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Enhanced IL-37-IL-1R8 axis is negatively associated with inflammatory and clinical severity of chronic rhinosinusitis with nasal polyps

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ABSTRACT

Background: The importance of IL-37 and downstream signal in the pathogenesis of chronic rhinosinusitis with nasal polyps (CRSwNP) demanding further investigation.

Objective: We sought to address the potential importance of the IL-37-IL-1R8 axis in regulating inflammatory response in patients with CRSwNP.

Methods: Nasal polyp (NP) tissues and control sinonasal tissues were obtained from adult CRSwNP, chronic rhinosinusitis without nasal polyps patients and healthy control subjects. The mRNA and protein levels of IL-37 and IL-1R8 in nasal tissues were examined by using quantitative PCR, immunohistochemical staining, and immunoblotting. In addition, the regulation of IL-1R8 expression was evaluated in human nasal epithelial cells (HNECs) in the presence of different stimuli.

Results: The mRNA and protein levels of IL-37 and IL-1R8 were significantly elevated in nasal polyps compared with that in control tissues. IL-37 and IL-1R8 were mainly distributed in the epithelial layer and lamina propria of tissues. IL-1R8 mRNA level in nasal polys was negatively associated with eosinophil and neutrophil infiltration, as well as endoscopic score and computed tomography score. Moreover, the mRNA expression of IL-1R8 in HNECs was significantly increased by toll-like receptor agonists, but significantly inhibited by proinflammatory cytokines, which can be rescued by using steroid (DEX).

Conclusion: Our findings showed that enhanced IL-37-IL-1R8 axis in NP tissues was negatively associated with inflammatory and clinical severity of CRSwNP patients, which could be considered as a future therapeutic target in CRSwNP patients.

Keywords: Chronic rhinosinusitis; IL-1 family; IL-1R8; IL-37; nasal polyps

1. Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a heterogeneous mucosa disorder with polyposis [1]. CRSwNP was usually characterized by type 2 (Th2) immune responses and tissue eosinophilia, whereas emerging evidence identified mixed type 1 and 3 (Th1 and Th17) immune responses and tissue neutrophilia involved in CRSwNP patients in some Asian countries [2]. Th2 inflammatory profile in CRSwNP patients has been generally ascribed to poor therapeutic prognosis and higher surgical recurrence. Xu et al. [3] provided evidence that periostin may play a role in the occurrence and progression of type 2 immune responses in eosinophilic CRSwNP patients. On the other hand, we also proved that CRSwNP patients with increased tissue neutrophils respond poorly to oral corticosteroids [4]. Liao et al. [5] detected elevated expression of IL-8 in some refractory CRSwNP patients. Kim et al. [6] identified tissue neutrophil infiltration predict a poor surgical result in patients with CRSwNP. Despite these research findings, key factors underlying poor or better prognosis in CRSwNP patients are not yet completely understood.

IL-37 is a newly identified cytokine belonging to the IL-1 family which has been demonstrated as a natural suppressor of innate immune response by inhibiting local and systemic inflammatory responses [7]. The IL-37 gene consists of 5 different splice variants (IL-37a to IL-37e), and IL-37b is the largest variant [8]. IL-37 binds to the receptor IL-1R8 and IL-18Rα to form a 3-type domain to silence the toll-like receptor (TLR) joint molecule MyD88 to exert an anti-inflammatory effect [9]. IL-1R8, also known as single immunoglobulin IL-1R-related molecule or toll/interleukin-1 receptor 8, is a component of the receptor recognizing the anti-inflammatory cytokine IL-37 [10]. Interestingly, anti-inflammatory cytokine IL-37 has been reported to be significantly upregulated in the peripheral blood of patients with rheumatoid arthritis, systemic lupus

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Table 1.
Demographics of subjects

