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ORIGINAL ARTICLE



Differential expression of CCL18 in moderate/severe and mild persistent allergic rhinitis and its correlation with disease parameters

Ashkan Pirayesh^a, Samira Ferdosi^b, Hedayatollah Shirzad^a, Soroush Amani^c, Hajar Bahadivand Chegini^a, Nader Bagheri^a, Ladan Sadeghian^a, and Farbod Torkamand^d

^aCellular and Molecular Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran; ^bGroup of genetics, cancer research center, Cancer institute of Iran, Tehran university of medical sciences (TUMS), Tehran, Iran; ^cDepartment of otorhinolaryngology, Shahrekord University of Medical Sciences, Shahrekord, Iran; ^dFaculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

Background and Aims: This study aimed to assess the level of the expression of CCL-18 on nasal inferior turbinate mucosa in patients with mild (M) and moderate-to-severe (M/S) persistent allergic rhinitis (PAR).

Methods: The participants in this case-controlled study were divided into three groups: patients with M/S PAR, patients with M PAR, and the healthy control group. Biopsies of nasal inferior turbinate mucosa were obtained from the participants. Expression of CCL-18 mRNA was evaluated by real-time PCR. The serum levels of CCL-18 were determined by ELISA. Total serum IgE levels and specific serum IgE levels were measured. The clinical manifestations were assessed using the total nasal syndrome score (TNSS).

Results: Gene expression and the serum level of CCL-18 in patients with M/S PAR increased significantly compared to the control group and patients with M PAR. The serum level of CCL-18 was found to correlate with TNSS in patients with M/S PAR. There was a statistical correlation between the serum level of CCL-18 and the total serum IgE in the treatment groups.

Conclusion: The results of the study indicate that there could be a relationship between the expression of CCL-18 in nasal turbinate mucosa and the severity of allergic rhinitis.

KEYWORDS

CCL-18; ELISA; disease severity; real-time PCR

Introduction

The most prevalent allergic disorder is allergic rhinitis (AR). Epidemiological studies propose that the prevalence of AR is increasing globally.^[1,2] About 400 million individuals suffer from AR,^[1,3] but the reason for the increase in AR is not known. Reports demonstrate that AR is prevalent in third-world countries because of climate change and the environment.^[1,4] The symptoms

of this disease are nasal pruritus, sneezing, airflow obstruction, and a clear nasal discharge. This type of allergy is an IgE-mediated inflammation of the nasal mucous membranes owing to the interaction of inhaled allergens as determined by the eosinophils, T cells, mast cells, and basophils that release chemokines and cytokines and communicate with the bone marrow and immune system.^[3,5]

These symptoms have a noticeable effect on the quality of life and health care.^[6] AR is determined by the T helper (Th)2-polarized immune response.^[7] It can be classified as persistent or intermittent.^[8,9] Persistent AR manifests on more than 4 days per week for more than 4 weeks. Intermittent AR occurs less than 4 days per week for less than 4 weeks.^[10,11] It can also be categorized based on a severity scale of mild (M) to moderate-to-severe (M/S). Patients with M/S AR experience abnormal sleep, inability to carry out daily activities or impairment of work and sports. Patients with M AR experience normal sleep, ability to carry out daily activities and sports and normal work.^[11]

The group of proteins known as chemokines recruit inflammatory cells into tissue by binding G protein-coupled receptors onto target cells.^[12,13] Overstated expression of chemokines can cause tissue damage and inflammatory illnesses by excessive recruitment of leukocytes. Consequently, chemokine receptors are potential targets for treating many inflammatory diseases.^[12,14,15] One of the most highly expressed chemokines is CC chemokine ligand 18 (CCL18). It has been observed in human chronic inflammatory ailments as secretions by monocytes and dendritic cells (DCs), but the receptor for this gene is not known.^[16,17]

