Alergologia Polska – Polish Journal of Allergology 2023; 10, 2: 100–106
DOI: https://doi.org/10.5114/pja.2023.129090
Received: 1.06.2023, Accepted: 7.06.2023.

Alergologia POLSKA
Polish Journal of Allergology

ORIGINAL PAPER/*PRACA ORYGINALNA*

The role of innate lymphoid cells in chronic rhinosinusitis severity in children: a cross-sectional study

Rola komórek limfoidalnych w nasileniu przewlekłego nieżytu nosa: badanie przekrojowe

Marta Latek[1], Piotr Lacwik[2,3], Katarzyna Molińska[1], Andrzej Błauż[4], Błażej Rychlik[4], Dominik Strapagiel[5], Joanna Majak[6], Dorota Czech[7], Piotr Kuna[1], Paweł Majak[8]

[1]Department of Internal Medicine, Asthma and Allergy, Medical University of Lodz, Lodz, Poland
[2]Collegium Medicum, Jan Kochanowski University, Kielce, Poland
[3]Holy Cross Centre for Lung Diseases, Chęciny, Poland
[4]Cytometry Lab, Department of Molecular Biophysics, University of Lodz, Lodz, Poland
[5]Biobank Lab, Department of Molecular Biophysics, University of Lodz, Lodz, Poland
[6]Audiology and Phoniatrics Clinic, Nofer Institute of Occupational Medicine, Lodz, Poland
[7]Department of Paediatric Otolaryngology, Audiology and Phoniatrics, Medical University of Lodz, Lodz, Poland
[8]Department of Paediatric Pulmonology, Medical University of Lodz, Lodz, Poland

ABSTRACT

Introduction: The microbiome has been identified as a significant factor in the pathogenesis of various inflammatory and autoimmune diseases, including chronic rhinosinusitis (CRS), a condition that affects up to 12% of the global population.

Aim: To evaluate the role of innate lymphoid cells (ILC1, ILC2, and ILC3) and their relationship with nasal microbiota in CRS in children.

Material and methods: We assessed the clinical, microbiological, and immunological characteristics of 63 children with CRS. We evaluated disease severity using the Sinus and Nasal Quality of Life Survey (SN-5) and measured ILC1, ILC2, and ILC3 levels in nasal scrapings; microbial diversity was expressed as OTU richness.

Results: We found a statistically significant relationship between ILC1 levels and CRS severity, suggesting a potential role of ILC1 in the development of the disease. ILC3 levels were significantly associated with lower microbial richness. While atopy was more common in children with high levels of ILC2, the relationship was not significant.

Conclusions: Our results indicate that innate lymphoid cells may play a significant role in the inflammatory processes underlying the development and severity of chronic rhinosinusitis, with ILC1 activation being particularly strongly associated with CRS severity in young children. Additionally, ILC3 may play a role in modulating the nasal microbiome in CRS patients, but the relationship is not strong enough to significantly impact the clinical characteristics.

KEY WORDS

microbiome, dysbiosis, chronic rhinosinusitis, ILC, innate lymphoid cells.

STRESZCZENIE

Wprowadzenie: Mikrobiom odgrywa istotną rolę w patogenezie wielu chorób zapalnych i autoimmunologicznych, w tym przewlekłego zapalenia zatok przynosowych (CRS) – schorzenia, które dotyka nawet do 12% światowej populacji.

Cel: Ocena wpływu komórek limfoidalnych (ILC1, ILC2, ILC3) na ciężkość objawów i stan mikrobioty u dzieci z przewlekłym nieżytem nosa.

Materiał i metody: W badaniu przeprowadzono ocenę klinicznych, mikrobiologicznych i immunologicznych wskaźników u 63 dzieci z CRS. Nasilenie choroby badano za pomocą wartości kwestionariusza SN-5. Oznaczono również poziomy ILC1, ILC2 i ILC3 w materiale z wymazów nosa. Stopień zróżnicowania mikrobiomu wyrażono jako OTU.

Wyniki: Stwierdzono statystycznie istotną zależność między poziomami ILC1 a nasileniem CRS, wskazującą na potencjalnie istotny udział tej interleukiny w rozwoju przewlekłego nieżytu nosa. Wyższe wartości ILC3 były związane z niższą różnorodnością mikrobiologiczną. Atopia była częstsza u dzieci z wysokimi poziomami ILC2, jednak ta zależność nie była istotna statystycznie.

