contributions of eosinophils and IL-5 to CRSwNP pathology are still being explored, they are both known to play an important role in NP inflammation. Eosinophils secrete numerous type 2 inflammatory mediators including granule proteins, enzymes, cytokines, chemokines, growth factors, lipids, and oxidative products. IL-5 is critical for the differentiation, migration, activation, and survival of eosinophils but is also implicated in the biological functions of mast cells, basophils, innate lymphoid cells, B cells, and epithelial cells. Results from clinical trials of therapeutics that target type 2 inflammatory mediators (including but not limited to anti–IL-5, anti–immunoglobulin-E, and anti–IL-4/13) may provide further evidence of how eosinophils and IL-5 contribute to CRSwNP. Finally, the association between eosinophilia/elevated IL-5 and greater rates of NP recurrence after endoscopic sinus surgery (ESS) suggests that these mediators may have utility as biomarkers of NP recurrence in diagnosing and assessing the severity of CRSwNP. This review provides an overview of eosinophil and IL-5 biology and explores the literature regarding the role of these mediators in CRSwNP pathogenesis and NP recurrence following ESS. Based on current published evidence, we suggest that although eosinophils play a key role in CRSwNP pathophysiology, IL-5, a cytokine that activates these cells, also represents a pertinent and effective treatment target in patients with CRSwNP.

Introduction

The pathology of chronic rhinosinusitis (CRS) is heterogeneous, with two main phenotypes recognized: CRS with nasal polyps (NP) (CRSwNP) and CRS without NP (CRSsNP)[1]. Approximately 25–30% of patients with CRS have CRSwNP.[1] Although crossover between phenotypes is increasingly evident,[2] CRSwNP is generally associated with an eosinophilic or type 2 inflammatory pathophysiological endotype in up to approximately 85% of patients.[3] This endotype is characterized by elevated levels of interleukin (IL)-4, IL-5, IL-9, IL-13, IL-25, IL-33, and increased eosinophil counts,[4, 5] although variation in cytokine profiles is seen between different geographical regions.[6] In contrast, CRSsNP is frequently associated with a non–type 2 inflammatory pathophysiological endotype, characterized by increased neutrophil counts and elevated interferon-γ and/or IL-17.[4] Symptoms overlap across both phenotypes, although CRSwNP is often associated with more severe sinonasal symptoms than CRSsNP.[1, 7] In addition, patients with CRSwNP experience more prevalent nasal obstruction and typically have comorbid bronchial asthma.[3, 8]

Current standard of care (SoC) for CRSwNP includes intranasal corticosteroids, saline nasal douching, and short courses of systemic corticosteroids.[9] For severe CRSwNP cases, endoscopic sinus surgery (ESS) to remove the NP tissue and diseased nasal mucosa is often required.[9] However, eosinophilia and elevated IL-5 is associated with greater rates of NP recurrence after the tissue has been removed by ESS.[10, 11] Given the association between CRSwNP and type 2 inflammation, the pursuit of novel treatment options for CRSwNP has focused on increasing understanding of the mechanistic role of mediators in this pathway.

This review provides an overview of eosinophil and IL-5 biology and explores the available evidence relating to the mechanistic role of eosinophils and IL-5, in addition to other type 2 inflammatory

mediators in CRSwNP pathogenesis. We also evaluate emerging evidence supporting the potential use of eosinophils and IL-5 as biomarkers of NP recurrence following ESS.

Eosinophils and IL-5

Eosinophils exist in almost all vertebrates, representing up to 6% of the bone marrow resident nucleated cells[12] and are involved in a plethora of cellular processes.[13] It is well established that eosinophils secrete inflammatory mediators involved in tissue damage during inflammatory responses,[12, 14] and increased eosinophil counts are observed in the tissue and/or peripheral blood of patients with eosinophilic disease. The Local Immunity And/Or Remodeling/Repair (LIAR) hypothesis, first proposed by Lee et al., also suggested that eosinophils play a beneficial role in homeostasis.[15] The known homeostatic roles of eosinophils include contributions to glucose homeostasis, fat deposition, tissue remodeling and development, liver and muscle repair, epithelial, neuronal, and microbiome regulation, and immunoregulation.[16, 17] The development and maturation of eosinophils in the bone marrow is regulated by several key cytokines including IL-5, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-3.[13] In particular, IL-5 is critical for the differentiation, migration, activation, and survival of eosinophils.[18, 19]