Studies have shown that the receptor for CCL18 is CCR8. CCL18 has a high affinity for CCR8 and results in its internalization. Determination of CCR8 for CCL18 (as a chemokine receptor) will assist in identification of its biological role in human disease.^[17] CCL18 is a pulmonary and activation-regulated chemokine, DC-chemokine 1 (DC-CK1), alternative macrophage activation-associated CC chemokine-1, and macrophage inflammatory protein-4. It is a 7.8-kDa protein (including 69 amino acids).^[12,18] Lymphocytes and immature DCs are targeted first by CCL18; however, the agonistic of the receptor is not known. CCL18 is mostly expressed by monocytes, macrophages, and DCs. Expression of *CCL18* is regulated by Th2 cytokines IL-4 and IL-13, as well as by IL-10.^[12,18] This gene can be involved in TH2-related inflammatory diseases like asthma and atopic dermatitis.^[12]

The present study was undertaken to investigate the human serum expression levels of CCL18 in patients with M/S persistent allergic rhinitis (PAR) and evaluate mRNA expression of CCL18 in human inferior turbinate mucosa in patients with M/S PAR as compared to M PAR and a control group. It also was undertaken to determine the correlation between serum levels of CCL18 and clinical parameters.

Material and methods

Subjects

The patients were split to one of three groups: M/S PAR ($n = 30$), M PAR ($n = 30$), and a healthy control group ($n = 30$). These selected patients had no history of nasal infection, allergy, smoking, or ongoing drug treatment. Inferior turbinate mucosal biopsies were obtained from these patients during surgery. The diagnosis of AR was established on the basis of a medical history and symptoms (sneezing, rhinorrhea, and nasal congestion on most days) for at least 2 years, positive skin test results, and positive specific IgE ELISA tests for house dust mites (Astra Biotech, Berlin, Germany). The severity of the nasal symptoms were ranked according to the principles defined by Okuda *et al.*^[18] in which three nasal symptoms (sneezing, rhinorrhea, and nasal obstruction) are rated on a 4-point scale from 0 to 3 (0: no symptoms, 1: minimal, well-tolerated symptoms, 2: bothersome but tolerated symptoms, 3: severe and hard to tolerate symptoms). Patients with AR were classified as mild or moderate/severe persistent according to the AR and its impact on asthma criteria.^[8] The exclusion criteria were current smoking, medical history of asthma or recurrent infections of the respiratory tract and use of anti-allergy medication during the 4 weeks that preceded the study.

Before the tissue specimens were obtained, all the protocols had been approved by the institutional review board and all participants gave their written informed consent. Venous blood samples were obtained from patients. Blood drawing, handling, and storage were performed by the same researchers. Some tissue was immediately frozen in liquid nitrogen and stored at -70°C for extraction of RNA and some was preserved in paraffin for hematoxylin and eosin (H&E) staining. Four-millimeter punch nasal biopsies were collected from the inferior turbinate of both treatment groups and the control group. Biopsy specimens were submerged immediately in 10% buffered formalin and prepared for paraffin embedding. The paraffin blocks were cut into sections of 4 μm in thickness and mounted on glass slides. They were prepared for routine H&E staining for conventional histopathology.

Real-time PCR analysis of CCL18

The total RNA was isolated from nasal tissue using Biozol reagent (BioFlux, Tokyo, Japan). The quantity and quality of the RNA were measured by spectrophotometry using the wavelength absorption ratio (260/280). Some RNA samples (1 mg/mL) were coupled with DNase1 (10 u/mL) for 30 min in order to avoid DNA contamination.

Following the second RNA extraction, cDNA was produced in a 20-mL reaction tube from 1 mg total RNA (Thermo Fisher Scientific, Vilnius, Lithuania) with random primer. The reactions were incubated at 25°C for

5 min, 42°C for 1 h, and 72°C for 5 min. The primer sequences pairs were as follows: CCL-18, 5'-GAG TGC TGC CTC GTC TAT ACC T-3' (forward) and 5'-ACC GGT GAC GAG GAT GAC ACC T-3' (reverse); β -actin, 5'-AGC GAG CAT CCC CCA AAG TT-3' (forward) and 5'-GGG CAC GAA GGC TCA TCA TT-3' (reverse). β -Actin was used as the internal control. Expression was determined by quantitative real-time PCR using SYBR Green master mix (Takara, Japan). Standard curves were drawn and efficiency was determined for each set of primers. The determined efficiency was typically above 90%. The data are expressed as fold change using a comparative cycle threshold ($\Delta\Delta C_t$ method). Relative gene expression was determined by the $2^{-\Delta\Delta C_t}$ method.