Wnioski: Wyniki naszej pracy wskazują na potencjalny udział komórek limfoidalnych w procesie zapalnym, który odgrywa kluczową rolę w rozwoju i nasileniu przewlekłego nieżytu nosa. Poziom ILC1 jest szczególnie silnie związany z nasileniem objawów u dzieci w wieku przedszkolnym. ILC3 mogą również odgrywać istotną rolę w modulacji mikrobiomu w nosie u pacjentów z CRS, jednak ta zależność nie jest na tyle silna, aby wpływać na nasilenie choroby.

SŁOWA KLUCZOWE

mikrobiom, dysbioza, przewlekły nieżyt nosa, ILC, komórki limfoidalne.

ADDRESS FOR CORRESPONDENCE

Piotr Lacwik, Collegium Medicum, Jan Kochanowski University, Kielce, Poland, e-mail: piotr.lacwik@ujk.edu.pl

INTRODUCTION

The role of microbiota in the pathogenesis of various inflammatory and autoimmune diseases is the subject of ever-evolving investigations. The microbiome has already been proven to act as a significant factor not only in diseases of the cardiovascular and gastrointestinal systems, as well as both the upper and lower respiratory tract, but even in oncological and psychiatric disorders [1–8].

Chronic rhinosinusitis (CRS) is a chronic inflammatory condition that affects up to 12% of the world's population. It can present with several different symptoms and is associated with many comorbidities, which can severely affect the patient's quality of life and cause a significant burden in populations of all age groups [9–11]. Although the aetiopathogenesis of chronic rhinosinusitis (CRS) is not yet fully understood, recent studies have suggested that the breakdown of the sinonasal microbiome plays a significant role in its development. There is emerging evidence that sinonasal dysbiosis may affect the clinical status of CRS through various mechanisms, including modification of the innate immune response [12–16]. Innate lymphoid cells (ILCs) play a key role in the human immune system by providing defence against microbes, maintaining tissue and organ homeostasis, promoting tissue healing and regulation, regulating adaptive immune processes, and regulating tumour growth. Recently, the role of ILCs in the development of CRS was suggested, but few data are available on the exact mechanisms in which they could affect its development and severity [17–19].

AIM

This study aimed to evaluate the role and impact of innate myeloid cells in children with chronic rhinosinusitis and assess the interactions between the nasal occurrence of ILC1, ILC2, and ILC3 and the clinical severity of CRS.

The present study was based on an open-label randomized control trial, which was part of the Response of the Airway in Sinusitis and Asthma (RAISe) study conducted to assess the role of innate immunity of the airways in children with rhinosinusitis. All methods were performed in accordance with relevant guidelines and regulations.

MATERIAL AND METHODS

This cross-sectional study was a part of the *Response of the Airway in Sinusitis and Asthma* (RAISe) study conducted to assess the role of innate immunity of the airways in children with rhinosinusitis. Sixty-three children aged 4–8 years with chronic rhinosinusitis were included in the current analysis. CRS was diagnosed by otorhinolaryngologists according to the EPOS (European Position Paper on Rhinosinusitis and Nasal Polyps) criteria [10]. The following exclusion criteria were considered: food allergy with symptoms affecting the respiratory tract, contraindication to nasal endoscopy or contraindication to nasal mucosa biopsy, hypertrophy of the third tonsil exceeding 60% of the nasopharynx (confirmed by endoscopy of the upper-respiratory-tract), confirmed immunodeficiency, exacerbation of asthma requiring systemic administration of glucocorticosteroids, obesity, exposure to tobacco smoke, or other chronic illnesses and clinical conditions, which in the opinion of the researcher could have influenced the evaluation and the course of the study. We also excluded patients who received intranasal corticosteroids within 4 weeks and/or had acute respiratory tract infection diagnosed within 2 weeks before the initial visit.

Data on the following: i) the clinical severity of CRS, ii) the nasal abundance of ILCs, and iii) the diversity of the microbiome of the nasopharynx, were included All methods were previously described [20].

SINUS AND NASAL QUALITY OF LIFE SURVEY (SN-5)

A validated questionnaire to assess the quality of life in children with CRS (5 symptom-cluster items covering the domains of sinus infection, nasal obstruction, allergy symptoms, emotional distress, and activity limitations) was administered to all patients.

