Type 3 innate lymphoid cells as an indicator of renal dysfunction and serum uric acid in hyperuricemia

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Conflict of interest
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Abstract

Background. Type 3 innate lymphoid cells (ILC3s) are a newly identified group of innate immune cells that participate in the progression of several metabolic diseases by secreting interleukin (IL)-17 and IL-22. These cytokines are associated with hyperuricemia (HUA) severity and development; however, the relationship between ILC3s and HUA remains unclear.

Objectives. To determine the characteristics of circulating ILC3s in patients with HUA.

Materials and methods. Type 3 innate lymphoid cells and their subsets were detected using flow cytometry in peripheral blood mononuclear cells (PBMCs) of 80 HUA patients and 30 healthy controls (HC). Plasma levels of IL-17A and IL-22 were measured with enzyme-linked immunosorbent assay (ELISA). Clinical data of enrolled subjects were collected from electronic medical records.

Results. In patients with HUA, the frequency of circulating ILC3s was elevated and positively correlated with levels of serum uric acid and serum creatinine (Scr). Although there was no significant difference in the plasma concentration of IL-17A between the patients with HUA and healthy controls, positive correlations between plasma IL-17A and the concentration of serum uric acid and frequency of circulating ILC3s were observed in the patients with HUA.

Conclusions. In patients with HUA, positive correlations were detected between circulating ILC3 levels, plasma IL-17A and serum uric acid. Therefore, ILC3s and IL-17A may be useful indicators of disease severity, and are potential new therapeutic targets in HUA.

Key words: uric acid, innate immunity, interleukin-17, creatinine, hyperuricemia

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Background

Hyperuricemia (HUA) is a prerequisite for the development of gout,[1] the most prevalent form of inflammatory arthritis,[2,3] and is primarily caused by impaired urate excretion.[4] Although the reported prevalence of HUA in the Chinese population has increased to 13.3% and is gradually rising,[5] factors accounting for the pathogenesis and development of HUA are not fully understood.

As the kidney is the major organ that mediates uric acid (UA) excretion, HUA in humans is closely associated with kidney damage and kidney diseases.[6] Furthermore, emerging evidence has highlighted the role of the intestine in HUA and gout development.[7,8] The gut is responsible for 1/3 of total UA excretion,[9] with HUA patients and murine models of the condition often exhibiting intestinal microbiota dysbiosis and barrier dysfunction, both of which contribute to the progression of HUA.[10,11] The studies highlighted above indicate that factors involved in maintaining homeostasis of the intestine might affect the excretion of UA.

A newly defined group of innate immune cells expressing the retinoic acid receptor-related orphan nuclear receptor gamma transcription factor, called type 3 innate lymphoid cells (ILC3s), are thought to play an important role in mucosal immunity.[12] They were identified as abundant in the intestinal mucosa and are associated with gut microbiota tolerance and intestinal barrier integrity.[12,13] Additionally, similar to T helper 17 cells, ILC3s produce a variety of distinct cytokines, including interleukin (IL)-17 and IL-22, that are associated with HUA severity and development.[14,15] Nonetheless, the association between HUA and ILC3s remains unclear.

Objectives

This study aimed to determine the characteristics of circulating ILC3s in patients with HUA, and to explore whether or not the proportion of circulating ILC3s and the concentration of ILC3-related cytokines (IL-17A and IL-22) correlate with disease severity.

Materials and methods

Subjects

In this cross-sectional study, adult patients with HUA and healthy controls (HC) were recruited from the First Affiliated Hospital of Guangdong Pharmaceutical University, China, between September 2020 and August 2021. Hyperuricemia was defined as a serum UA ≥ 420 μmol/L (7.0 mg/dL) in men and ≥360 μmol/L (6.0 mg/dL) in women.[16] Patients suffering from carcinoma and intestinal diseases (such as Crohn's disease and ulcerative colitis) were excluded. Demographic data and UA-associated parameters (serum UA, serum creatinine (Scr) and blood urea nitrogen (BUN)) were collected from electronic medical records. This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangdong Pharmaceutical University, China (approval No. 2021146). Informed consent was obtained from each patient.

Separation of peripheral blood mononuclear cells and plasma

Morning fasting blood samples were collected from each subject using a heparin anticoagulant tube (Huabo Medical Instrument Co. Ltd., Heze, China) to isolate peripheral blood mononuclear cells (PBMCs) and plasma. Peripheral blood mononuclear cells were obtained using density gradient centrifugation (Ficoll-Paque™ PLUS; GE Healthcare, Chicago, USA) (400 × g, 30 min, room temperature). Plasma was isolated by centrifugation of whole blood (800 × g, 20 min, room temperature) and stored at –80°C for further use in enzyme-linked immunosorbent assay (ELISA).