Assessment of CCL18 level by ELISA

CCL-18 levels in normal, M PAR, and M/S PAR serum were measured using ELISA following manufacturer protocol (Abnova, Taipei, Taiwan). Data were expressed as ng/ml of protein. Protein concentration was determined using the Starsat ELISA reader (Awarness, Phoenix, AZ, USA).

Statistical analysis

Statistical analysis was carried out using SPSS for Windows (IBM SPSS statistics, version 16.0.0; SPSS, Chicago, IL, USA). One-way ANOVA with post hoc Tukey tests were performed in order to evaluate whether or not values obtained by real-time PCR and ELISA differ between the nasal mucosa of healthy controls and patients with mild and M/S PAR. The Student's *t*-test was used to analyze differences in specific IgE values between M/S PAR and M PAR. Correlations were assessed using the Pearson correlation test. A value of $P < 0.05$ was considered to be statistically significant.

Results

Clinical characteristics of the subjects

The characteristics of patients with persistent AR and healthy controls are shown in Table 1. The age distribution was similar between the healthy controls and patients with PAR. The duration of the disease did not significantly differ between the M and M/S PAR groups (Table 1). The serum total IgE levels were higher in patients with M PAR and M/S PAR than in individuals with healthy nasal mucosa (Table 1).

Table 1. Participants characteristics.

Variable	Healthy control	M PAR	M/S PAR
Gender (male/female)	18/12	20/10	22/8
Age	28.5 ± 6.42	26.03 ± 4.03	26.7 ± 4.87
Specific IgE for house dust mite (IU/mL)	0	0.5 ± 0.15	4.56 ± 5.56
Total IgE (IU/mL)	82.63 ± 43.88	236.3 ± 33.24	1061.1 ± 88.41
Blood eosinophil count (absolute count)	74.5 ± 40.02	255.73 ± 70.96	618.97 ± 114.17
The degree of eosinophil infiltration into the nasal mucosa (eos/HPF)	0.5 ± 0.5	1.7 ± 0.59	3.63 ± 1.88
Disease duration (years)	–	15.1 ± 2.64	17.16 ± 4.38

Gene expression levels of CCL-18 in nasal mucosa

The gene expression level of CCL-18 was determined in healthy, M PAR, and M/S PAR nasal mucosa using real-time PCR. The expression level of CCL-18 increased significantly in the nasal mucosa of patients with M/S PAR nasal mucosa compared to the nasal mucosa of patients with M PAR and the control group (Figure 1). The gene expression of CCL-18 was statistically different between the M PAR and control group.

Serum levels of CCL-18 in patients with M/S PAR, M PAR, and healthy controls

The CCL-18 levels (ng/mL) were measured in serum from patients with M/S PAR, M PAR, and healthy controls (Figure 2). Significantly higher levels of CCL-18 were found in serum from patients with M/S PAR when compared with that from the healthy subjects ($P < 0.05$) and patients with M PAR. Likewise, the differences between M PAR and healthy controls were statistically significant ($P < 0.05$) (Figure 2).

Association of serum levels of CCL-18 with immunopathogenesis of M PAR

There was no statistically significant correlation between serum CCL-18 levels and the total nasal symptom score (TNSS) as the sum of sneezing, rhinorrhea, and congestion scores ($R = 0.298$; $P > 0.05$; Figure 3a). The congestion score significantly and positively correlated with the serum levels of CCL-18 ($R = 0.366$; $P < 0.05$), whereas the rhinorrhea ($R = 0.009$; $P > 0.05$) and sneezing ($R = 0.282$; $P > 0.05$) scores did not. There were significant associations between serum levels of CCL-18 and the blood eosinophil count ($R = 0.725$; $P < 0.05$; Figure 3b), the degree of eosinophil infiltration into the nasal mucosa ($R = 0.447$; $P < 0.05$; Figure 3c), and TIgE ($R = 0.518$; $P < 0.05$; Figure 3d). No statistically significant correlation was found between serum levels of CCL-18 and SIgE ($R = 0.266$; $P > 0.05$; Figure 3e).