PROCESSING OF NASAL EPITHELIUM

The curette with a nasal epithelium specimen was placed in a 15-ml tube containing 2 ml of cold sterile RPMI 1640 (Gibco, Thermo Fisher Scientific Inc., Waltham, MA, USA) and transported to the biological laboratory within 3 h after the collection. The medium was then centrifuged (100 g, 10 min, RT), and cell and tissue pellets were further processed. The sample was digested by incubation with 200 µg/ml bovine pancreas DNAse I and 125 µg/ml Liberase TM for 60 min at 37°C. The resulting cell suspension was stained with respective antibodies for 60 minutes at RT in dark and then cells were analysed on a BD™ LSR II flow cytometer. A population of mononuclear cells was identified as a homogeneous population in FSC/SSC dot plot and further analysed using specific immune markers. $LIN^-CD56^+IL12RB2^+CD127^-$ and $LIN^-CD56^-IL12RB2^+CD127^+$ were considered ILC1, $LIN^-CTRH2^+CD127^+$ were considered ILC2, and $LIN^-CD117^+CD127^+$ were considered ILC3 cells. Results were expressed as the percentage of LIN^- cells.

NGS LIBRARY PREPARATION

16S sequencing libraries were prepared according to the 16S Metagenomic Sequencing Library Preparation Illumina protocol. Taxonomic classification was performed using the feature-classifier classify-consensus-search plugin based on pre-formatted SILVA reference sequence and taxonomy files from Qiime2 data resources.

ETHICS

The protocol was approved by the Medical University of Lodz Ethics Committee. Written consent from the patients' parents was obtained before any procedures.

STATISTICAL ANALYSIS

Linear regression analysis was used to define variables associated with a nasal abundance of ILCs (dependent variables). The abundance of ILC1 and ILC3 as well as Shannon and OUT indices were log-transformed before analyses. Linear regression analysis was performed in the univariate model followed by the multivariate model. Finally, a multivariate model was built according to the step -forward selection approach; only coefficients associated with the dependent variable in the univariate model with p-value < 0.1 were included. Linear correlation was followed using the Spearman test. The Fisher exact test was used to assess the association between the presence of ILC2 and atopy. A p-value of less than 0.05 was assumed as statistically significant. Statistica 13.1 (TIBCO Software Inc.) was used to perform all analyses.

RESULTS

The clinical characteristics of the participants in each of the study arms are shown in Table 1.

THE ROLE OF ILC1

Linear regression analysis showed that nasal abundance of ILC1 is significantly associated with SN-5 score only (RR = 0.320, 95% CI: 0.148–0.619; $p = 0.0366$). A significantly higher concentration of ILC1 was observed in children with more severe clinical presentation of CRS (higher SN-5 score). We did not observe any correlation between ILC1 and biodiversity indices (Table 2, Figure 1).

TABLE 1. Baseline characteristics of study participants. Data are presented by the number (%) of observation, otherwise indicated; the number of missing values are given

Parameter	Total ($n = 63$)	
	n	%
Age [years], mean (SD)	6.1 (1.3)	
Male sex	38	60.3
Preterm delivery	13	20.6
Natural delivery	32	50.8
Family history of allergy	44	69.8
Food allergy in infancy	29	46.0
BMI [kg/m^2], mean (SD)	15.5 (2.1)	
Atopic dermatitis	4	6.6
Asthma	42	66.7
Atopy	31	49.21
Antibiotic courses/year > 2 (median)	36	57.1
Baseline Shannon index < 3.92 (median), missing values = 8	26	47.3
Baseline OTU richness < 53 (median), missing values = 8	26	47.3
Baseline SN-5 score < 3.6 (median)	31	49.2

SD – standard deviation, BMI – body mass index, SN-5 – Sinus and Nasal Quality of Life Survey.