Characteristic	Control subjects	Patients with CRSsNP	Patients with CRSwNP
No.	18	18	36
Gender: male/female	8/10	9/9	27/9
Age (y), mean (range)	41.3 (66–18)	48.7 (70–18)	43.5 (64–18)
Tissue sampled	UP	UP	NP
Atopy, n (%)	0	2 (0.11)	5 (0.14)
Asthma, n (%)	0	2 (0.11)	3 (0.08)
Aspirin intolerance triad, n (%)	0	0	0
Blood eosinophils (10^9/L), mean ± SD	0.13 ± 0.10	0.19 ± 0.04	0.29 ± 0.20
CT score, mean ± SD	NA	6.31 ± 2.29	9.89 ± 3.52
Endoscopic score, mean ± SD	NA	3.32 ± 2.16	5.39 ± 2.61

CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; CT, computed tomography; NA, not applicable; NP, nasal polyp; SD, standard deviation; UP, uncinate process.

erythematosus and allergic rhinitis [7, 11], as well as in nasal polyps of CRSwNP patients [11], indicating the importance of IL-37 and downstream signal in the pathogenesis of CRSwNP demanding further investigation. Thus, in this study, we tried to address the potential importance of IL-37-IL-1R8 axis in regulating inflammatory response in CRSwNP patients.

2. Methods

2.1. Subjects and tissue samples

Ethical approval for this study (approval number 2017-0301) was provided by the Ethics Committee of Eye & ENT Hospital of Fudan University, Shang hai, China (Chairperson Prof. Dehui Wang) on March 01, 2017, and every participant provided written informed consent. Patients were diagnosed according to the EPOS guideline [1], and the clinical severity of CRSwNP patients was determined by means of the endoscopic score (Lund-Kennedy staging system) and sinus computed tomography (CT) score (Lund-Mackay staging system). As healthy controls, the nonatopic patients who underwent endoscopic optic nerve decompression for traumatic optic neuropathy or transnasal cranial surgery for cerebrospinal fluid leak were enrolled. The demographics of all subjects are listed in Table 1. Polyp tissues from patients with CRSwNP, sinonasal tissues from patients with chronic rhinosinusitis without nasal polyps (CRSsNP), and healthy controls were collected during endoscopic surgery. Each sample was divided into 3 pieces: one was fixed overnight in a fixative containing 4% paraformaldehyde in phosphate buffered saline (pH 7.4) and embedded in paraffin for histological assessment, and the other 2 were stored in a refrigerator at −80°C for subsequent RNA and protein extraction.

2.2. Histological staining

Paraffin sections (4 μm) were used for histological staining. Hematoxylin and eosin (H&E) staining for eosinophil and immunohistochemical staining for IL-37, IL-1R8, and neutrophil (indicated by human neutrophil elastase [HNE]) were performed according to the manufacturer's instructions as we described elsewhere [4]. Rabbit anti-IL-37 antibody (Abcam, ab153889, 1:250), rabbit anti-IL-1R8 antibody (Abcam, ab233146, 30 μg/mL) and rabbit anti-HNE antibody (Abcam, ab131260, 1:500) were used as the primary antibodies. The number of eosinophils (H&E staining), neutrophils (HNE positive cells), IL-37 and IL-1R8 positive cells were counted, by observing 10 randomly selected fields at a 400× high magnification field and taken as the mean.

Table 2.
Primer sequences for qPCR

Gene	Forward primer (5′–3′)	Reverse primer (5′–3′)
IL-37b	TTTATAGGGCTCAGGTGGGC	ACCCCAACAGGCTCATTACA
IL-1R8	CATGCTGATTCTTCGAGGCC	AGATCCGAGACGTCCACTTC
β-actin	GCAGAAGGAGATCACTGCCCT	GCTGATCCACATCTGCTGGAA

qPCR, quantitative PCR.

2.3. Quantitative RT-PCR analysis

Total RNA extraction and reverse transcription were performed as we previously reported [12]. Expression of mRNA was analyzed using the LightCycler 480II RT-PCR System (Roche). For the relative quantification of the mRNA level, the expression of β-actin served as the internal control. The primer sequences are listed in Table 2.