Flow cytometry

Peripheral blood mononuclear cells were stained using the following antibodies: anti-CD3-FITC (clone: HIT3a), anti-CD5-FITC (clone: UCHT2), anti-CD11c-FITC (clone: 3.9), anti-CD16-FITC (clone: B73.1), anti-CD19-FITC (clone: HIB19), anti-TCRαβ-FITC (clone: IP26), anti-CD117-PE (clone: A3C6E2), anti-CD127-PE/Cyanine7 (clone: A019D5), anti-CD294-APC (clone: BM16), and anti-CD45-APC/Cyanine7 (clone: H130) (all from BioLegend, Beijing, China). Dead cells were stained with 7-aminoactinomycin D (7-AAD) viability staining solution (BioLegend). Total ILCs were identified as 7-AAD$^-$ CD45$^+$ lineage (CD3, CD5, CD11c, CD16, CD19, and TCRαβ) $^-$CD127$^+$ lymphocytes. The ILC1s were CD117$^-$CD294$^-$, whilst ILC2s were CD294$^+$, and ILC3s were CD117$^+$CD294$^-$. Flow cytometry was performed using a CytoFLEX flow cytometer (Beckman Coulter, Brea, USA), and data were analyzed using CytoExpert v. 2.3 software (Beckman Coulter).

Enzyme-linked immunosorbent assay

Plasma levels of IL-17A and IL-22 were measured using the ELISA MAX™ Deluxe Set Human IL-17A (No. 433914) and the ELISA MAX™ Deluxe Set Human IL-22 (No. 434504) (both from BioLegend), according to the manufacturer's instructions.

Statistical analyses

Statistical analyses were performed using GraphPad Prism v. 8.0 software (GraphPad Software, San Diego, USA.). Data distributions were assessed using the Shapiro–Wilk test (Table 1). Normally distributed data are presented as mean ± standard deviation (M ±SD), whereas

Table 1. Results of normality test

Variable	W-value	p-value
Patients with hyperuricemia		
ILCs/lymphocytes [%]	0.8518	<0.0001
ILC1s/ILCs [%]	0.9510	0.0039
ILC2s/ILCs [%]	0.9623	0.0187
ILC3s/ILCs [%]	0.9571	0.0090
Plasma IL-17A [pg/mL]	0.9533	0.2760
Plasma IL-22 [pg/mL]	0.5434	<0.0001
Serum uric acid [μmol/L]	0.9174	<0.0001
Scr [μmol/L]	0.6294	<0.0001
Blood urea nitrogen [mmol/L]	0.8111	<0.0001
Healthy controls		
ILCs/lymphocytes [%]	0.8040	<0.0001
ILC1s/ILCs [%]	0.9657	0.4301
ILC2s/ILCs [%]	0.9724	0.6065
ILC3s/ILCs [%]	0.9873	0.9695
Plasma IL-17A [pg/mL]	0.8487	0.0021

ILCs – innate lymphoid cells; IL – interleukin; Scr – serum creatinine. Data distribution was assessed using the Shapiro–Wilk test.

non-normally distributed data are presented as median (interquartile range (IQR)). The Spearman's rank-order correlation was used for nonparametric correlations. The value of $p < 0.05$ was considered statistically significant.

Results

The frequency of circulating ILC3s was increased in patients with HUA

A total of 80 patients with HUA (mean age 52.85 ±15.99 years, 49 males (61.25%)) and 30 HC (mean age 37.57 ±12.37 years, 9 males (30.00%)) were included in the study. A positive correlation between serum UA and Scr concentrations was found in patients with HUA ($r_s = 0.501$, $p < 0.001$), which suggests an association between HUA and the impairment of renal function. The gating strategy used to separate ILCs and their subgroups is shown in Fig. 1A. First, the levels of ILCs and their subgroups in PBMCs were compared between HC and patients with HUA. Statistical comparisons showed that the percentage of total ILCs in the live lymphocyte population did not differ significantly between the 2 groups (0.09% (0.05–0.17%) compared to 0.07% (0.05–0.10%), U = 959.5, p = 0.07; Fig. 1B). For ILC subgroups, a marked elevated frequency of circulating ILC3s (22.27% (11.28–32.32%) compared to 17.11% (10.83–21.29%), U = 868, p = 0.03) was observed in HUA patients, although the frequencies of circulating ILC1s (23.24% (13.83–38.20%) compared to 32.80% (18.91–54.08%), U = 924.5, p = 0.06) and ILC2s (46.87% (31.37–67.91%) compared to 48.32% (27.26–66.32%), U = 1139, p = 0.69) did not differ significantly between the 2 groups (Fig. 1C and Table 2).

