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ORGINAL ARTICLE

Circulating and Mucosal Associated Type 2 Innate Lymphoid Cells in Asthma

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ABSTRACT

Background: Type 2 innate lymphoid cells (ILC2s) are introduced as a key player in type 2 inflammation. **Objectives:** To assess the correlation between ILC2s in peripheral blood, sputum, and colonic biopsies among patients with asthma, and to assess the relation between ILC2s frequency and severity of asthma. **Methods:** ILC2s numbers were assessed in peripheral blood, and sputum among 29 patients with asthma (asthma group) and 29 healthy controls (control group). Colonic biopsies were obtained from twelve mild to moderate asthma patients and nine healthy controls. ILC2s were determined by multicolor flow cytometer in all specimens. **Results:** ILC2s numbers in peripheral blood were higher among the asthma group compared to the control group (P<0.001). ILC2 in peripheral blood and sputum were significantly elevated in severe asthma (P <0.001). There was a strong positive correlation between ILC2s numbers in peripheral blood, and sputum (P<0.001) and severity of asthma. ILC2s were not detected in the colonic biopsy of the controls but was detected in the asthma patients. **Conclusion:** Type 2 innate lymphoid cells were increased in peripheral blood, sputum, and colonic biopsies among asthma patients, particularly severe asthma, suggesting its role in the pathophysiology of asthma.
Clinical implication:
The lack of Knowledge regarding relation between ILC2s in blood, sputum and gut mucosa to assess the value of ILC2s as an indicator among patients with asthma,

Keywords: Innate lymphoid cells; asthma; peripheral blood; colon; sputum.

INTRODUCTION

Asthma is a chronic respiratory disorder which is characterized by airway inflammation, hyperresponsiveness, remodeling and reversibility. Allergic asthma was traditionally considered to be mediated by T helper (Th) 2 cells, but recently the pathophysiology of asthma becomes clear to be more complicated where multiple different cells are incriminated [1,2].

Innate lymphoid cells (ILCs) recently considered the main cells in asthma pathophysiology. These cells are a unique subset of innate immune cells. These cells are distinguished by lacking both B-cell and T-cell receptors [3,4]. Depending on the cytokines produced, ILCs have been classified into three types (ILC1, 2 & 3). Type 2 innate lymphoid cells (ILC2s) release Th2 cytokines. These cells have been detected in mucosal tissue, lymph nodes, gut-associated lymphoid tissue, spleen, and lungs [5,6]. Moreover, ILC2s cells migrate from gut to different organs, including lungs, in response to the inflammatory cytokines [7].

In humans, it was found that ILC2s accumulate at the site of eosinophilic inflammation [8]. Allergic asthma is characterized by lung eosinophilia where ILC2s produce IL-5 constitutively [9, 10]. Interestingly, the identified ILC2s in both lung and gut express the same cell surface markers [11, 12, 13, 14, 15].

The mechanisms of ILC2s circulation in human are essential in understanding type 2

inflammation and explaining the gut-lung axis. To the best of our knowledge, it needs to be more investigated.

Therefore, we aimed to study the correlation between ILC2s in peripheral blood, sputum, and colonic biopsies of patients with asthma, and to investigate the association between the severity of asthma and ILC2s.

PATIENTS AND METHODS

This case-control study was conducted over a period of twelve months, from June 2020 to June 2021. It was carried out in Medical Microbiology and Immunology, Clinical Pathology, Chest, Histology & Cell Biology and Tropical Departments, Zagazig University, Zagazig, Egypt.

The study was approved by the institutional review board (IRB) no 5572/23, Faculty of Medicine, Zagazig University. Informed written consents were obtained from all participants. It was carried out in accordance with the revised Declaration of Helsinki.

Study Subjects

Twenty-nine adult asthma patients were enrolled in the asthma group and 29 apparently healthy participants of matched age and sex were enrolled in the control group. Diagnosis of asthma and its severity was done in accordance with the Global Initiative for Asthma (GINA) guidelines [16].

Inclusion criteria were: (1) a pre-bronchodilator forced expiratory volume in the first second (FEV1) of less than 70% of the predicted normal with a post-bronchodilator flow rise of more than 12%, (2) positive skin prick to at least one of the common aeroallergens.