2.4. Immunoblotting

Total protein extraction and immunoblotting were performed as we described elsewhere [13]. The polyvinylidene fluoride membranes were blocked and incubated with primary antibody (Rabbit anti-IL-37 antibody, 1:1500; Rabbit anti-IL-1R8 antibody, 1:1200; Mouse anti-β-actin antibody, 1:2000; all were from Abcam, Cambridge) and then incubated with the anti-Rabbit/Mouse IgG secondary antibody and detected using enhanced chemiluminescence reagent (Weiao Biotechnology, Shanghai). The immunoblotting image displayed on the film

Table 3.
Stimuli for HNECs

Stimuli	Concentration	Company
poly (I:C)	20 μg/mL	Sigma-Aldrich
LPS	10 μg/mL	Invivogen
Pam3CSK4	5 μg/mL	Invivogen
Flagellin	200 ng/mL	Invivogen
R848	5 μg/mL	MedChemExpress
IFN-γ	50 ng/mL	PeproTech
IL-1β	50 ng/mL	PeproTech
IL-4	50 ng/mL	PeproTech
IL-5	50 ng/mL	PeproTech
IL-13	50 ng/mL	PeproTech
IL-17	100 ng/mL	PeproTech

HNECs, human nasal epithelial cells.

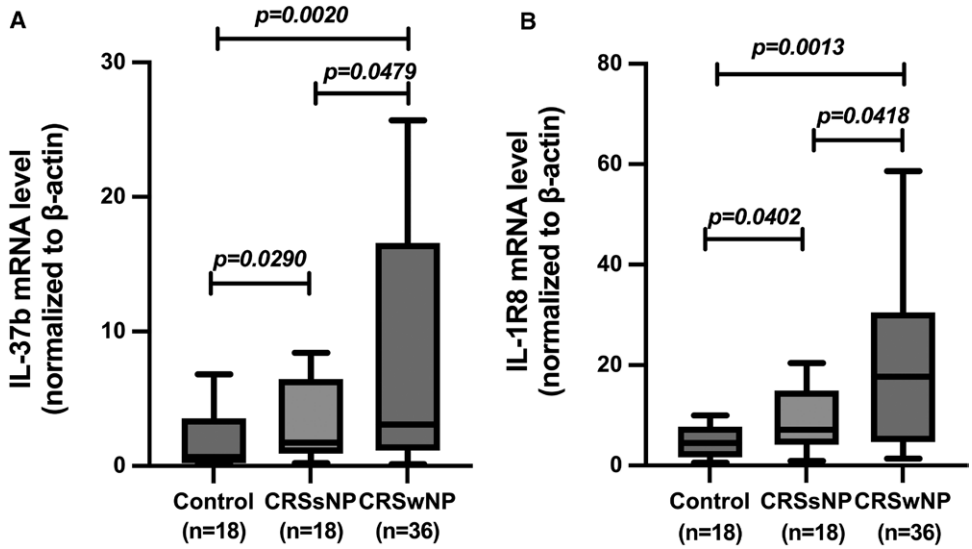

Figure 1. Increased mRNA expression of IL-37 and IL-1R8 in nasal polyp (NP) tissues of CRSwNP patients. (A, B) The mRNA levels of IL-37 and IL-1R8 in sinonasal tissues of healthy controls and CRSsNP and CRSwNP patients. CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps.

was scanned and then analyzed using Image J software (version 1.8).

2.5. Cell culture and stimulation

Human nasal epithelial cells (HNECs) were cultured as previously described [12]. When cells reached 80%–90% confluency, they were washed and treated for 8 hours with various TLR agonists and inflammatory cytokines, respectively. Stimuli are listed in Table 3. In addition, some HNECs were pretreated with dexamethasone (Millipore) for 3 hours.

2.6. Statistical analysis

Data were expressed as the medians and interquartile ranges and analyzed using the nonparametric Mann–Whitney *U* test in GraphPad Prism 9 software. For in vitro assays, the data were expressed as mean and standard errors of the mean (SEM) of 3 independent experiments, and unpaired Student *t* test was used for the statistical analysis. Pearson correlation coefficient test was used to assess the associations between data sets. A $P < 0.05$ was considered statistically significant.