The predominant sources of IL-5 include CD34+ progenitor cells, group 2 innate lymphoid cells (ILC-2), Th2 lymphocytes, invariant natural killer T cells, and mast cells,[20-22] although IL-5 can also be released by eosinophils in an auto/paracrine manner.[21, 22] Following the release of eosinophils from the bone marrow, eosinophil recruitment into tissues is promoted by chemokines such as eotaxin-1 (CCL11), -2 (CCL24), and -3 (CCL26).[23, 24] Eosinophil activation is essential for effective responses to

stimuli and can be elicited via a range of mechanisms including those induced by IL-5, IL-3, and GM-CSF, resulting in the release of mediator products.[25, 26]

IL-5 signals through IL-5 receptors (IL-5R), which are composed of transmembrane α and β chains; however, IL-5 can also bind to a soluble form of the IL-5Rα chain, which antagonizes IL-5R signaling.[27, 28] As such, the sensitivity of eosinophils to IL-5 is dependent on the relative expression of transmembrane and soluble IL-5Rα, which in turn is dependent on eosinophil activation state, maturation, and eosinophil location.[27] Tissue eosinophils have a lower expression of transmembrane IL-5Rα (**Figure 1**) and demonstrate lower responsiveness to IL-5 than eosinophils in the peripheral circulation[27]; this could explain the larger reductions in peripheral blood versus tissue eosinophils seen with anti–IL-5 therapy in patients with eosinophilic disease.[29, 30] Notably, soluble IL-5Rα expression in blood and tissue eosinophils is increased in patients with CRSwNP, with further increases in patients with comorbid asthma.[27, 31] Consequently, although endogenous concentrations of soluble IL-5Rα might be insufficient to block IL-5 activity, the higher concentrations observed in eosinophilic disease may be sufficient. It should, however, also be noted that since IL-5 is substantially elevated in CRSwNP compared with healthy controls,[32] higher levels of IL-5Rα may not necessarily translate to greater regulation.

Beyond its role in eosinophil biology, IL-5 can act on several other cell types with important biological functions. Functionally active IL-5R have been identified on tissue-resident human-activated B cells (plasma cells) from patients with non-steroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD).[33] Moreover, IL-5Rα chain expression is upregulated in activated human B cells.[34] These findings suggest a critical role for IL-5 in the regulation of lymphocyte responses, which will be important for future studies to investigate. Single cell sequencing of nasal sinus tissue has demonstrated that IL-5R are expressed on plasma cells, mast cells and ciliated epithelial cells.[35] In addition, stimulation of cultured human airway epithelial cells with IL-5 leads to downregulation

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of a range of cell adhesion molecules; this suggests a direct effect of IL-5 on epithelial cells that may weaken epithelial barrier integrity through the modification of cell-to-cell and cell-matrix adhesions.[36] Since IL-5 stimulation also decreases epithelial epidermal growth factor receptor (EGFR) gene expression[36] and EGFR is upregulated during epithelial repair,[37] local IL-5 release may cause NP epithelial cells to have a persistent epithelial damage/repair phenotype. Despite advances in our understanding of the involvement of eosinophil and IL-5 biology in type 2 inflammatory pathways, their role in CRSwNP pathophysiology is only starting to be uncovered.

Mechanistic role of eosinophils, IL-5, and other type 2 inflammatory mediators in CRSwNP

An accumulation of eosinophils infiltrating the nasal mucosa is characteristically observed in the majority of patients with CRSwNP.[38-40] This accumulation may be facilitated by prolonged survival, likely due to protection from cell death by locally produced cytokines, including IL-5, in the nasal tissue.[41] Eosinophils are activated upon recruitment to NP tissue and eosinophil activation status is important for disease pathology, as evidenced by the positive correlation between expression of the eosinophil activation marker CD69 and NP scores, in addition to the negative correlation between CD69 expression and lung function.[42] Following activation, eosinophils generate and secrete a plethora of factors including granule proteins, enzymes, cytokines, chemokines, growth factors, lipids, and oxidative products that contribute to type 2 inflammatory responses (**Figure 2; Figure 3; Table 1**).[12, 14, 43] In particular, IL-5 is upregulated in NP tissue compared with control samples,[31, 32, 44] and higher levels of IL-5 have been associated with more severe NP.[45] Interestingly, significant correlations have been reported between the number of epithelial eosinophils and the extent of

epithelial damage or sense of smell impairment in patients with NP.[46, 47] Moreover, the ability of IL-5 to downregulate the expression of cell adhesion molecules[36] may increase epithelial susceptibility to eosinophil-directed damage. Epithelial damage in response to eosinophil mediators triggers a repair response, leading to growth factor generation and fibroblast activation and collagen deposition.[14, 48] Consistent with this, there is a positive correlation between eosinophilic NP inflammation and the extent of fibrosis within polyps.[47]