Patients who were suffering from chronic obstructive pulmonary disease (COPD), or any associated respiratory disorder, were excluded from the study. Current or previous smokers were not included in our study. Also, patients received corticosteroids, biologic medication, immunotherapy in the last six weeks were excluded from the study.

Peripheral blood, and sputum were obtained from all asthma patients and controls for flow-cytometric analysis of ILC2s. Colonic biopsies were obtained from nine healthy control, who were relatives of colorectal cancer during screening colonoscopy, and twelve asthma patients. Skin prick test (SPT) was done for all patients. Complete blood count and serum total IgE were estimated in all asthma patients and controls.

Skin Prick Test (SPT)

Skin testing was performed according to Bernstein et al., 2008. Children were asked to stop antihistamines a week before skin testing. A panel for the most common locally encountered inhaled allergens was used including: mixed mites, mixed molds, house dust, and mixed pollens. Histamine dihydrochloride was used as a positive control, while saline was used as a negative control. The largest diameter of the wheal was measured and it was considered positive if it was ≥ 3 mm [17].

Allergen extracts of skin testing were locally prepared at Allergy and Immunology Unit, Department of Medical Microbiology and Immunology, Faculty of Medicine, Zagazig University according to allergen extract preparation guidelines developed by the AAAAI/ACAAI/ JCAAI 2003 [18]. All aqueous allergen extracts were stored at 4 °C.

Peripheral blood collection

Peripheral blood samples (5ml) were collected under complete aseptic condition. Half of the blood sample were obtained on ethylene – diamintetracetic acid di-potassium (EDTA) tube at final concentration of 1.5 mg/ml for complete blood count and flow cytometric analysis. The remaining part of blood samples were allowed to clot then centrifuged **(**Fisher Centrific ™ Centrifuge**)** at 1000 xg for 15 minutes where sera were collected and stored at -20 °C for measurement of the serum total IgE level.

Sputum Cells Isolation

Sputum induction was done by inspiration of nebulized hypertonic sterile saline [19]. The mucus plug of the sputum specimen was mixed with an equal volume of N-acetyl-L-cysteine (NALC) in phosphate buffer saline (PBS) (Biochrom AG, Germany) for flow cytometer analysis [20].

Colon Cells Isolation

Colon samples were minced and incubated in 5 ml of Hanks' Balanced Salt Solution (HBSS) (Thermo Fischer, Gibco ®, USA) containing 100 U/ml penicillin and 0.1 mg/ml streptomycin for 15 min, at 37 °C. Crypt epithelial cells were dissociated by strong handshaking to have a supernatant enriched in these cells. Cold HBSS was added to the supernatant and the shaking step was repeated then centrifuged at 200 x g for 15 min at 4 °C. Supernatants were incubated with trypsin (T2600000, Sigma-Aldrich) for 30 min at 37 °C, to have single-cell suspensions. Fetal bovine serum (FBS) (12107C, Sigma –Aldrich) was added to terminate the trypsin reaction. Cells were collected by centrifugation at 150 x g, 10 min, 4 °C. Cells

were re-suspended in 1.5 ml of 2% FBS in PBS, to be analyzed on a flow cytometer [21].

Flow Cytometer Sorting of ILC2s

Peridinin chlorophyll protein complex (Percp) labeled antibody to CD45, Fluorescein isothiocyanate (FITC,) labelled antibody to CD3, CD16; phycoerythrin (PE) labellalled antibody to CD56 and CD19, were used to exclude B and NK cells. PE labeled antibody CRTH2/CD294, intracellular IL-5 FITC, and Percp labelled antibody to CD127 were used in order to identify true ILC2s population [22]. All reagents were purchased from BD Biosciences (San Jose, USA).

Gating is done sequential on CD45 +high intensity, CRTH2 /CD294+, CD127+ and intracellular IL-5 to detect ILC2s population as described in Fig 1,2. Gating was done in the lymph-mononuclear zone (low forward scatter /low side scatter) with at least 20,000 events. Cell Quest software was used to analyze the data using FACSCalibur Flow cytometer (Instrument, Becton-Dickinson, San Diego, California, USA).