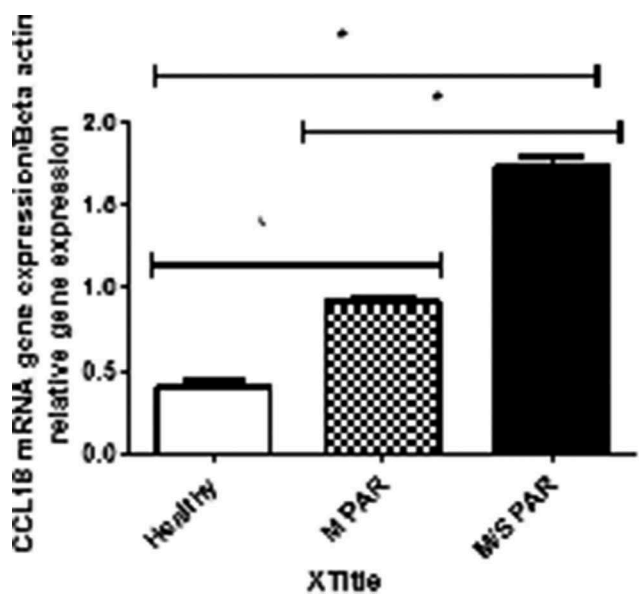


Figure 1. Real-time PCR of CCL-18 mRNA in inferior turbinate nasal mucosal tissue from the study groups. *denotes a significant difference in the expression levels of CCL-18 between groups ($P < 0.05$). The results are shown as mean $\pm$ SD ($n = 30$ per group).

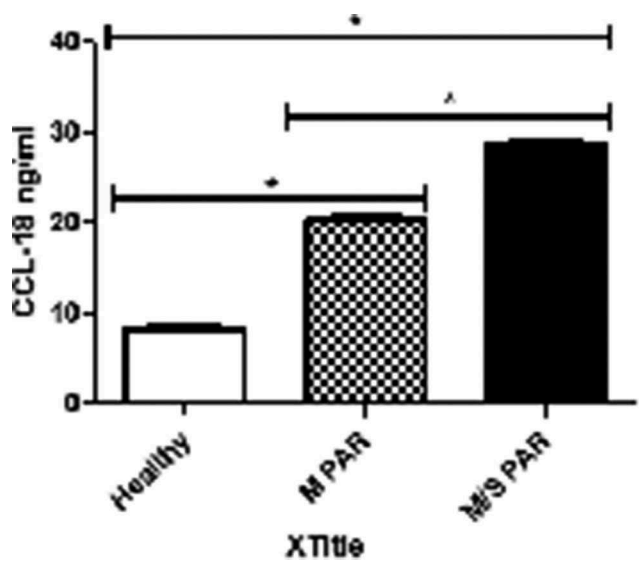


Figure 2. Comparison of serum levels of CCL-18 in control, M PAR, and M/S PAR groups. *denotes a significant difference in the expression levels of CCL-18 between groups ($P < 0.05$). Results are shown as mean $\pm$ SD ($n = 30$ per group).

Association of serum levels of CCL-18 with immunopathogenesis of M/S PAR

A significant and positive correlation was seen between serum levels of CCL-18 and TNSS ($R = 0.583$; $P < 0.05$; [Figure 4a](#)). In detail, the rhinorrhea score per se