Eosinophils release lipid mediators (**Table 1**), which are found in higher levels in the NP of patients with CRSwNP compared with patients with CRSsNP.[49] Among these, cysteinyl leukotrienes (LT) promote edema and nasal congestion via the induction of vascular leakage and vasodilation, as well as airway remodeling and inflammatory cell recruitment.[50] Oxidative products released by eosinophils (**Table 1**) are significantly upregulated in eosinophilic NP tissue compared with healthy controls, suggesting increased oxidative burden in patients with CRSwNP.[51] Eosinophils also generate extracellular DNA traps and release Charcot–Leyden crystals (CLC), both of which are strongly associated with CRSwNP disease severity.[52-55] In patients with CRSwNP, a correlation between the number of neutrophils and the extent of eosinophil extracellular DNA traps and CLC has been observed.[53] Moreover, elevated levels of CLC gene expression in patients with CRSwNP inversely correlate with olfactory threshold.[44] This may suggest that CLC contribute to olfactory dysfunction and loss of smell, which is more common in patients with CRSwNP than patients with CRSsNP.[46, 56]

Beyond eosinophils, several other IL-5R-expressing immune cells including mast cells, basophils, group 2 innate lymphoid cells (ILC2s), and IgG+ B cells, are elevated in patients with CRSwNP,[57-59] suggesting a potential role of these cells and IL-5 in disease pathology (**Figure 3**). In several eosinophilic disorders, eosinophils have the capacity to modulate mast cell functions via mediators including IL-5, platelet activating factor, granule proteins, and nerve growth factor.[60] Conversely, mast cells can release *de novo* synthesized mediators including IL-5 and GM-CSF, which can

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modulate eosinophils and other cells expressing the IL-5R.[60] In the context of allergic skin disorders, activated basophils modulate eosinophil tissue infiltration via the delivery of IL-4 to the endothelium, inducing endothelial vascular cell adhesion molecule-1, which is required for eosinophil accumulation.[61] Furthermore, both basophils and mast cells upregulate leukotriene E_4 (LTE_4) production in response to IL-5.[62, 63] In eosinophilic asthma, ILC2s are a source of IL-5 and may drive the initiation of eosinophil processes, via IL-5 signaling.[58] In patients with unexplained eosinophilia, eosinophil and B-cell counts are correlated, suggesting that factors secreted by activated eosinophils may lead to increased B-cell proliferation.[64] Additionally, in plasma cells from the NP tissue of patients with CRSwNP and N-ERD, IL-5 stimulation leads to the upregulation of transcripts involved in cell proliferation, suggesting that IL-5 may increase immunoglobulin (Ig) generation in NP tissue.[33]

Implications for treatment

Several therapeutic agents that directly or indirectly target eosinophils, including intranasal and systemic corticosteroids, biologics, and dexpramipexole (mechanism unknown) have been studied in patients with CRSwNP (**Figure 2**). Corticosteroids have a broad mechanism of action, improving the clinical symptoms of CRSwNP and reducing tissue eosinophil counts, eosinophil cationic protein (ECP) and IL-5 levels.[65] However, long-term use of systemic corticosteroids is associated with an increased risk of health complications.[66] Biologic therapies targeting type 2 inflammation may therefore represent an important treatment approach for patients with CRSwNP who have had surgery and fail to respond to short courses of systemic corticosteroids.[67]

Several biologics targeting IL-5 or the IL-5-R are associated with clinical benefits in patients with CRSwNP. For example, the anti–IL-5 monoclonal antibodies (mAbs) mepolizumab and reslizumab reduce eosinophil counts, nasal and peripheral IL-5, soluble IL-5Rα, and ECP levels in patients with CRSwNP.[68, 69] Mepolizumab also reduces several other local and systemic markers of type 2 inflammation, such as IgE and periostin, in addition to nasal matrix metallopeptidase 9 and myeloperoxidase.[68] Moreover, mepolizumab decreases numbers of circulating basophils and nasal levels of the pro-inflammatory mediators prostaglandin D2 (PGD_2), prostaglandin F2 alpha ($PGF_{2\alpha}$), leukotriene B4 (LTB_4), and thromboxane in patients with CRSwNP and N-ERD.[35] Although there are currently no data available on the impact of mepolizumab on B cells in CRSwNP, results from the MATERIAL trial in patients with mild asthma and rhinovirus infection suggested that mepolizumab can reduce blood and alveolar lavage fluid B-cell counts.[70] An initial investigation of the anti–IL-5 receptor mAb benralizumab suggested that treatment improves clinical symptoms and decreases eosinophil counts in patients with CRSwNP.[71] The subsequent Phase III, randomized OSTRO study demonstrated that compared with placebo, benralizumab in addition to SoC reduced nasal polyp score, nasal blockage, and difficulties with sense of smell in patients with CRSwNP.[38] However, statistically significant improvements in sinonasal outcome test (SNOT)-22 score at Week 40, time to first sinonasal surgery, and systemic corticosteroid use for NP were not observed between treatment groups. These results therefore warrant further investigation into the effects of benralizumab on type 2 inflammation in CRSwNP.