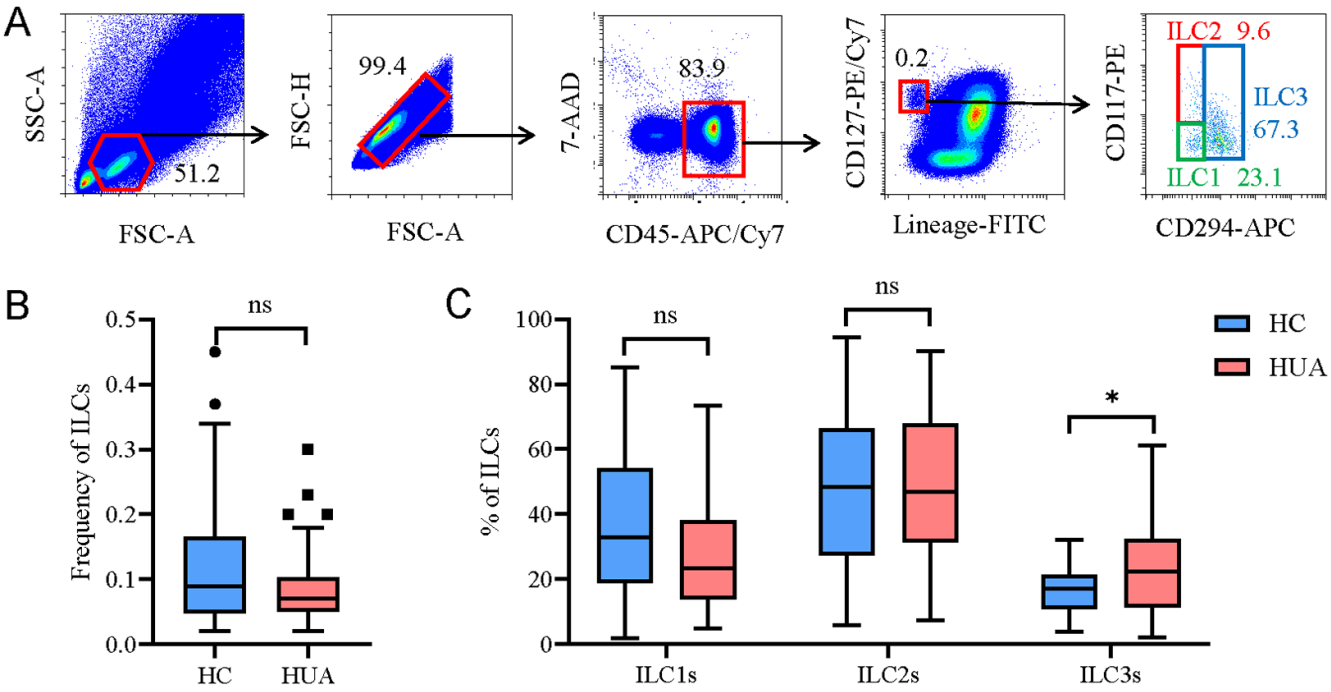

Fig. 1. Circulating type 3 innate lymphoid cells (ILC3s) increased in patients with hyperuricemia. A. Representative dot plots showing the gating strategy used to identify ILC3s among human peripheral blood mononuclear cells (PBMCs). Percentages of ILCs (B) and their subsets (C) in PBMCs from healthy controls (HC) and patients with hyperuricemia (HUA) (Mann–Whitney U test). Lineage = CD3, CD5, CD11c, CD16, CD19, TCRαβ. Boxplots represent median, interquartile ranges (IQRs) and Tukey-style whiskers. Data points beyond the whiskers represent outliers

* $p < 0.05$; ns – not significant.