TABLE 2. Linear regression analysis with ILC1 (log-transformed) as a dependent variable and clinical data and biodiversity indices as covariates

Parameter	*P*-level	RR	95% CI	
Clinical data:				
Age	0.8421	–0.031	0.156	0.284
Male gender	0.3201	0.155	–0.156	0.467
BMI (continuous)	0.4912	0.109	0.157	0.427
Family history of allergy	0.7529	–0.049	–0.364	0.266
Food allergy in infancy	0.4531	0.117	–0.196	0.431
Frequent antibiotics	0.0930	0.259	–0.045	0.564
Atopy	0.0600	0.321	–0.014	0.656
SN5 score (continuous)	0.0366	0.320	0.148	0.619
SN5 < 3.5 (median value)	0.0765	–0.273	–0.576	0.030
Biodiversity indices:				
Shannon index (continuous, log-transformed)	0.9952	0.001	0.169	0.344
Shannon index < 3.92 (median value)	0.9779	0.005	–0.338	0.348
OTU (continuous, log-transformed)	0.5294	–0.107	0.168	0.234
OTU < 53 (median value)	0.3991	0.143	–0.197	0.482

THE ROLE OF IL3

Linear regression analysis showed that higher nasal abundance of ILC3 was observed in children with lower OTU index (below the median value) (RR = 0.320, 95%CI: 0.148–0.619; $p = 0.0366$). We did not detect any correlation between ILC3 and SN-5 score (Table 3, Figure 1).

ILC2 was identifiable only in nasal samples from 8 patients; the observed abundance of ILC2 was low. We observed only a trend of higher prevalence of the