Other biologics targeting type 2 inflammation include the anti-IgE mAb, omalizumab, and the anti-IL-4Rα (the common signaling receptor subunit of IL-4 and IL-13) mAb, dupilumab.[72, 73] Studies have shown that omalizumab improves clinical symptoms of CRSwNP and reduces serum periostin, ECP, and soluble IL-5Rα levels, but with limited effect on local IL-5 and blood eosinophil counts.[68, 72] Dupilumab improves clinical symptoms along with decreasing NP levels of CCL24, CCL26, ECP, IL-5,

IgE, and pulmonary and activation-regulated chemokine.[73, 74] The SINUS-24/52 studies showed improvements in symptoms with dupilumab, despite a transient increase in blood eosinophil counts, which returned to pre-treatment baseline by 52 weeks post-treatment initiation.[74] This may indicate dupilumab is effective in inhibiting the recruitment of eosinophils from the blood into tissue, which is the proposed mechanism of dupilumab treatment benefits in severe asthma.[75] However, an analysis of patients in SINUS-52 revealed no significant association between higher blood eosinophil counts and treatment response to dupilumab, suggesting that eosinophils may not be a key mediator of dupilumab treatment benefits in CRSwNP.[76]

Studies of biologics that target type 2 inflammation may also provide more specific evidence of the roles of eosinophils and type 2 inflammatory mediators in CRSwNP pathophysiology. For example, the consistently demonstrated efficacy of IL-5–targeting biologics in reducing NP size and relieving symptoms in patients with CRSwNP[71, 77-79] suggests that IL-5 may be a particularly important treatment target for CRSwNP. Accordingly, patients with CRSwNP or eosinophilic CRS who have higher levels of IL-5 demonstrate greater responses to anti–IL-5 therapy.[69, 80] Further insight into the role of eosinophils in CRSwNP may be gained from two recently investigated molecules: antolimab and dexpramipexole. Phase I results suggested that antolimab, which targets siglec-8 (a cell surface receptor expressed by human eosinophils and mast cells) can decrease blood eosinophil counts in a dose-dependent manner,[81] whilst Phase II results suggested that it reduces NP score and has a similar safety profile to placebo.[82] However, CRSwNP has not been further pursued as an indication of antolimab. Dexpramipexole is a synthetic aminobenzothiazole developed as an oral treatment for amyotrophic lateral sclerosis (ALS), which despite promising early results, was discontinued for this indication following failure to meet the primary endpoint in a large Phase III trial.[83] However, it was observed that dexpramipexole reduced blood eosinophil counts in patients with ALS by an unknown mechanism of action[84]; therefore, it was further investigated in patients with eosinophil-associated

disease.[84, 85] In a proof-of-concept study of 16 patients with CRSwNP, dexpramipexole reduced blood and NP tissue eosinophils by up to 94% and 97%, respectively, whilst significantly increasing mast cell numbers.[85] Despite these observations, dexpramipexole was not associated with decreased NP size in a subgroup analysis of 10 patients.[85] Since markers of eosinophil activation status such as ECP were not reported, it remains uncertain if this lack of clinical benefit was due to a limited impact on eosinophil activation status.[86] Moreover, given the open-label design and small sample size of the proof-of-concept study, further, more rigorous investigation into the effects of dexpramipexole in CRSwNP is warranted.[85]

The results for dexpramipexole in patients with CRSwNP suggest that decreasing eosinophil counts alone is not sufficient for treatment benefits. Importantly, they also raise the question of whether eosinophils themselves represent the main target for effective NP treatments or whether in type 2 disease, the action of IL-5 on other cell populations, including B cells[87] and epithelial cells,[35] is key to the influence of anti–IL-5 biologic therapy. Indeed, one effect of mepolizumab treatment is the upregulation of nasal epithelial tight junction genes, consistent with this treatment improving epithelial barrier integrity.[35] Another potential factor might be the stage of the disease; it is plausible that although eosinophils drive initial NP formation, polyps become more resistant to therapeutic intervention once fibrosis has occurred.