3. Results

3.1. Expression of IL-37 and IL-1R8 gene and protein in NP tissues of CRSwNP patients

Firstly, we examined the expression of IL-37 and IL-1R8 in nasal polyps of CRSwNP patients and sinonasal tissues of CRSsNP and healthy control subjects. We found the mRNA levels of IL-37b and IL-1R8 in nasal polyps were significantly increased compared with control sinonasal tissues (shown in Fig. 1). We found IL-37 and IL-1R8 were mainly distributed in epithelial layer and lamina propria of tissues, as determined by immunohistochemical staining (shown in Fig. 2A). Be consistent with the mRNA results, the positive cells of IL-37 and IL-1R8 in nasal polyps were significantly increased than that in control tissues (shown in Fig. 2B, C). As to the protein levels, we found IL-37 and IL-1R8 protein levels were also significantly elevated in nasal polyps compared with control tissues, as determined by immunoblotting (shown in Fig. 3).

3.2. Association of IL-1R8 mRNA level with clinical severity of CRSwNP patients

We next analyzed the association of IL-1R8 mRNA level with tissue neutrophilia and eosinophilia in nasal polyps as well as the endoscopic score and CT score of CRSwNP patients. As shown in Figure 4, IL-1R8 mRNA level was negatively associated with

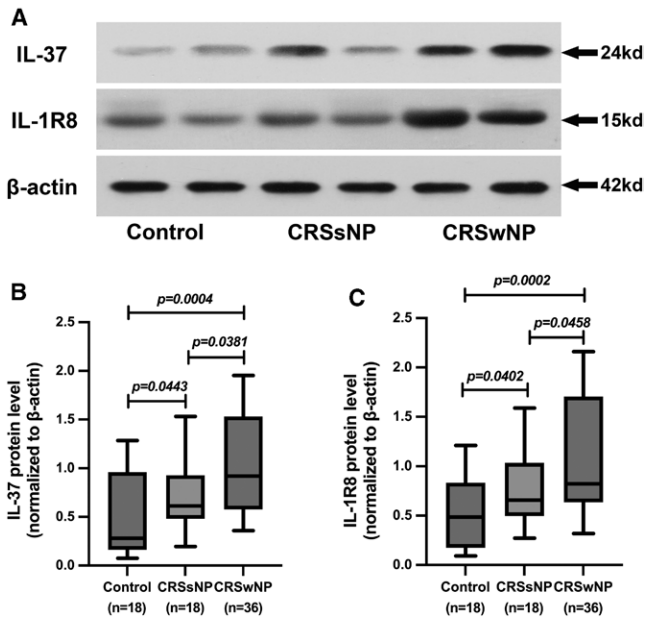

Figure 2. Immunoreactivity of IL-37 and IL-1R8 in nasal polyp (NP) tissues of CRSwNP patients. (A) Representative immunohistochemistry staining for IL-37 and IL-1R8 in sinonasal tissues of healthy controls and CRSsNP and CRSwNP patients. (B, C) The IL-37-positive cells and IL-1R8-positive cells in sinonasal tissues of healthy controls and CRSsNP and CRSwNP patients. CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps.