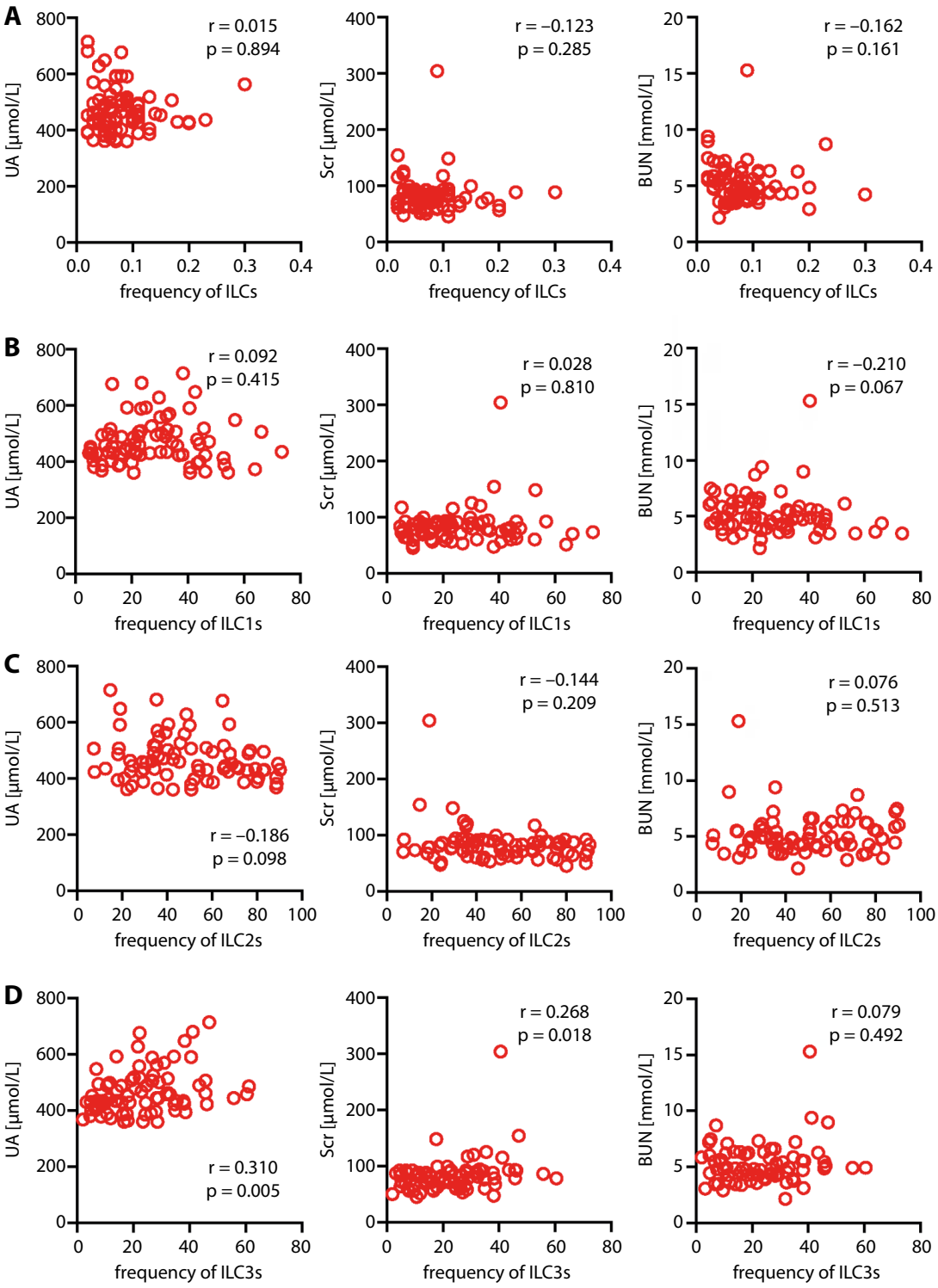

Fig. 2. Frequency of circulating type 3 innate lymphoid cells (ILC3s) positively correlated with serum uric acid (UA) and serum creatinine (Scr) in patients with hyperuricemia. Spearman correlation coefficients between the frequencies of circulating ILCs (A), ILC1s (B), ILC2s (C), ILC3s (D), and concentrations of serum UA, Scr and blood urea nitrogen (BUN) in patients with hyperuricemia

Circulating ILC3s positively correlated with serum UA and Scr levels in patients with HUA

Correlations between the levels of circulating ILCs and their subgroups with UA-associated parameters (serum UA, Scr and blood urea nitrogen) in patients with HUA were assessed. As shown in Fig. 2A–C, no significant correlations were found between the frequencies of circulating ILCs, ILC1s or ILC2s, and UA-associated parameters. In contrast, the frequency of ILC3s in PBMCs from patients with HUA positively correlated with serum levels of UA ($r_s = 0.310$, $p = 0.005$) and Scr ($r_s = 0.268$, $p = 0.018$) (Fig. 2D).

Plasma IL-17A positively correlated with the frequency of circulating type ILC3s and serum UA levels

Plasma concentrations of ILC3-related cytokines (IL-17A and IL-22) were compared between the 2 groups, with

Table 2. The proportion of circulating ILC subgroups and the concentrations of plasma cytokines between healthy controls and patients with hyperuricemia

Variable	Healthy controls	Patients with hyperuricemia	U-value	p-value
ILCs/lymphocytes [%]	0.09 (0.05–0.17)	0.07 (0.05–0.10)	959.5	0.07
ILC1s/ILCs [%]	32.80 (18.91–54.08)	23.24 (13.83–38.20)	924.5	0.06
ILC2s/ILCs [%]	48.32 (27.26–66.32)	46.87 (31.37–67.91)	1139	0.69
ILC3s/ILCs [%]	17.11 (10.83–21.29)	22.27 (11.28–32.32)	868	0.03
Plasma IL-17A [pg/mL]	3.36 (2.47–4.70)	3.26 (2.75–4.00)	289	0.66
Plasma IL-22 [pg/mL]	29.25 (12.31–49.13)	45.15 (16.69–86.51)	186.5	0.14

ILCs – innate lymphoid cells; IL – interleukin. Data are presented as median (interquartile range (IQR)). Differences between the 2 groups were assessed with Mann–Whitney U tests.

samples from 26 HUA patients and 24 HC being available for ELISA analysis. Although no differences in plasma IL-17A (3.36 (2.47–4.70) compared to 3.26 (2.75–4.00) pg/mL, U = 289, p = 0.66) or IL-22 (29.25 (12.31–49.13) compared to 45.15 (16.69–86.51) pg/mL, U = 186.5, p = 0.14, Table 2) concentrations were detected between the 2 groups, a positive correlation was observed between plasma IL-17A concentration and the frequency of circulating ILC3s in patients with HUA (Fig. 3).