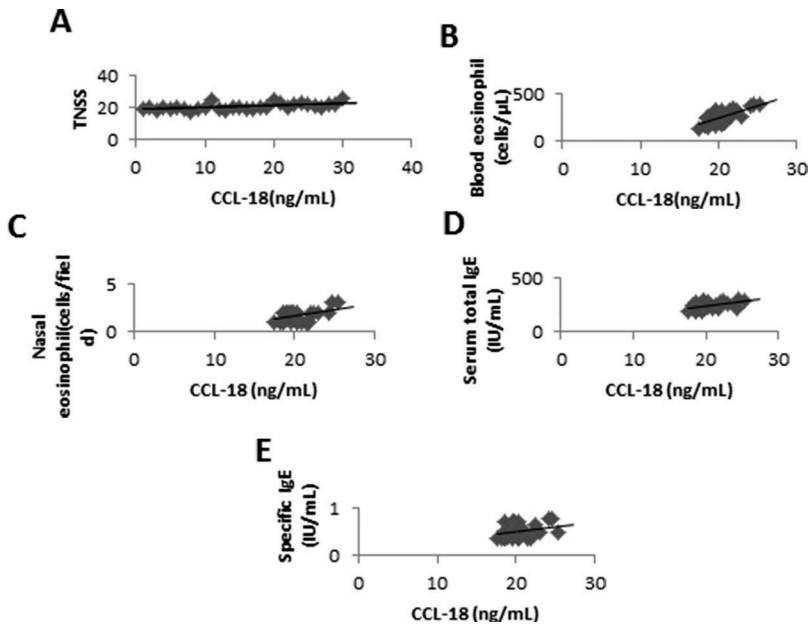


Figure 3. Correlation between: serum levels of CCL-18 and (a) TNSS, (b) blood eosinophil count, (c) nasal eosinophil count, (d) TIgE, and (e) SIgE in patients with M PAR.

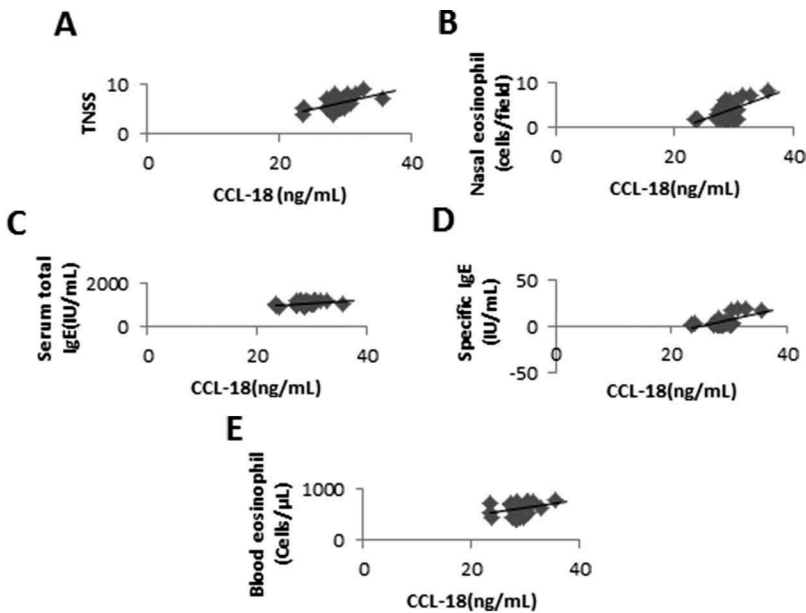


Figure 4. Correlation between serum levels of CCL-18 and (a) TNSS, (b) nasal eosinophil count, (c) TIgE, (d) SIgE, and (e) blood eosinophil count in patients with M/S PAR.

($R = 0.438$; $P < 0.05$) and congestion ($R = 0.529$; $P < 0.05$) were significantly and positively correlated with the serum levels of CCL-18, whereas sneezing was not ($R = 0.154$; $P > 0.05$). The association between serum Levels of CCL-18 and the degree of eosinophil infiltration into the nasal mucosa ($R = 0.604$; $P < 0.05$;

Figure 4b), TIgE ($R = 0.401$; $P < 0.05$; Figure 4c), and SIgE ($R = 0.623$; $P < 0.05$; Figure 4d) was statistically significant. By contrast, there was no statistically significant correlation between serum levels of CCL-18 and blood eosinophil count ($R = 0.295$; $P > 0.05$; Figure 3e).