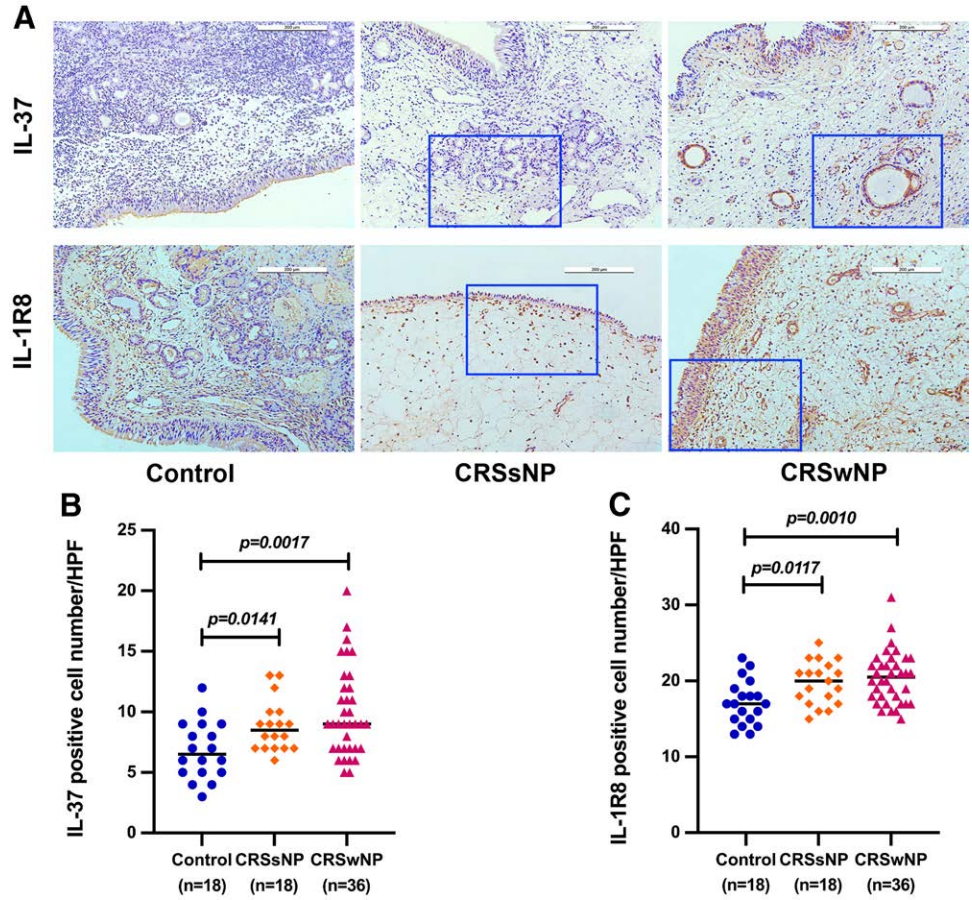

Figure 3. The protein levels of IL-37 and IL-1R8 in nasal polyp (NP) tissues of CRSwNP patients. (A) Representative immunoblotting results of IL-37 and IL-1R8 in sinonasal tissues of healthy controls and CRSsNP and CRSwNP patients. (B, C) The IL-37 and IL-1R8 protein levels in sinonasal tissues of healthy controls and CRSsNP and CRSwNP patients. CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps.