Statistical Analysis

The data were analyzed using SPSS version 20 (SPSS Inc., Chicago, IL, USA). Shapiro-Wilk test used to test the normality of data. Quantitative data were presented as mean and standard deviation (SD) or median (min-max). Categorical data were expressed as numbers and percent. Mann-Whitney test and t-test were used to detect differences for quantitative variables between two groups as appropriate. The strength of the correlation between two continuous sets of data was detected by Pearson's correlation coefficient (r). A significance level of $P<0.05$ was considered in all tests at 95% confidence interval.

RESULTS

Patients' Baseline Characteristics

Twenty-nine asthma patients and twenty-nine healthy controls were enrolled. Table 1 showed the patients' characteristics categorized by the severity of asthma.

ILC2s Enumeration in Blood, Sputum, and Colonic Biopsies

The number of ILC2s in the peripheral blood was significantly increased in the asthma group compared to the control group (median= 110 & range=24-5994; median=8 & range=2-8; ***P*** <0.001) (Fig 3) with significant increase in severe asthma compared to mild to moderate asthma (***P*** <0.001) (table 2). The ILC2s was not detected in the sputum samples of healthy control. The number of ILC2s in the sputum of patients with severe asthma is significantly increased in comparison to mild and moderate asthma (***P*** <0.001) (table 2). Regarding colonic biopsies, ILC2s were not detected in the control specimens but were detected in mild to moderate asthma patients (median=4 & range=2-6).

Correlation between Peripheral Blood, and Sputum ILC2s among Patients with Asthma

The correlation between ILC2s in blood and sputum showed a strong statistically positive correlation between each other (r=0.863, $P < 0.001$). We also found a strong positive correlation of ILC2s in peripheral blood, and sputum with asthma severity (r=0.741, $P < 0.001$; r=0.851, $P < 0.001$ respectively).

Table (1): Baseline characteristics of the study participants.

Characteristic	Control group (n =29)	Asthma group (n =29)	Mild to moderate asthma (n =18)	Severe asthma (n =11)
Age (years)	41.69 ± 3.44	40.45±9.61	38.83±8.21	43.09±11.48
Sex (male), no (%)	17 (58.6)	14 (48.3)	12 (66.7)	2 (18.2)
Allergic rhinitis, no (%)	-	17 (58.6)	10 (55.6)	7 (63.6)
Blood total leukocytes($x10^6$/mL)	7.64 ± 1.69	7.12 ± 2.49	7.02 ± 2.79	7.28 ± 2.03
Blood eosinophils ($x10^6$/mL)	0.4 ± 0.1	0.5 ± 0.14	0.53 ± 0.16	0.44 ± 0.11
Serum IgE (IU/mL)	84.31 ± 17.71	224.69±133.26	188.17 ± 70.49	284.45±186.66
Allergen immunotherapy (%), no (%)	-	3 (10.3)	1 (5.6)	2 (18.2)

Characteristic	Control group (n =29)	Asthma group (n =29)	Mild to moderate asthma (n =18)	Severe asthma (n =11)
FEV1 (%)	98.45±0.51	72.28 ± 12.29	80.39 ±7.53	59 ± 3.8
Medications, no (%)				
ICS	-	18 (62.1)	9 (50)	9 (81.8)
LABA	-	3 (10.3)	1 (5.6)	2 (18.2)
SABA	-	13 (44.8)	5 (27.8)	8 (72.7)
LTM	-	8 (27.6)	4 (22.2)	4 (36.4)
Skin test, positive/subjects tested, no (%)				
Dust mite	-	13 (44.8)	8 (44.4)	5 (45.5)
Mixed pollens	-	25 (86.2)	15 (83.3)	10 (90.9)
Mixed molds	-	7 (24.1)	4 (22.2)	3 (27.3)
House dust	-	8 (27.6)	6 (33.3)	2 (18.2)

Unless otherwise stated, data are presented as mean ± SD. ICS, Inhaled corticosteroids; LABA, long-acting beta agonists; LTM, leukotriene modifiers; SABA, short-acting bronchodilators; FEV1, forced expiratory volume in first second