Finally, the associations between ILC3-related cytokines and UA-associated parameters were assessed with the Spearman's rank-order correlation. Plasma IL-17A positively correlated with serum UA levels (r_s = 0.445, p = 0.023); however, no correlations were observed between IL-22 and UA-associated parameters (Fig. 4).

Discussion

In the present study, the expansion of circulating ILC3s was observed in patients with HUA. Moreover, the proportion of ILC3s among PBMCs positively correlated with

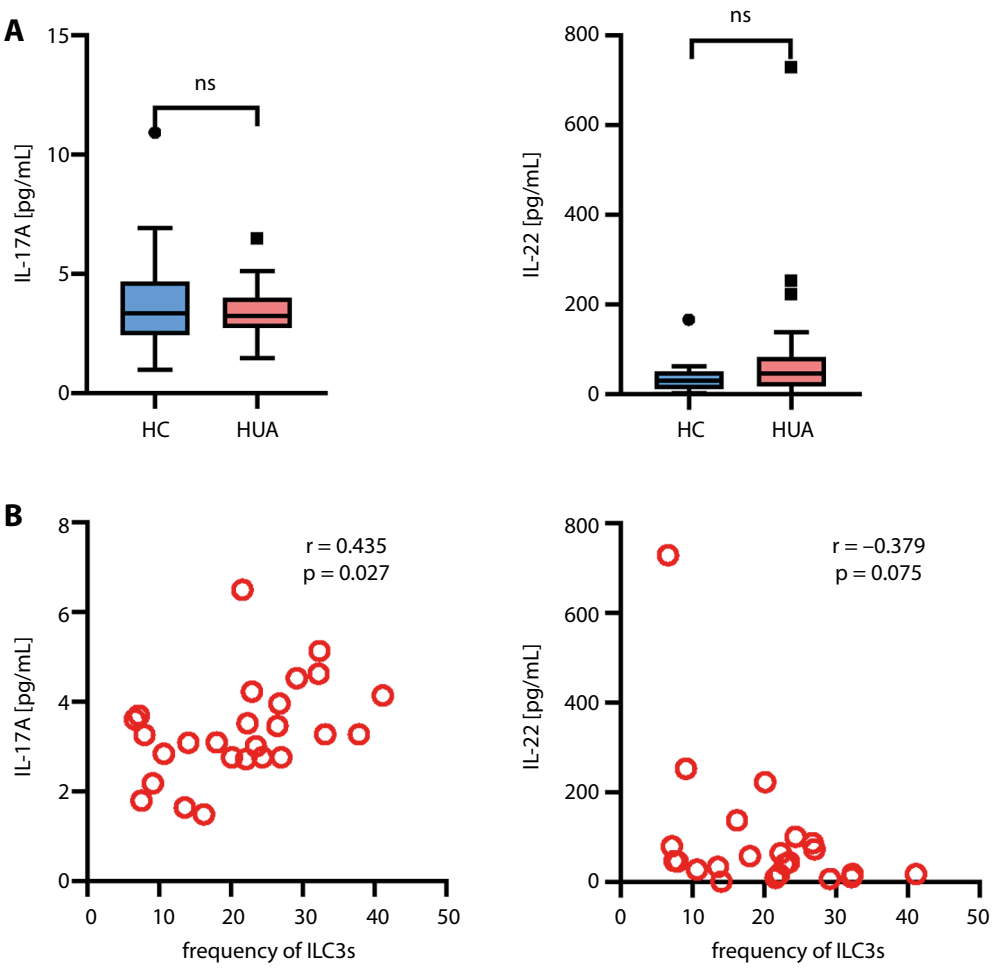

Fig. 3. Plasma interleukin (IL)-17A concentration positively correlated with circulating type 3 innate lymphoid cell (ILC3) frequency in patients with hyperuricemia. A. Quantitative analysis of the plasma concentrations of IL-17A and IL-22 in healthy controls (HC) and patients with hyperuricemia (HUA) (Mann–Whitney U test); B. Spearman correlation coefficients between plasma IL-17A and IL-22 levels, and the frequency of circulating ILC3s in patients with HUA. Boxplots represent median, interquartile ranges (IQRs) and Tukey-style whiskers. Data points beyond the whiskers represent outliers

ns – not significant.