Eosinophil counts as a biomarker of NP recurrence risk

The importance of eosinophils in CRSwNP pathophysiology is supported by data indicating that eosinophils play a prominent role in NP recurrence after surgery.[88-93] In a study conducted by Brescia et al, elevated levels of serum eosinophils and basophils were correlated with increased risk of NP

recurrence, with patients with serum eosinophil counts ≥3.8% more than twice as likely to experience NP recurrence than those with counts <3.8%.[88] Other studies have also demonstrated a significant association between the presence of tissue or blood eosinophils and NP recurrence.[89-93] Two studies have demonstrated an association between tissue IL-5 levels and NP recurrence.[11, 89] Together, these findings suggest eosinophils and IL-5 levels may have utility as biomarkers of NP recurrence in patients with CRSwNP.

NP tissue can be assessed during removal to directly quantify local eosinophil counts; however, peripheral blood eosinophil counts may also be a useful biomarker for NP recurrence. In patients with severe asthma, blood eosinophil counts are more predictive of anti–IL-5 treatment responses than tissue eosinophil counts; in chronic obstructive pulmonary disease, the two measures are correlated.[94-96] However, the relationship between peripheral blood and tissue eosinophils in patients with CRSwNP remains unclear, with most studies reporting a weak to moderate correlation between the two measures, and one study finding no correlation.[39, 40, 97-100] The European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) and Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) have suggested that peripheral blood eosinophil count be incorporated into algorithms for the diagnosis and assessment of CRSwNP severity.[3, 101] Although more challenging to measure, tissue eosinophil counts could be used as an alternative biomarker, since peripheral blood eosinophil counts can be impacted by factors such as systemic corticosteroid use.[102] Other alternatives for measuring tissue eosinophil counts include measuring ECP in nasal secretions,[11, 68] and analyzing mucus secretions for eosinophils.[92, 103] However, at present these techniques are mainly used for research purposes rather than in routine clinical practice.

Further insight into the use of blood eosinophil counts as a biomarker, including the determination of a relevant cutoff to assess the risk of NP recurrence in patients with CRSwNP, may come from

clinical trials such as the Phase III SYNAPSE study.[79] In SYNAPSE, patients with CRSwNP in need of revision ESS demonstrated significant improvements from baseline in total endoscopic NP score and nasal obstruction visual analogue score, with mepolizumab versus placebo (both in addition to SoC). Whether there is an association between treatment benefit and specific blood eosinophil counts remains to be determined. Blood eosinophil counts ≥300 cells/μL and/or the presence of comorbid asthma have been proposed as part of an algorithm to determine whether patients have type 2 inflammation, which may be useful to guide treatment decisions.[3]

Conclusions

Despite advances in our understanding of eosinophil biology and the involvement of eosinophils in type 2 inflammatory pathways, their exact role in CRSwNP pathophysiology requires further investigation. Currently, evidence suggests that eosinophil activation status or type 2 inflammatory cytokines, such as IL-5, play a key role in CRSwNP pathophysiology. Moreover, IL-5 is likely to act on immune cells other than eosinophils that are involved in type 2 inflammatory responses. Therefore, we suggest that in addition to eosinophils, IL-5 also represents a pertinent and effective treatment target in patients with CRSwNP. Evidence suggests blood eosinophil counts in addition to comorbid asthma may be a useful marker for assessing the risk of NP recurrence following ESS. Eosinophilia in CRSwNP may be best measured by less invasive techniques including blood eosinophil counts and nasal secretions. However, further research is needed to confirm these findings and to drive the development of effective treatment and nasal and systemic monitoring options in patients with CRSwNP.

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Tables

Table 1. Evidence for the mechanistic role of eosinophil-associated type 2 inflammatory mediators in CRSwNP

Inflammatory mediator	**Role in CRSwNP**
IL-3	• Upregulates eosinophil CD69 expression[104] • Present in increased concentrations in NP tissue compared with healthy controls[105] • Resistant to suppression by corticosteroid therapy[106]
IL-5	• Upregulates eosinophil CD69 expression[104] • Present in increased concentrations in NP tissue compared with healthy controls[105] • Higher levels associated with more severe CRSwNP[45] • Downregulates the expression of cell adhesion molecules which may increase epithelial susceptibility to eosinophil-directed damage[36]
IL-13	• Upregulated in patients with CRSwNP vs CRSsNP[107]
GM-CSF	• Upregulates eosinophil CD69 expression[104] • Present in increased concentrations in NP tissue compared with healthy controls[105]
CCL11, CCL13, CCL24, CCL26	• Upregulated in patients with CRSwNP vs CRSsNP[107]
ECP	• Upregulated in patients with CRSwNP vs CRSsNP[107] • Causes epithelial damage (altered permeability)[14] and therefore may disrupt olfaction
Eosinophil-derived neurotoxin	• Damaging to neurons and therefore may disrupt olfaction[14]