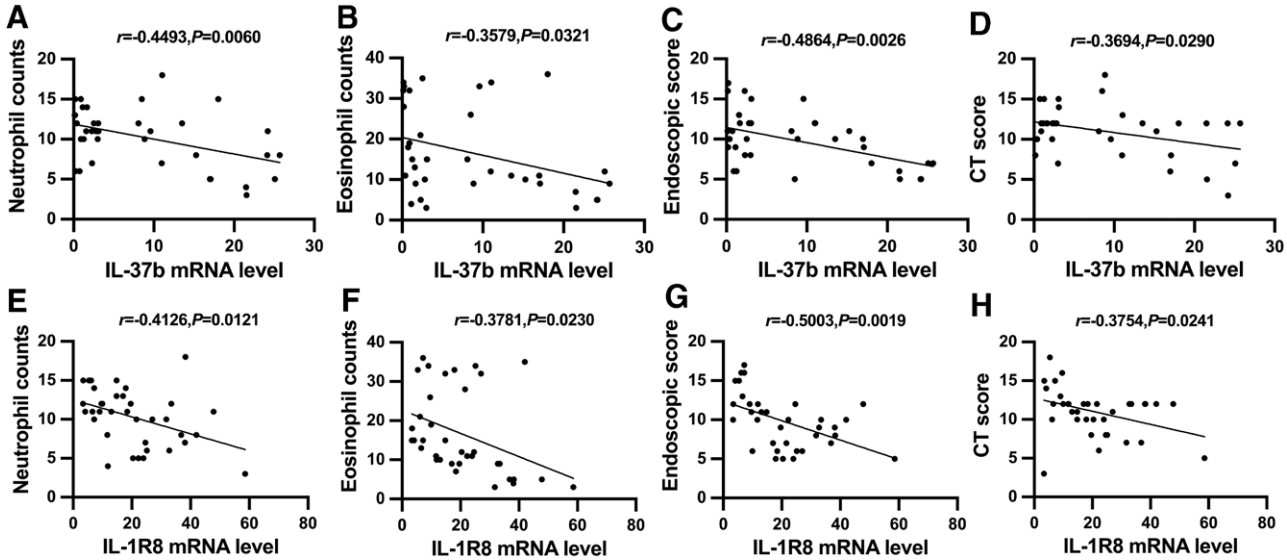

Figure 4. Association of IL-1R8 mRNA level with clinical severity of CRSwNP patients. (A–D) The association of IL-1R8 mRNA level with the number of infiltrated neutrophils and eosinophils, endoscopic score, and CT score of CRSwNP patients. CRSwNP, chronic rhinosinusitis with nasal polyps; CT, computed tomography.

the number of infiltrated neutrophils and eosinophils in nasal polyps. In addition, we found IL-1R8 mRNA level was also negatively associated with the endoscopic score and CT score of patients with CRSwNP.

3.3. Regulation of IL-1R8 mRNA expression in HNECs

Finally, we evaluated the mRNA level of IL-1R8 in vitro. As shown in Figure 5, HNECs were stimulated respectively with various TLR agonists and inflammatory cytokines for 8 hours