Table 2: Comparison of blood and sputum ILC2s between mild to moderate and severe asthma

ILC2s	Mild to moderate asthma (n =18)	Severe asthma (n= 11)	*P*-value
Peripheral blood	84.5 (24-134)	4104 (2103-5994)	$P < 0.001$
Sputum	143.5 (95-179)	2894 (1232-4209)	$P < 0.001$

ILC2s, type 2 innate lymphoid cells

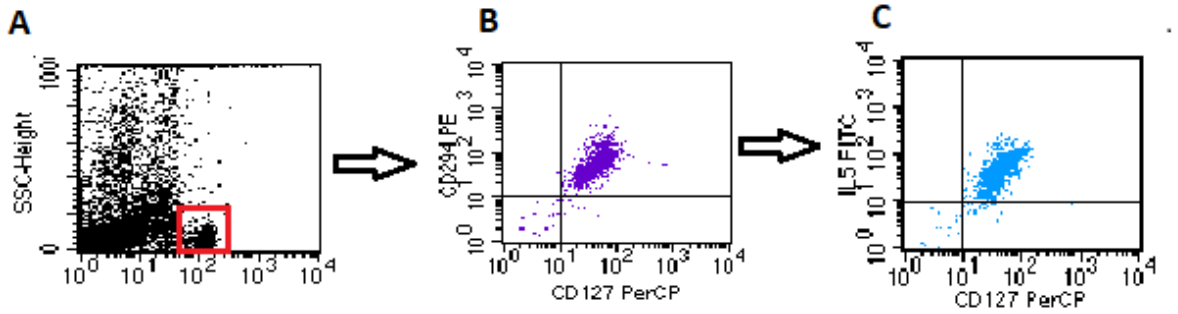

Figure 1: Gating strategy to isolate ILC2s populations in PB of sever asthmatic patients. Lymphocytes were isolated from whole PB mononuclear cells by (A) CD45+ /SCC cells, further characterization of ILC2s cells by lin- (CD45 +,CD19-, CD16– and CD56–); CD45 + cells expressing CRTH2/CD294 +CD127+;(B) . ILC2s were identified by CD127 + IL-5+ (C).