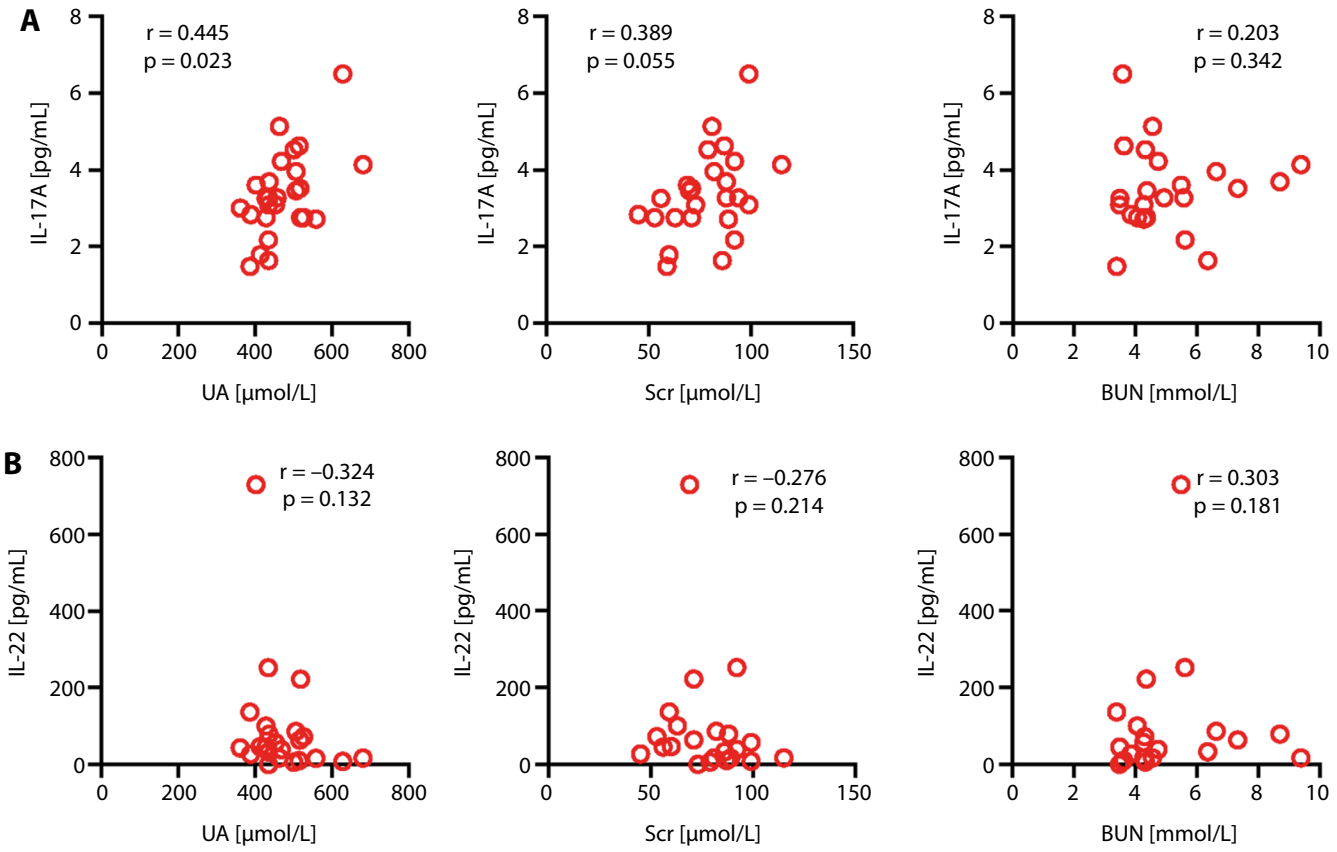

Fig. 4. Plasma interleukin (IL)-17A concentration positively correlated with serum uric acid (UA) level in patients with hyperuricemia (HUA). Spearman's rank-order correlation analysis between the concentrations of plasma IL-17A (A) and IL-22 (B) with serum UA, serum creatinine (Scr) and blood urea nitrogen (BUN) in patients with HUA

serum UA and Scr concentrations, indicating that circulating ILC3s could serve as an indicator of HUA severity. To the best of our knowledge, this is the first study to determine the characteristics of circulating ILC3s in patients with HUA.

Multiple mechanisms could explain the findings of this study. First, HUA may result in increased levels of ILC3s. Recent studies have revealed gut microbiota dysbiosis, characterized by a decrease in species diversity and an increased abundance of inflammation-related microbiota, in HUA patients and mouse models.[8,11,17] In addition, HUA can lead to intestinal barrier dysfunction that presents as enhanced intestinal permeability and gut inflammation.[11,18,19] Such gut dysbiosis and intestinal barrier injury can contribute to the enrichment of ILC3s.[20,21] Furthermore, ILC3s can secrete several pro-inflammatory cytokines, including IL-17 and granulocyte-macrophage colony-stimulating factor,[22] which may promote kidney and intestine inflammation,[22–24] reduce UA excretion and subsequently exacerbate UA accumulation in patients with HUA. Thus, targeting ILC3s may be a novel therapeutic strategy for HUA.