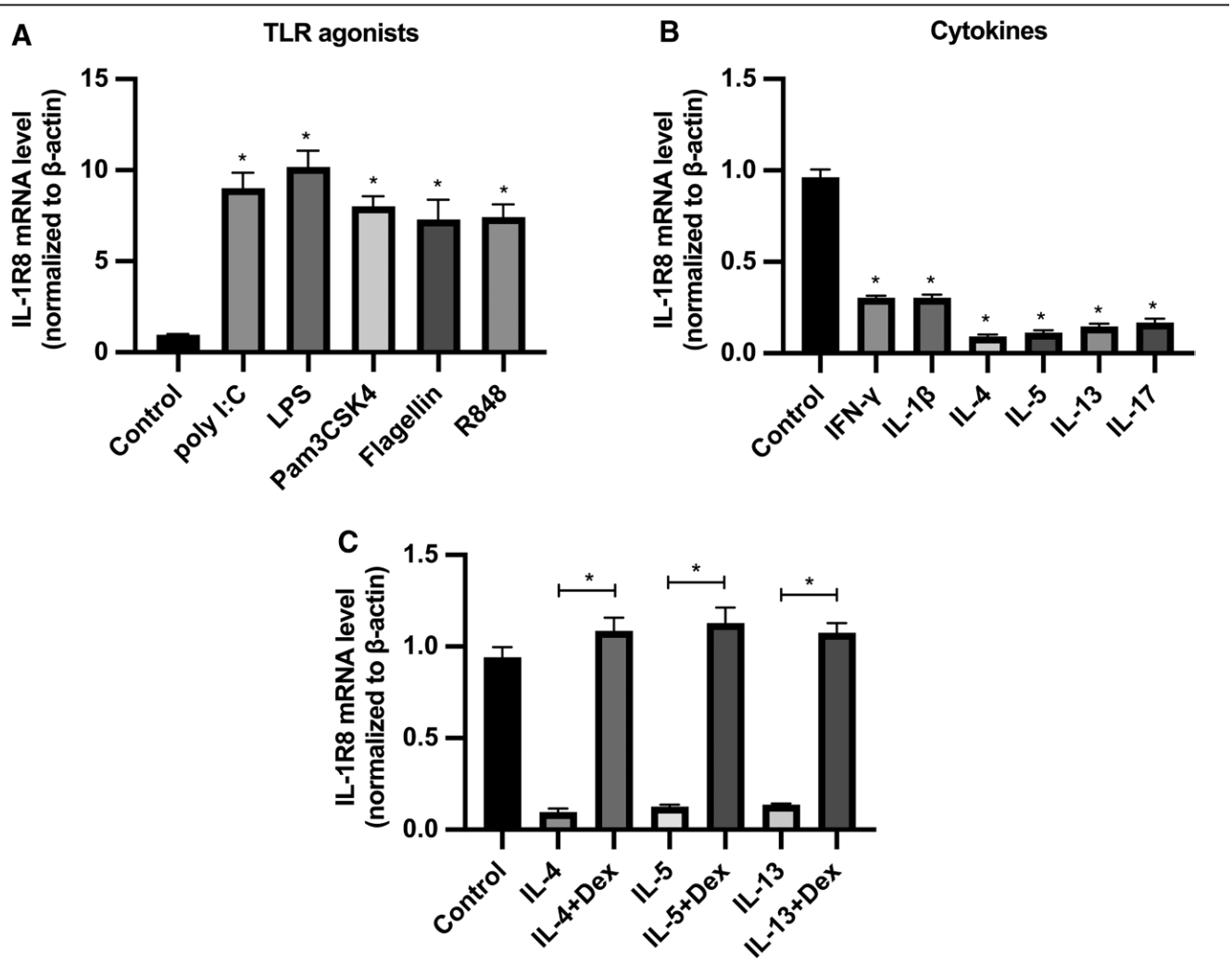

Figure 5. Expression of IL-1R8 in nasal epithelial cells in the presence of different stimuli. (A–C) The mRNA expression of IL-1R8 in human nasal epithelial cells after stimulation with TLR agonists, cytokines, or steroid. Cells were cultured alone or with TLR agonists (poly [I:C], LPS, Pam3CSK4, Flagellin, R848), cytokines (IFN-γ, IL-1β, IL-4, IL-5, IL-13, IL-17) as well as dexamethasone (DEX) for 8 h (n = 3). *$P < 0.05$. TLR, toll-like receptor.

and harvested. We observed that these TLR agonists could significantly increase the mRNA level of IL-1R8 in HNECs. As to the inflammatory cytokines, type 1 (IFN-γ, IL-1β), type 2 (IL-4, IL-5, IL-13), and type 3(IL-17) cytokines could all significantly decrease the mRNA level of IL-1R8 in HNECs. Furthermore, DEX could significantly increase the IL-1R8 mRNA level in HNECs in the presence of Th2 cytokines.

4. Discussion

This study revealed that the mRNA and protein levels of IL-37 and IL-1R8 were significantly increased in nasal polyps of CRSwNP patients, indicating an enhanced regulatory IL-37-IL-1R8 axis in orchestrating the complicated pathogenesis of CRSwNP. Moreover, we also observed IL-1R8 mRNA level was negatively associated with tissue eosinophil and neutrophil accumulation (inflammatory severity), as well as the clinical severity indicating by endoscopic score and CT score, in these CRSwNP patients. These findings might provide the first evidence that IL-37-IL-1R8 axis is involved in the pathogenesis of CRSwNP patients as a negative regulator.

CRSwNP was characterized by Th2 immune responses and enhanced eosinophils infiltration [1]. Recently, neutrophilic inflammation has been suggested to play an important role in driving the pathogenesis of CRSwNP as well [2]. In this study, we firstly demonstrated the mRNA and protein levels of IL-37 and IL-1R8 in nasal polyp (NP) tissues were significantly increased in NP tissues compared with the control sinonasal tissues, indicating an enhanced IL-37-IL-1R8 axis in CRSwNP patients. IL-37 has been demonstrated to play fundamental immunosuppressive roles by broadly reducing both innate inflammation and acquired immunity. Paradoxically, elevated, or decreased IL-37 expression was observed in various inflammatory conditions including NP tissues [14, 15], demanding a further investigation of IL-37 downstream signal molecule in regulating the inflammatory response.