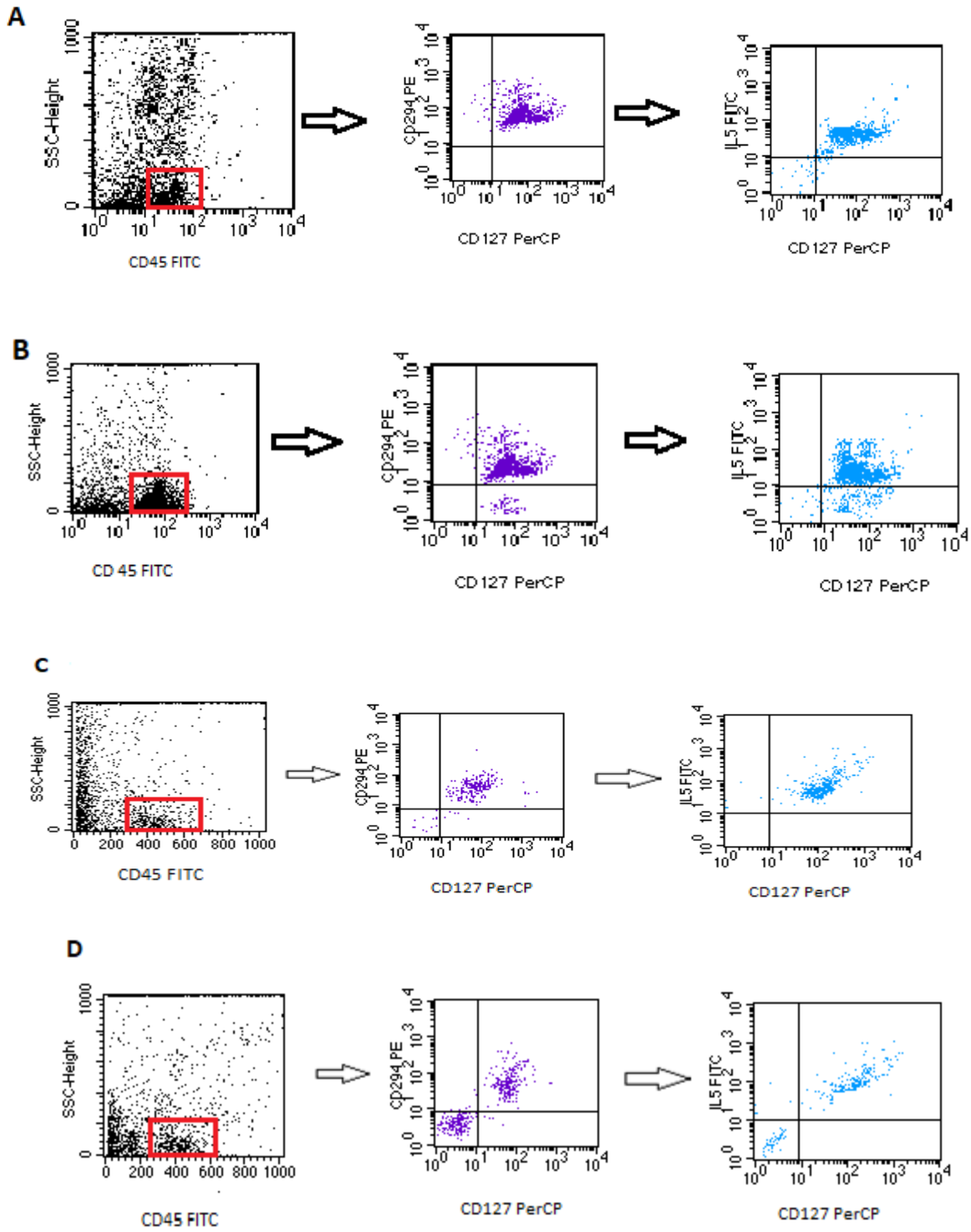

Figure 2: (A) Dot plot showed ILC2s (CD294/CD127/IL-5) in peripheral blood of mild to moderate asthma; (B) ILC2s in sputum of severe asthma; (C) ILC2s in sputum of mild to moderate asthma; (D) ILC2s in colonic biopsies in mild to moderate asthma.

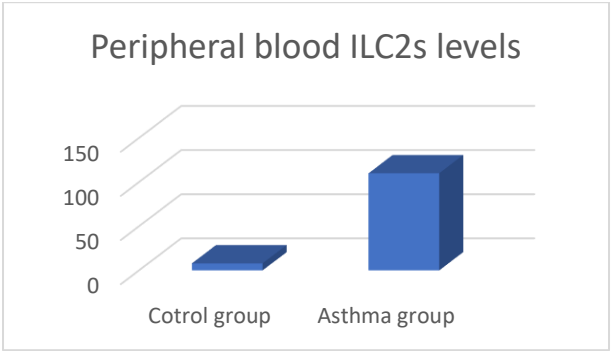

Figure 3: Comparison of median blood ILC2s levels between control and asthma groups

DISCUSSION

In the current study, we used PE labeled antibody CD294 (CRTH2), Percp labelled antibody to CD127 and IL-5 to identify true ILC2s population by flow cytometry in the peripheral blood, sputum, and colonic biopsies of healthy subjects as well as asthma patients. Our study demonstrated high levels of ILC2s in the blood and sputum of asthmatic patients. ILC2s were detected in the colonic biopsies of asthmatic patients. We also reported a positive strong correlation between ILC2s levels in blood, and sputum with a significant association between ILC2s levels and asthma severity.

In the current study, ILC2s levels were higher in the peripheral blood of asthma patients compared to the non- asthmatic group. These findings were similar to previous studies [8, 23, 24]. Liu and his co-workers reported a high level of ILC2 in the peripheral blood of asthmatic patients particularly in the eosinophilic asthmatic subgroup [23]. Bartemes et al., 2014 attributed the unregulated ILC2s levels in the blood in asthma to the increased IL-33 and IL-25 levels [8]. On the other hand, Barnig et al., 2013 had demonstrated no significant difference in levels of blood ILC2s between the control and asthma group which may be attributed to the different ethnicity and sample size [25].