Alterations of ILC3s have been reported in several metabolic diseases. Both the frequency and absolute number of ILC3s were significantly increased in small intestinal lamina propria of nonobese diabetic mice compared to healthy mice, which was accompanied by intestinal dysbiosis and an impaired intestinal barrier.[25] Furthermore, increased proportions of IL-22$^+$ILC3s and IL-17A$^+$ NKp44$^-$ ILC3s were detected among PBMCs from patients with axial spondyloarthritis and dyslipidemia.[26] Conversely, type 2 diabetes patients infected with tuberculosis exhibited an obvious reduction in circulating ILC3s relative to those without diabetes.[27] Additionally, ILC3s have been shown to participate in the progression of other metabolic diseases, such as fatty liver disease.[28] Despite the increased levels of circulating ILC3s in HUA patients observed in this study, whether or not ILC3s contribute to HUA development requires further investigation.

The IL-17, a distinct cytokine produced by ILC3s, is widely reported to be associated with acute gout arthritis. Liu et al. showed that serum IL-17 levels were significantly elevated in patients with acute gout arthritis, which positively correlated with disease severity.[29] Furthermore, targeting IL-17 with neutralizing antibodies reduced leukocyte infiltration, decreased pro-inflammatory cytokine levels and attenuated arthritis.[15] However, plasma IL-17 levels did not differ markedly between patients with intercritical gout and HC.[30] Similarly, we found no significant difference in plasma IL-17A concentration between patients with HUA and HC, whereas in patients with HUA, positive correlations were observed between plasma IL-17A, serum UA and frequency of circulating

ILC3s. This suggests that HUA may induce ILC3 expansion and activation, and that plasma IL-17A could be a useful indicator of HUA severity.

Limitations

The present study had several limitations. Only 2 of the enrolled HUA patients had gout, meaning the association between ILC3s and gout could not be assessed. Also, as this was a cross-sectional study, only the associations between UA level, IL-17 and ILC3 could have been investigated. Indeed, it could not be determined if the relationship between UA level, IL-17 and ILC3s was causal. Furthermore, the sample size was relatively small, particularly for the HC group. Thus, studies with a larger sample size should be conducted to validate our findings.

Conclusions

In conclusion, we demonstrated that patients with HUA have an elevated frequency of circulating ILC3s. Furthermore, circulating ILC3 levels and plasma IL-17A concentration were positively correlated with HUA severity. Therefore, ILC3s and IL-17A could be useful indicators of HUA severity and have potential as new therapeutic targets in this disease.