Discussion

The present study characterized the serum level of CCL-18 in the pathogenesis of persistent AR. Although the increased gene expression of CCL-18 in AR has previously been reported,^[19] in this study, patients were classified into subgroups and attempts were made to focus on pathological studies, determination of serum levels of CCL-18, and mRNA expression of CCL-18 in particular, and assessment of their relation to clinical manifestations.

In this well-characterized cohort study, it has been shown for the first time that gene expression and serum CCL-18 level increased in patients with M/S PAR compared with patients with M PAR and the healthy control group. A particular strength of the present study is the investigation of the association between serum CCL-18 level and the immunopathogenesis of PAR. Serum levels of CCL-18 significantly correlated with TNSS in patients with M/S PAR. By contrast, there was no statistically significant correlation between CCL-18 levels and TNSS in patients with M PAR. One interpretation of this finding is that CCL-18 level is closely associated with the disease severity of M/S PAR, but not with M PAR.

When the individual symptoms were analyzed separately, only the congestion score correlated with the serum levels of CCL-18 in patients with M/S PAR and M PAR. There was no statistical correlation detected between serum CCL-18 level and sneezing in patients with M/S PAR and M PAR. Moreover, the serum CCL-18 level statistically correlated with rhinorrhea in patients with M/S PAR.

Other differences were that the serum CCL-18 level statistically correlated with SIgE in patients with M/S PAR but not in patients with M PAR. There also was no correlation between serum CCL-18 levels and blood eosinophil count in patients with M/S PAR, but there was in patients with M PAR.

The results of the present study show that CCL-18 levels in both patients with M PAR and M/S PAR were noticeably and positively correlated with the number of eosinophils infiltrating the nasal mucosa. Restricted persistent inflammation and the priming effect are induced by eosinophil infiltration into the nasal mucosa, both of which can heighten nasal hyperactivity. The hypothesis arising from these observations is that the serum level of CCL-18 may induce inflammation by increasing eosinophilic inflammation. Future studies will be required to investigate the production of CCL-18 in the inferior turbinate of patients with persistent AR. CCL18 is mainly secreted by antigen-presenting cells, in particular by eosinophils^[20] and by mast cells after FcεRI cross-linking.^[21,22]

Besides its constitutive expression, CCL-18 also displays characteristic features of inflammatory chemokines, such as IL-4, IL-13, and IL-33, which are functionally upregulated in AR.^[23] The mechanisms involve direct production of CCL18 by allergen-activated plasmacytoid DCs and indirect production by monocytes through IL-4 and IL-13 production by allergen-activated CD4+ T cells. Furthermore, CCL18 attracted Th2 cells and basophils.^[24] In a similar study, CCL-18 mRNA was shown to be upregulated in patients with AR compared to healthy controls.^[19] An association between CCL18 and allergic asthma also has been described. Increased CCL18 production was found in bronchoalveolar lavage and sera from allergic asthmatics and compared with normal controls.^[24]

In conclusion, the current study provides new evidence for the involvement of CCL18 in nasal inflammation and suggests that this factor might be linked to the immunopathogenesis of PAR, including disease severity and clinical characteristics. The results demonstrate that high levels of CCL-18 in patients with M/S PAR are associated with disease severity and increased markers of inflammation, especially specific IgE and number of eosinophils infiltrating the nasal mucosa. Taken together, these findings support the notion that CCL-18 is more than a simple biomarker in AR but can be considered as an active player, at least for the increase in symptom severity.

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Disclosure statement

The authors have declared that no competing interests exist. All authors have approved this manuscript.

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References

- [1] Cagnani, B.; Canonica, W. G.; Helal, M. Z.; Gómez, R. M.; Compalati, E.; Zernott, M. E.; Borges, M. S.; Castro, F. M.; Aguttes, M. M.; Garcia, A. L.; et al. The International