We next investigated ILC2s in peripheral blood with asthma severity. We found the levels of blood ILC2s were elevated in severe asthma in relation to mild to moderate asthma patients. Our findings were in consistent with other studies [8, 20, 23.] On the other hand, other studies reported no significant differences in blood levels of ILC2s regarding to asthma severity [25, 26]. These studies expressed ILC2s levels as a ratio of the lymphocytes which might explain these inconsistent findings as the ratio can be affected by the levels of other cells, particularly ILC2s only represented a very little counts [27]. Regarding ILC2s in sputum, the present study showed higher ILC2s in the sputum of severe asthma compared to mild to moderate asthma. Our results were in agreement a previous study [20].

We reported a positive correlation of ILC2s levels in the peripheral blood, and sputum with the asthma severity, while Ishimori and his coworkers reported no significant correlation [26]. These discrepant findings of correlation could be contributed to the dominant airway inflammatory type and the corticosteroid treatment in severe asthma [24, 27]. Moreover, the effect of the local cytokines on ILC2s plasticity and function was an essential factor [24, 28]. Also, the identification extracellular markers of ILC2s were different among the previously mentioned studies. Although ILC2s are identified by extracellular marker CRTH2, and ILCs are identified by CD127, most of respiratory $lin^{-}CD45^{+}$ cells were $CD127^{-}$and nearly half of them were $CRTH2^{-}$. On contrary, almost all human studies identified and reported the prevalence of airway ILCs in the terms of surface markers as a part of its definition [24, 29]. Further investigations are required to study the association between ILCs and asthma severity.

Regarding colonic ILC2s, it can be found in human colorectal cancer and it is activated by IL-33 which accelerates tumor growth and metastasis development [30]. Elevated levels of the ILC2s were associated with poor prognosis [31]. ILC2s have a role in immune response against helminths and parasites [32]. ILC2s levels are elevated in colonic biopsies from inflammatory bowel disease [33]. In our study, ILC2s were detected in the colonic biopsies of asthma patients but it was not detected in the control specimens.

The ILCs circulation mechanism is critical for understanding the different processes of inflammatory and how to treat it. In order to

understand that mechanism we correlate ILC2s levels in blood and sputum where we found a strong positive correlation between ILC2s in blood, and sputum ($P< 0.001$) these results highlighted the striking ILC2s gut-lung recruitment axis, in which the intestine was considered an important origin of ILC2s recruited to the lung [32]. Huang and his co-workers reported that ILC2s could be recruited to lungs in response to inflammatory cytokines and they are not obligate tissue-resident cells [32].

ILC2s were detected in the blood as well as lymphatic vessels of the gut, suggesting that ILC2s circulate through the lymphatic system into the peripheral blood. In supporting of this, activated airways ILC2s express sphingosine 1-phosphate (S1P) receptors, which suggest that ILC2s can cross lymphatic endothelial cells, in a mechanism similar to T lymphocytes [7, 34]**.** Moreover, it reported that the blood ILCs precursors can enter different tissues and differentiate into the different ILCs subtypes [35]**.** However, it is still undetermined how much recruitment of circulating, differentiated or undifferentiated, ILC2s versus local proliferation and plasticity contribute to the total ILCs pool in an organ[32] .

CONCLUSION

The elevated innate type 2 immune cells in peripheral blood, sputum among patients with asthma suggesting the possible role of ILC2s in asthma pathogenesis. Peripheral blood ILC2s could be a marker of asthma severity. Research on a wider scale targeting ILC2s needs to be investigated. Some researchers reported that blocking ILC2s-derived cytokines could improve the asthma control [35, 36, 37]. So, estimating the ILC2s levels could identify asthma patients most likely to respond to these biological treatment, particularly steroid-refractory patients.

Limitation

The limitation of this study was the small sample size that did not allow us to do subgroup analysis. Also, the rarity of ILC2s in induced sputum specimens precluded statistical analysis in healthy individuals. It was difficult to obtain colonic biopsies from healthy individuals that the number of colonic biopsies in our study could not reach a statistical analysis level.

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