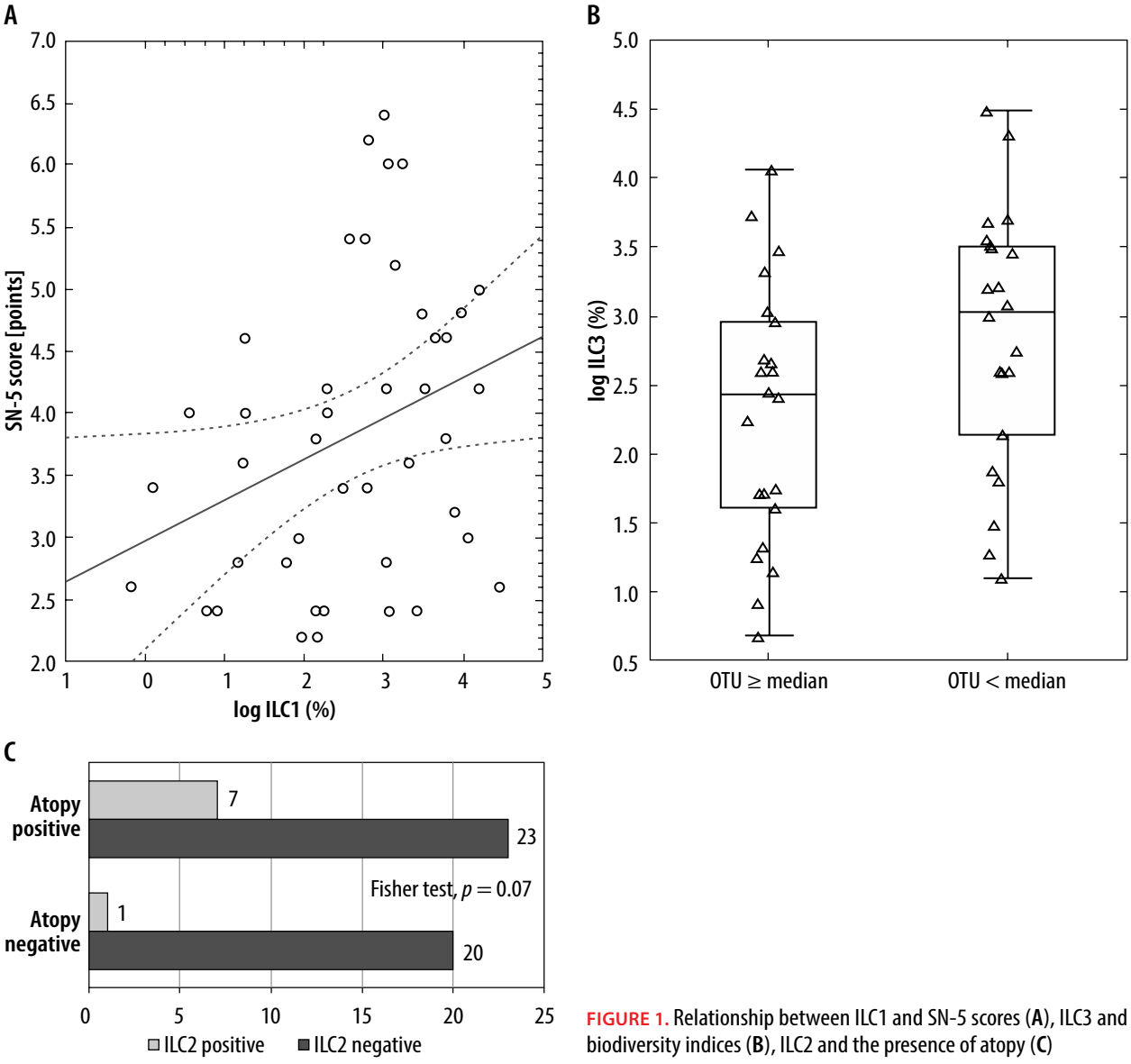

FIGURE 1. Relationship between ILC1 and SN-5 scores (**A**), ILC3 and biodiversity indices (**B**), ILC2 and the presence of atopy (**C**)

ILC2-positive sample among atopic children (Figure 1), but this finding was not statistically significant in Fisher's exact test ($p = 0.07$).

DISCUSSION

In this cross-sectional study, we evaluated the abundance of nasal innate lymphoid cells in children with chronic rhinosinusitis. Our most prominent finding was that nasal ILC1 levels were significantly increased in patients with more severe symptoms of this debilitating disease. Interestingly, although increased ILC3 levels were associated with microbial dysbiosis, they did not significantly affect CRS severity. Additionally, we observed that increased ILC2 levels were more common in atopic children.

The exact mechanism behind Th1-Th2 imbalance, which drives the development of chronic rhinosinusitis, is undeniably complex and remains a subject of ever-evolving discussion [21–23]. Various factors have been proposed as possible drivers of this phenomenon, including innate lymphoid cells and their corresponding cytokines, which act as important mediators of the early stages of the immune response during inflammation, tissue repair, and maintenance of epithelial integrity [16–18]. However, the impact of various types of ILC on chronic rhinosinusitis is poorly understood. Similarly, although studies have shown an increased prevalence of bacterial dysbiosis in patients with CRS compared to healthy individuals, the exact role of biodiversity changes in the development, and the severity of the disease remains unknown [24].

TABLE 3. Linear regression analysis with ILC3 (log-transformed) as a dependent variable and clinical data and biodiversity indices as covariates

Parameter	*P*-level	RR	95% CI	
Clinical data:				
Age	0.0554	0.28	–0.01	0.56
Male gender	0.1092	–0.23	–0.52	0.05
BMI (continuous)	0.8666	0.02	–0.27	0.32
Family history of allergy	0.1498	–0.21	–0.50	0.08
Food allergy in infancy	0.0679	0.26	–0.02	0.55
Frequent antibiotics	0.1896	0.19	–0.10	0.48
Atopy	0.3040	0.16	–0.15	0.48
SN5 score (continuous)	0.3633	0.13	–0.16	0.42
SN5 < 3.5 (median value)	0.2091	–0.18	–0.47	0.11
Biodiversity indices:				
Shannon index (continuous, log-transformed)	0.4812	0.11	–0.20	0.42
Shannon index < 3.92 (median value)	0.3510	–0.14	–0.45	0.16
OTU (continuous, log-transformed)	0.5762	–0.09	–0.40	0.22
OTU < 53 (median value)	0.0499	0.30	0.00	0.59

ILC1 AND CRS SEVERITY

Our analysis revealed a statistically significant relationship between the ILC1 levels and CRS severity. This is consistent with previous studies that confirmed ILC1 as a natural defence against bacteria, which is strongly affected by exposure to bacterial and microbiological stimuli [25–27]. As the immune system learns through inflammation, intense ILC1 activation leads to more severe clinical symptoms [28, 29]. These results suggested that CRS may be significantly affected by the environment, particularly through peer contact and exposure to various bacteria. The fact that our study group comprised preschool children, who are subject to exceptionally intense, regular peer exposure, reinforces our findings. Because it has already been reported that the number of bacteria determines the clinical presentation of CRS, it is not surprising that ILC1 levels also correlate with the disease severity [13–15, 30]. These findings suggest that ILC1 may play a significant role in determining the development and symptoms of CRS, and further investigation into the underlying biological mechanisms is warranted.