- Survey on the Management of Allergic Rhinitis by Physicians and Patients (ISMAR). *World Allergy Organ. J.* **2015**, *8*, 1–10. DOI: [10.1186/1939-4551-8-1](https://doi.org/10.1186/1939-4551-8-1).
- [2] Blomme, K.-A.; Tomassen, P.-A.; Lapeere, H. B.; Huvenne, W. A.; Bonny, M.; Acke, F.; Bachert, C.; Gevaert, P. Prevalence of Allergic Sensitization versus Allergic Rhinitis Symptoms in an Unselected Population. *Int. Arch. Allergy Immunol.* **2013**, *160*, 200–207. DOI: [10.1159/000339853](https://doi.org/10.1159/000339853).
 - [3] Pawankar, R.; Ori, M. S.; Ozu, C.; Kimura, S. Overview on the Pathomechanisms of Allergic Rhinitis. *Asia Pac. Allergy* **2011**, *1*, 157–167. DOI: [10.5415/apallergy.2011.1.3.157](https://doi.org/10.5415/apallergy.2011.1.3.157).
 - [4] Wheatley, L. M.; Togias, A. Allergic Rhinitis. *N. Engl. J. Med.* **2015**, *372*, 456–463. DOI: [10.1056/NEJMcp1412282](https://doi.org/10.1056/NEJMcp1412282).
 - [5] Tille, K. S.; White, M. K. Acupuncture for Seasonal Allergic Rhinitis: Is It Ready for Prime Time? *Ann. Allergy Asthma Immunol.* **2015**, *115*(4), 258–259. DOI: [10.1016/j.anai.2015.07.007](https://doi.org/10.1016/j.anai.2015.07.007).
 - [6] Ciprandi, G.; Corsico, A. Pisati. Serum-Soluble HLA-G Is Associated with Specific IgE in Patients with Allergic Rhinitis and Asthma. *Inflammation* **2014**, *37*(5), 1630–1634. DOI: [10.1007/s10753-014-9890-5](https://doi.org/10.1007/s10753-014-9890-5).
 - [7] Jun, Y. J.; Park, S. J.; Hwang, J. W.; Kim, T. H.; Jung, K. J.; Jung, J. Y.; Hwang, G. H.; Lee, S. H. Differential Expression of 11b -Hydroxysteroid Dehydrogenase Type 1 and 2 in Mild and Moderate/Severe Persistent Allergic Nasal Mucosa and Regulation of Their Expression by Th2 Cytokines. *Clin. Exp. Allergy* **2014**, *44*, 197–211. DOI: [10.1111/cea.12195](https://doi.org/10.1111/cea.12195).
 - [8] Bousquet, J.; Cauwenberge, V. P.; Taev, K. N. Allergic Rhinitis and Its Impact on Asthma. *J. Allergy Clin. Immunol.* **2001**, *108*, S147– 334. DOI: [10.1067/mai.2001.117929](https://doi.org/10.1067/mai.2001.117929).
 - [9] Bauchau, V.; Durham, S.-R. Epidemiological Characterization of the Intermittent and Persistent Types of Allergic Rhinitis. *Allergy* **2005**, *60*(3), 350–353. DOI: [10.1111/j.1398-9995.2005.00751.x](https://doi.org/10.1111/j.1398-9995.2005.00751.x).
 - [10] Alyasin, S.; Amin, R. The Evaluation of New Classification of Allergic Rhinitis in Patients Referred to a Clinic in the City of Shiraz. *Iran J. Allergy Asthma Immunol.* **2007**, *6*, 1, 27–31.
 - [11] Peterson, S.; Poposki, J. A.; Nagarkar, D. R.; Chustz, R. T.; Peters, A.-T.; Suh, L. A.; Carter, R.; Norton, J.; Harris, K. E.; Grammer, L. C.; et al. Elevated Expression of the Chemokine CCL18 in Chronic Rhinosinusitis with Nasal Polyps. *J. Allergy Clin. Immunol.* **2012**, *129*(1), 119–127.
 - [12] Charo, I.-F.; Ransohoff, R. M. The Many Roles of Chemokines and Chemokine Receptors in Inflammation. *N. Engl. J. Med.* **2006**, *354*, 610–621. DOI: [10.1056/NEJMra052723](https://doi.org/10.1056/NEJMra052723).
 - [13] Horuk, R.; Chemokine Receptor Antagonists: Overcoming Developmental Hurdles. *Nat. Rev. Drug Discov.* **2009**, *8*, 23–33. DOI: [10.1038/nrd2998](https://doi.org/10.1038/nrd2998).
 - [14] Schall, T.-J.; Proudfoot, A.-E. Overcoming Hurdles in Developing Successful Drugs Targeting Chemokine Receptors. *Nat. Rev. Immunol.* **2011**, *11*, 355–363. DOI: [10.1038/nri2972](https://doi.org/10.1038/nri2972).
 - [15] Günther, C.; Fernandez, B. C.; Kopp, T.; Kund, J.; Perrig, N.-C.; Hinteregger, S.; Fassl, S.; Schwärzler, C.; Lametschwandner, G.; Stingl, G.; Biedermann, T.; Carballido, J. M. CCL18 Is Expressed in Atopic Dermatitis and Mediates Skin Homing of Human Memory T Cells. *J. Immunol.* **2005**, *174*, 3, 1723–1728.
 - [16] Sabina, A.; Morris, F. I.; Leung, J.; Shreffler, W. G. Identification of Human CCR8 as a CCL18 Receptor. *JEM* **2013**, *210*(10), 1889–1898. DOI: [10.1084/jem.20130240](https://doi.org/10.1084/jem.20130240).
 - [17] Schutyser, E.; Richmond, A.; Damme, J. V. Involvement of CC Chemokine Ligand 18 (CCL18) in Normal and Pathological Processes. *J. Leukoc. Bio.* **2005**, *78*(1), 14–26. DOI: [10.1189/jlb.1204712](https://doi.org/10.1189/jlb.1204712).