IL-1R8 is a member of the IL-1 receptor family with distinct structural and functional characteristics, it has been known to be act as the receptor of IL-37 and exert a negative regulator of ILR and TLR downstream signaling pathways and inflammation [10]. Molgora et al. [16] proved that knocking down IL-1R8 can release NK-cell-mediated resistance to hepatic carcinogenesis, hematogenous liver and lung metastasis. Jia et al. [17] reported that IL-37 can reduce endothelial cell apoptosis and inflammatory response in Kawasaki disease via the IL-1R8 pathway. Since IL-37 is known to be an anti-inflammatory cytokine which is involved in various inflammatory disorders, we thus assume there may exist a brake mechanism of IL-1R8 to

negatively regulate the inflammatory response in NP tissues. To address this issue, we then analysis the association of IL-1R8 mRNA with tissue inflammatory severity (eosinophil and neutrophil), as well as clinical severity (indicating by endoscopic score and CT score) of CRSwNP patients. As expected, we found IL-1R8 mRNA level was negatively associated with tissue eosinophil and neutrophil accumulation, as well as the clinical severity of CRSwNP patients. In the previous study, Liu et al. [15] observed increased IL-37 expression in NP tissues, but reduced IL-37 levels in nasal secretions in patients with eosinophilic CRSwNP, which may be the result of suppression by local Th2 cytokines. This finding provides a possibility that IL-37 might be acted as a good prognostic marker of CRSwNP patients. However, unlike IL-37, the role of IL-1R8 in CRSwNP has not been well understood.

Since IL-1R8 serves as the pivotal downstream molecule of IL-37 signal pathway, we thus examined the expression and regulation of IL-1R8 in HNECs in response to TLR agonists, cytokines, and steroids. Interestingly, we found IL-1R8 mRNA level in HNECs was significantly upregulated by TLR agonists, but was significantly downregulated by Th1, Th2 and Th17 cytokines. Moreover, Th2 cytokines (IL-4, IL-5, and IL-13) were the most prominent inhibitor of IL-1R8 expression in HNECs, testifying the finding that IL-37-IL-1R8 axis is negatively associated with the inflammatory and clinical severity of CRSwNP patients. On the other hand, it is known that steroid is the most effective treatment for CRSwNP patients by comprehensive inhibiting inflammatory, both oral and intranasal steroid can reduce NP size and improve nasal symptoms [4]. Therefore, we further evaluated the expression of IL-1R8 in HNECs in the presence of both Th2 cytokines and DEX. Consequently, we found the inhibition of IL-1R8 mRNA level in response to IL-4, IL-5 and IL-13 was significantly rescued by adding DEX, indicating IL-1R8 may act as a critical component in negatively regulating inflammatory response in CRSwNP patients.

5. Conclusion

In summary, we found an enhanced IL-37-IL-1R8 axis in NP tissues, which was negatively associated with inflammatory and clinical severity of CRSwNP patients. IL-1R8 expression in HNECs was stimulated by TLR agonists but was inhibited by Th2 cytokines that can be rescued by adding steroids. These findings may provide a new insight into the possible role of the enhanced IL-37-IL-1R8 axis in regulating immune and inflammatory response in CRSwNP patients, which could be considered as a future therapeutic target.

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Conflicts of interest

The authors have no conflicts of interest.

Author contributions

Jia Zhang: Methodology, investigation, formal analysis, and writing—original draft. Yujie Cao: Resources, investigation, and data curation. Kun Chen, Xianting Hu, Chun Zhou, Lei Li, and Miaomiao Han: Data curation. Huabin Li: Conceptualization, validation, writing—review and editing, and funding acquisition. Dehui Wang: Supervision.

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