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References

1. Diaz-Torne C, Ortiz MA, Garcia-Guillen A, et al. The inflammatory role of silent urate crystal deposition in intercritical gout. *Rheumatology*. 2021;60(11):5463–5472. doi:10.1093/rheumatology/keab335
2. Dalbeth N, Gosling AL, Gaffo A, Abhishek A. Gout. *Lancet*. 2021; 397(10287):1843–1855. doi:10.1016/S0140-6736(21)00569-9
3. Dalbeth N, Choi HK, Joosten LAB, et al. Gout. *Nat Rev Dis Primers*. 2019;5(1):69. doi:10.1038/s41572-019-0115-y
4. Major TJ, Dalbeth N, Stahl EA, Merriman TR. An update on the genetics of hyperuricaemia and gout. *Nat Rev Rheumatol*. 2018;14(6):341–353. doi:10.1038/s41584-018-0004-x
5. Liu R, Han C, Wu D, et al. Prevalence of hyperuricemia and gout in mainland China from 2000 to 2014: A systematic review and meta-analysis. *BioMed Res Int*. 2015;2015:762820. doi:10.1155/2015/762820
6. Li H, Zhang H, Yan F, et al. Kidney and plasma metabolomics provide insights into the molecular mechanisms of urate nephropathy in a mouse model of hyperuricemia. *Biochim Biophys Acta Mol Basis Dis*. 2022;1868(6):166374. doi:10.1016/j.bbadis.2022.166374
7. Vieira AT, Macia L, Galvão I, et al. A role for gut microbiota and the metabolite-sensing receptor GPR43 in a murine model of gout. *Arthritis Rheum*. 2015;67(6):1646–1656. doi:10.1002/art.39107
8. Song S, Lou Y, Mao Y, et al. Alteration of gut microbiome and correlated amino acid metabolism contribute to hyperuricemia and Th17-driven inflammation in Uox-KO mice. *Front Immunol*. 2022;13:804306. doi:10.3389/fimmu.2022.804306
9. Yun Y, Yin H, Gao Z, et al. Intestinal tract is an important organ for lowering serum uric acid in rats. *PLoS One*. 2017;12(12):e0190194. doi:10.1371/journal.pone.0190194
10. Wang J, Chen Y, Zhong H, et al. The gut microbiota as a target to control hyperuricemia pathogenesis: Potential mechanisms and therapeutic strategies. *Crit Rev Food Sci Nutr*. 2022;62(14):3979–3989. doi:10.1080/10408398.2021.1874287
11. Lv Q, Xu D, Zhang X, et al. Association of hyperuricemia with immune disorders and intestinal barrier dysfunction. *Front Physiol*. 2020;11: 524236. doi:10.3389/fphys.2020.524236
12. Chun E, Lavoie S, Fonseca-Pereira D, et al. Metabolite-sensing receptor Ffar2 regulates colonic group 3 innate lymphoid cells and gut immunity. *Immunity*. 2019;51(5):871.e6–884.e6. doi:10.1016/j.immuni.2019.09.014
13. Zhou L, Zhou W, Joseph AM, et al. Group 3 innate lymphoid cells produce the growth factor HB-EGF to protect the intestine from TNF-mediated inflammation. *Nat Immunol*. 2022;23(2):251–261. doi:10.1038/s41590-021-01110-0
14. Chen Y, Ma H, Du Y, et al. Functions of 1,25-dihydroxy vitamin D3, vitamin D3 receptor and interleukin-22 involved in pathogenesis of gout arthritis through altering metabolic pattern and inflammatory responses. *PeerJ*. 2021;9:e12585. doi:10.7717/peerj.12585
15. Raucci F, Iqbal AJ, Saviano A, et al. IL-17A neutralizing antibody regulates monosodium urate crystal-induced gouty inflammation. *Pharmacol Res*. 2019;147:104351. doi:10.1016/j.phrs.2019.104351
16. Li H, Zeng R, Liao Y, et al. Prevalence and risk factors of left ventricular diastolic dysfunction in patients with hyperthyroidism. *Front Endocrinol*. 2021;11:605712. doi:10.3389/fendo.2020.605712
17. Sheng S, Chen J, Zhang Y, et al. Structural and functional alterations of gut microbiota in males with hyperuricemia and high levels of liver enzymes. *Front Med*. 2021;8:779994. doi:10.3389/fmed.2021.779994
18. Xu D, Lv Q, Wang X, et al. Hyperuricemia is associated with impaired intestinal permeability in mice. *Am J Physiol Gastrointest Liver Physiol*. 2019;317(4):G484–G492. doi:10.1152/ajpgi.00151.2019
19. Guo Y, Li H, Liu Z, et al. Impaired intestinal barrier function in a mouse model of hyperuricemia. *Mol Med Rep*. 2019;20(4):3292–3300. doi:10.3892/mmr.2019.10586
20. Seidelin JB, Bahl MI, Licht TR, et al. Acute experimental barrier injury triggers ulcerative colitis-specific innate hyperresponsiveness and ulcerative colitis-type microbiome changes in humans. *Cell Mol Gastroenterol Hepatol*. 2021;12(4):1281–1296. doi:10.1016/j.jcmgh.2021.06.002
21. Valiente GR, Munir A, Hart ML, et al. Gut dysbiosis is associated with acceleration of lupus nephritis. *Sci Rep*. 2022;12(1):152. doi:10.1038/s41598-021-03886-5
22. Zheng M, Zhu J. Innate lymphoid cells and intestinal inflammatory disorders. *Int J Mol Sci*. 2022;23(3):1856. doi:10.3390/ijms23031856
23. Paquissi FC, Abensur H. The Th17/IL-17 axis and kidney diseases, with focus on lupus nephritis. *Front Med*. 2021;8:654912. doi:10.3389/fmed.2021.654912
24. Wang C, Li Q, Lv J, et al. Alpha-hemolysin of uropathogenic *Escherichia coli* induces GM-CSF-mediated acute kidney injury. *Mucosal Immunol*. 2020;13(1):22–33. doi:10.1038/s41385-019-0225-6
25. Miranda MCG, Oliveira RP, Torres L, et al. Frontline Science: Abnormalities in the gut mucosa of non-obese diabetic mice precede the onset of type 1 diabetes. *J Leukoc Biol*. 2019;106(3):513–529. doi:10.1002/JLB.3HI0119-024RR
26. Min HK, Moon J, Lee SY, et al. Expanded IL-22^{+} group 3 innate lymphoid cells and role of oxidized LDL-C in the pathogenesis of axial spondyloarthritis with dyslipidaemia. *Immune Netw*. 2021;21(6):e43. doi:10.4110/in.2021.21.e43
27. Ssekamatte P, Nakibuule M, Nabatanzi R, et al. Type 2 diabetes mellitus and latent tuberculosis infection moderately influence innate lymphoid cell immune responses in Uganda. *Front Immunol*. 2021;12: 716819. doi:10.3389/fimmu.2021.716819
28. Hamaguchi M, Okamura T, Fukuda T, et al. Group 3 innate lymphoid cells protect steatohepatitis from high-fat diet induced toxicity. *Front Immunol*. 2021;12:648754. doi:10.3389/fimmu.2021.648754
29. Liu Y, Zhao Q, Yin Y, McNutt MA, Zhang T, Cao Y. Serum levels of IL-17 are elevated in patients with acute gouty arthritis. *Biochem Biophys Res Commun*. 2018;497(3):897–902. doi:10.1016/j.bbrc.2018.02.166
30. Yang QB, He YL, Zhang QB, Mi QS, Zhou JG. Downregulation of transcription factor T-Bet as a protective strategy in monosodium urate-induced gouty inflammation. *Front Immunol*. 2019;10:1199. doi:10.3389/fimmu.2019.01199