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LTs	• Significantly increased in CRSwNP vs CRSsNP (LTC_4, LTD_4, and LTE_4)[49] • Significantly correlated with IL-5 and ECP levels[49] • Promote edema and nasal congestion via the induction of vascular leakage and vasodilation, as well as airway remodeling and inflammatory cell recruitment[50]
PGE_2	• Levels inversely correlated with eosinophilic inflammation[49, 50, 108, 109] • Reduced expression in CRSwNP[49, 50, 108, 109]
PAF	• Potent mediator of inflammation in CRSwNP[110] • Increased levels associated with CRSwNP disease severity[110] • Levels correlate with tissue eosinophilia[110]
O2−•	• Significantly upregulated in eosinophilic NP tissue compared with healthy controls, suggesting increased oxidative burden in patients with CRSwNP[51]
NADPH oxidase 1 and 4	• Significantly upregulated in eosinophilic NP tissue compared with healthy controls, suggesting increased oxidative burden in patients with CRSwNP[51]
DNA traps and CLC	• Strongly associated with CRSwNP disease severity[52-55] • Extent of eosinophil extracellular DNA traps and CLC correlated with the number of neutrophils in patients with CRSwNP[53] • Elevated levels of CLC gene expression in patients with CRSwNP inversely correlated with olfactory threshold,[44] suggesting that CLC may contribute to olfactory dysfunction and loss of smell (although further studies are needed to determine this)

CCL11, eotaxin-1; CCL24, eotaxin-2; CCL26, eotaxin-3; CD69, cluster of differentiation 69 (an eosinophil activation marker); CLC, Charcot-Leyden crystals; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; ECP, eosinophil cationic protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; LT, leukotrienes; NADPH, nicotinamide adenine dinucleotide phosphate; NP, nasal polyps; O2−•, a superoxide radical anion; PAF, platelet activating factor; PGE_2, the anti-inflammatory prostaglandin.

Figure legends

Figure 1. IL-5 regulation of IL-5Rα isoforms[27, 28]

IL-5 promotes eosinophil activation and survival and reduces the responsiveness of eosinophils to IL-5 by regulating expression of the soluble and transmembrane IL-5Rα isoforms.

mRNA, messenger ribonucleic acid; sol-IL-5Rα, soluble interleukin-5 alpha receptor; TM-IL-5Rα; transmembrane interleukin-5 alpha receptor.