ILC3 AND BACTERIAL RICHNESS

We observed a negative relationship between ILC3 levels and bacterial richness, as measured by OTU in nasal scrapings. This finding supports previous research showing that ILC3 is a marker of dysbiosis [30, 31]. However, because increased ILC3 levels were associated with lower bacterial richness, they did not significantly affect the clinical severity of chronic rhinosinusitis. In another study by Latek *et al.* the ILC3 levels were significantly affected by nasal steroids, which may increase biodiversity by reducing antibacterial defence mechanisms, creating a better environment for bacterial development and increasing bacterial richness [20]. These results suggest that ILC3 plays a role in modulating the nasal microbiome in CRS patients, but the relationship is not strong enough to significantly impact the clinical characteristics, probably driven by the microbe-load stimulated ILC1.

ILC2 AND ATOPIC CHILDREN

We observed that atopic children more commonly presented with increased ILC2 levels. However, while the trend was visibly recognizable, we could not reach statistically significant conclusions regarding the relationship between atopy and ILC2. Previous research has implicated ILC2 in the pathogenesis of allergic diseases [32–34]. Further studies with larger sample sizes are needed to investigate the relationship between ILC2 and CRS in atopic children.

STRENGTHS AND LIMITATIONS

One of the main limitations of the study was the underpowered detection of ILC2 levels, which could have been caused by a relatively low sample size or the methodology of specimen collection. This might be explained by the location of innate lymphoid cells, which are typically found deep within tissues and possibly beyond the reach of our nasal scrapings. Alternatively, the method of preparation could have affected

the low levels of ILC2s in our observations, as certain surface antigens, including ILC2s proteins, may have been lost during the material preparation. Additionally, the lack of a healthy control group diminishes the impact on defining the real role of ILCs in CRS found in our study.