- [18] Okuda, M.; Okamoto, M.; Nomura, Y.; Saito, Y. Clinical Study on Beclomethasone Dipropionate Powder Preparation (TL-102) in Perennial Nasal Allergy. *Rhinology* **1986**, *24*, 113–123.
- [19] Zhang, R.-X.; Yu, S.-Q.; Jiang, J.-Z.; Liu, G.-J. Complementary DNA Microarray Analysis of Chemokines and Their Receptors in Allergic Rhinitis. *J. Investig. Allergol. Clin. Immunol.* **2007**, *17*, 5, 329–336.
- [20] Kato, A.; Chustz, R.-T.; Ogasawara, T.; Kulka, M.; Saito, H. Dexamethasone and FK506 Inhibit Expression of Distinct Subsets of Chemokines in Human Mast Cells. *J. Immunol.* **2009**, *182*, 7233–7243. DOI: [10.4049/jimmunol.0802775](https://doi.org/10.4049/jimmunol.0802775).
- [21] Feuser, K.; Thon, K.-P.; Bischoff, S.-C.; Lorentz, A. Human Intestinal Mast Cells Are a Potent Source of Multiple Chemokines. *Cytokine* **2012**, *58*, 178–185. DOI: [10.1016/j.cyto.2012.01.001](https://doi.org/10.1016/j.cyto.2012.01.001).
- [22] Schraufstatter, I.; Takamori, H.; Sikora, L.; Sriramaraio, P.; Discipio, R. G. Eosinophils and Monocytes Produce Pulmonary and Activation-Regulated Chemokine, Which Activates Cultured Monocytes/ Macrophages. *Am. J. Physiol. Lung Cell Mol. Physiol.* **2004**, *286*, 494–501. DOI: [10.1152/ajplung.00323.2002](https://doi.org/10.1152/ajplung.00323.2002).
- [23] Tsicopoulos, A.; Chang, Y.; Yahia, S. A.; de Nadai, P.; Chenivresse, C. Role of CCL18 in Asthma and Lung Immunity. *Clin. Exp. Allergy* **2012**, *43*, 716–722. DOI: [10.1111/cea.12065](https://doi.org/10.1111/cea.12065).
- [24] de Nadai, P.; Charbonnier, A.-S.; Chenivresse, C.; Sénéchal, S.; Fournier, C.; Gilet, J.; Vorng, H.; Chang, Y.; Gosset, P.; Wallaert, B.; et al. Involvement of CCL18 in Allergic Asthma. *J. Immunol.* **2006**, *176*, 6286–6293.