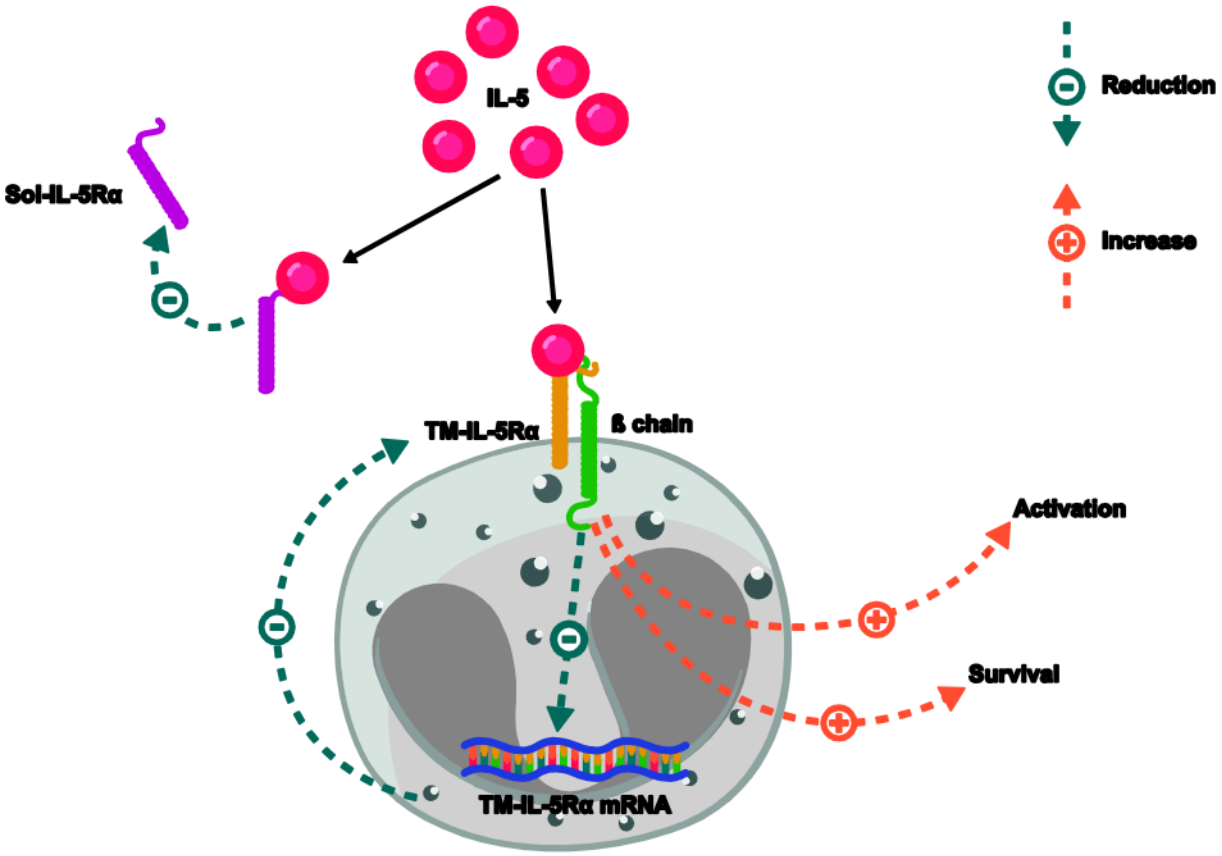

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Figure 2. Type 2 inflammatory mediators and biologic therapies targeting type 2 inflammation in CRSwNP[47, 68, 69, 71-73, 77-79, 81, 85, 111]

CRSwNP, chronic rhinosinusitis with nasal polyps; Ig, immunoglobin; IL, interleukin; ILC2, group 2 innate lymphoid cell; Th, T helper.