CONCLUSIONS

The results of our cross-sectional study indicate that innate lymphoid cells may significantly affect various mechanisms of inflammation, thus affecting the severity of symptoms in CRS patients with chronic rhinosinusitis. In particular, the activation of ILC1 caused by exposure to microbial stimuli appears to be significantly associated with CRS severity. Further studies are needed to confirm this relationship and to consider the possible potential for targeted therapeutic strategies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Lloyd-Price J, Abu-Ali G, Huttenhower C. The healthy human microbiome. Genome Med 2016; 8: 51.
2. Nikolova VL, Hall MRB, Hall LJ, et al. Perturbations in gut microbiota composition in psychiatric disorders: a review and meta-analysis. JAMA Psychiatry 2021; 78: 1343-54.
3. Budden KF, Shukla SD, Rehman SF, et al. Functional effects of the microbiota in chronic respiratory disease. Lancet Respir Med 2019; 7: 907-20.
4. Peng J, Xiao X, Hu M, Zhang X. Interaction between gut microbiome and cardiovascular disease. Life Sci 2018; 214: 153-7.
5. Moffatt MF, Cookson WO. The lung microbiome in health and disease. Clin Med 2017; 17: 525-9.
6. Hayes RB, Ahn J, Fan X, et al. Association of oral microbiome with risk for incident head and neck squamous cell cancer. JAMA Oncol 2018; 4: 358-65.
7. Tang WHW, Kitai T, Hazen SL. Gut microbiota in cardiovascular health and disease. Circ Res 2017; 120: 1183-96.
8. Invernizzi R, Lloyd CM, Molyneaux PL. Respiratory microbiome and epithelial interactions shape immunity in the lungs. Immunology 2020; 160: 171-82.
9. Orlandi RR, Kingdom TT, Smith TL, et al. International consensus statement on allergy and rhinology: rhinosinusitis 2021. Int Forum Allergy Rhinol 2021; 11: 213-739.
10. Fokkens WJ, Lund VJ, Hopkins C, et al. Executive summary of EPOS 2020 including integrated care pathways. Rhinol J 2020; 58: 82-111.
11. Sivasubramaniam R, Douglas R. The microbiome and chronic rhinosinusitis. World J Otorhinolaryngol Head Neck Surg 2018; 4: 216-21.
12. Bordin A, Sidjabat HE, Cottrell K, Cervin A. Chronic rhinosinusitis: a microbiome in dysbiosis and the search for alternative treatment options. Microbiol Aust 2016; 37: 149-52.
13. Psaltis AJ, Mackenzie BW, Cope EK, Ramakrishnan VR. Unraveling the role of the microbiome in chronic rhinosinusitis. J Allergy Clin Immunol 2022; 149: 1513-21.
14. Cope EK, Goldberg AN, Pletcher SD, Lynch SV. Compositionally and functionally distinct sinus microbiota in chronic rhinosinusitis patients have immunological and clinically divergent consequences. Microbiome 2017; 5: 53.
15. Copeland E, Leonard K, Carney R, et al. Chronic rhinosinusitis: potential role of microbial dysbiosis and recommendations for sampling sites. Front Cell Infect Microbiol 2018; 8: 57.
16. Luong AU, Sun H, Yao WC. Contributions of innate lymphoid cells in chronic rhinosinusitis. Curr Allergy Asthma Rep 2019; 19: 28.
17. Ogulur I, Pat Y, Ardicli O, et al. Advances and highlights in biomarkers of allergic diseases. Allergy 2021; 76: 3659-86.
18. Padro Dietz C, Luong A. Innate lymphoid cells: the innate counterpart to t helper cells. Adv Otorhinolaryngol 2016; 79: 58-68.
19. Kato A. Group 2 innate lymphoid cells in airway diseases. Chest 2019; 156: 141-9.
20. Latek M, Lacwik P, Molinska K, et al. Effect of an intranasal corticosteroid on quality of life and local microbiome in young children with chronic rhinosinusitis: a randomized clinical trial. JAMA Pediatr 2023; 177: 345-52.
21. Kato A, Schleimer RP, Bleier BS. Mechanisms and pathogenesis of chronic rhinosinusitis. J Allergy Clin Immunol 2022; 149: 1491-503.
22. Klingler AI, Stevens WW, Tan BK, et al. Mechanisms and biomarkers of inflammatory endotypes in chronic rhinosinusitis without nasal polyps. J Allergy Clin Immunol 2021; 147: 1306-17.
23. Huntley KS, Raber J, Fine L, Bernstein JA. Influence of the microbiome on chronic rhinosinusitis with and without polyps: an evolving discussion. Front Allergy 2021; 2: 737086.
24. Cherian LM, Bassiouni A, Cooksley CM, et al. The clinical outcomes of medical therapies in chronic rhinosinusitis are independent of microbiomic outcomes: a double-blinded, randomised placebo-controlled trial. Rhinology 2020; 58: 559-67.
25. Colonna M. Innate lymphoid cells: diversity, plasticity, and unique functions in immunity. Immunity 2018; 48: 1104-17.
26. Annunziato F, Romagnani C, Romagnani S. The 3 major types of innate and adaptive cell-mediated effector immunity. J Allergy Clin Immunol 2015; 135: 626-35.
27. Nabekura T, Shibuya A. Type 1 innate lymphoid cells: soldiers at the front line of immunity. Biomed J 2021; 44: 115-22.
28. Vivier E, Artis D, Colonna M, et al. Innate lymphoid cells: 10 years on. Cell 2018; 174: 1054-66.
29. Kortekaas Krohn I, Shikhagaie MM, Golebski K, et al. Emerging roles of innate lymphoid cells in inflammatory diseases: clinical implications. Allergy 2018; 73: 837-50.
30. Huntley KS, Raber J, Fine L, Bernstein JA. Influence of the microbiome on chronic rhinosinusitis with and without polyps: an evolving discussion. Front Allergy 2021; 2: 737086.
31. Ham J, Kim J, Choi S, et al. Interactions between ncr+ILC3s and the microbiome in the airways shape asthma severity. Immune Netw 2021; 21: e25.
32. Zheng H, Zhang Y, Pan J, et al. The role of type 2 innate lymphoid cells in allergic diseases. Front Immunol 2021; 12: 586078.
33. Jin J, Sunusi S, Lu H. Group 2 innate lymphoid cells (Ilc2s) are important in typical type 2 immune-mediated diseases and an essential therapeutic target. J Int Med Res 2022; 50: 3000605211053156.
34. Maspero J, Adir Y, Al-Ahmad M, et al. Type 2 inflammation in asthma and other airway diseases. ERJ Open Res 2022; 8: 00576-02021.