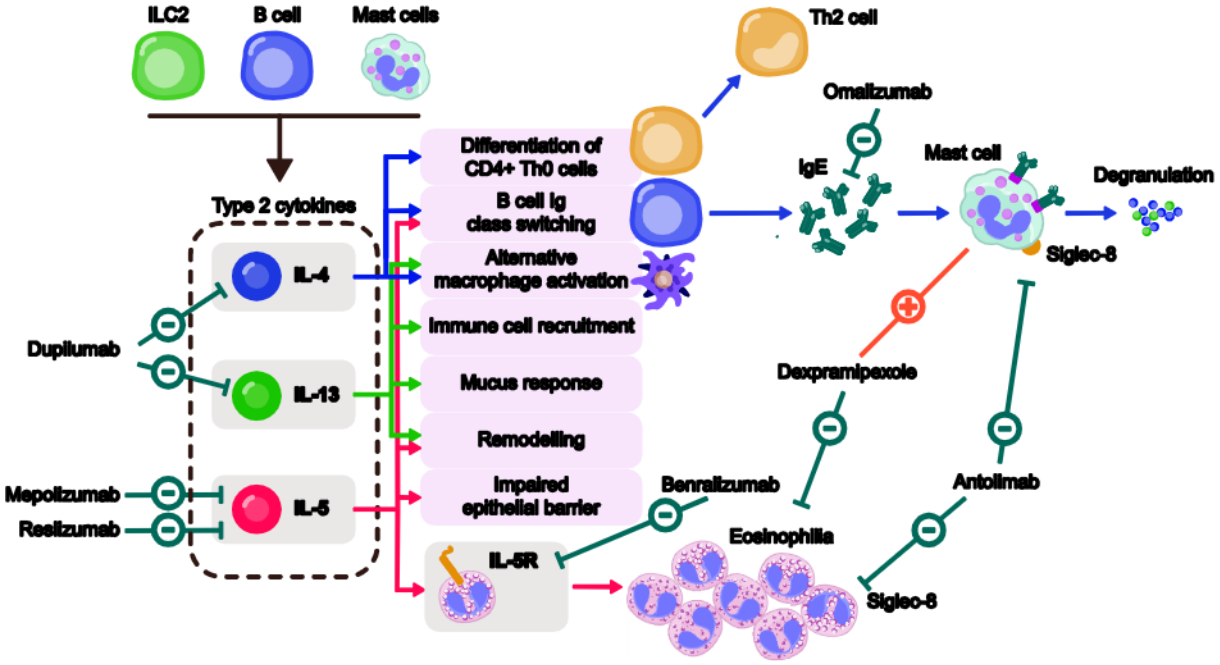
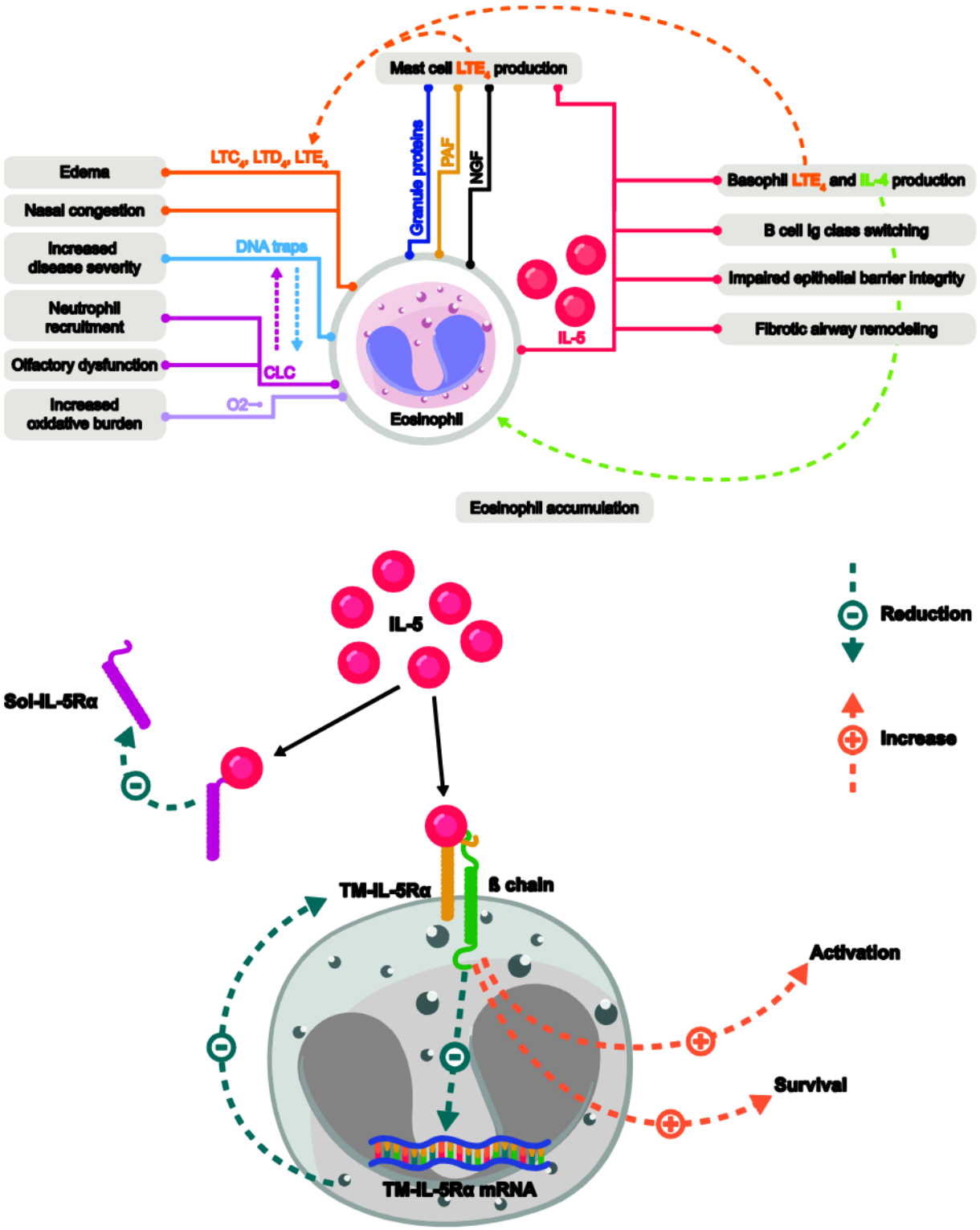


Figure 3. The role of IL-5 and eosinophils in the pathophysiology of CRSwNP[14, 44, 47, 50-55, 58, 61-63, 112]

CLC, Charcot–Leyden crystals; CRSwNP, chronic rhinosinusitis with nasal polyps; GM-CSF, granulocyte-macrophage colony-stimulating factor; Ig, immunoglobulin; IL, interleukin; ILC2, group 2 innate lymphoid cell; LTC_4, leukotriene C_4; LTD_4, leukotriene D_4; LTE_4, leukotriene E_4; NGF, nerve growth factor; O2−•, superoxide radical anion; PAF, platelet-activating factor.



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