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Tonsillitis exacerbates renal injury in IgA nephropathy through promoting Th22 cells chemotaxis

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Abstract

Background Tonsillitis can promote the progression of IgA nephropathy (IgAN) by aggravating immunopathologic response. Th22 cell disorder is involved in the pathogenesis of IgAN with tonsillitis. This study was determined to explore the possible mechanism of IgAN with tonsillitis underlying Th22 cell chemotaxis response to the effect of CCL20, CCL22, and CCL27.

Methods This research was conducted on 65 subjects including 16 healthy controls (HC group), 5 patients with renal carcinoma (HTC group) and 44 patients with IgAN between 2015 and 2016. According to clinical symptoms and results of throat swab culture, patients with IgAN were divided into two groups: IgAN with tonsillitis (IgAN + tonsillitis, $n = 14$) and IgAN patients without tonsillitis (IgAN, $n = 30$). Distribution of Th22 cells in IgAN patients was determined. The expression of CCL20, CCL22, and CCL27 in both peripheral blood and kidneys of IgAN patients was investigated. Severity of pathological lesions in IgAN patients was analyzed. Coculture assay and transwell assay were performed to explore the impacts of human mesangial cells (HMC) on Th22 cell chemotaxis and Th22 cell local accumulation under *hemolytic streptococcus* (HS) infection.

Results Th22 cell percentages in IgAN patients increased compared with healthy controls. This increased Th22 cell percentage was positively correlated with the renal lesions of IgAN patients. Correspondingly, the expression of CCL20, CCL22, and CCL27 in renal tissue increased in IgAN patients. Tonsillitis exacerbated these overrepresentations of Th22 cells and chemokines. It was found that HMC could produce CCL20, CCL22, and CCL27. The supernatant of HMC was chemotactic for Th22 cells. This activity of HMC was stimulated by HS infection, whereas treatment of anti-CCL20, anti-CCL22, and anti-CCL27 antibodies partly blocked this chemoattractant effect of HMC.

Conclusions Tonsil infection may aggravate the renal pathological lesions of IgAN by exacerbating Th22 cell accumulation. Our data suggested a collaboration between HMC and Th22 cells in IgAN with tonsillitis underlying the effects of CCL20, CCL22, and CCL27.

Keywords IgA Nephropathy · Tonsillitis · Th22 Cells · CCL27 · CCL22 · CCL20

Introduction

IgA nephropathy (IgAN) is the most common cause of primary glomerular disease [1]. Tonsillitis induced by *hemolytic streptococcus* (HS) infection plays an important role in the exacerbation of IgAN by promoting immune disorder and inflammatory response [2, 3].

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Lymphocytes disorder is involved in the immunopathologic and inflammatory processes of IgAN [4]. IL-22-producing help T (Th22) lymphocyte is a newly identified $CD4^+$ T helper (Th) lymphocyte subset, which is characterized by secreting IL-22 and expressing CC chemokine receptor, i.e., CCR4, CCR6, and CCR10. Current researches have set forth that Th22 cell is involved in many autoimmune diseases, including rheumatoid arthritis, psoriatic arthritis, and glomerulonephritis, such as lupus nephritis and IgAN [5, 6].

Chemokines participate in inflammatory response and the progress of glomerulonephritis by promoting leukocytes infiltration [7]. CCL20, CCL22, and CCL27 are important members of CC chemokine family, which is involved in the pathogenesis of IgAN [8]. CCL20, CCL22, and CCL27 are the specific ligands for CCR4, CCR6, and CCR10. By interacting with this cell surface receptor, CCL20, CCL22, and CCL27 participate in the regulation of Th22 cell chemotaxis and local inflammatory injury. In the present study, we investigated the distribution of Th22 cell in IgAN patients and explored the possible mechanism of IgAN with tonsillitis underlying Th22 cell chemotaxis.

Materials and methods

Subjects

A total of 65 subjects were recruited for this study, consisting of 5 patients with renal carcinoma (HTC group), 16 healthy controls (HC group), 30 IgAN without tonsillitis (IgAN group), and 14 IgAN with tonsillitis (IgAN + tonsillitis group). The demographic, clinical, and biochemical characteristics and pathology of all subjects in HC group, IgAN group, and IgAN + tonsillitis group are shown in Table 1.

For IgAN patients without tonsillitis (IgAN group), the inclusion criteria are (1) ≥ 16 years old; and (2) diagnosed with IgAN based on a renal biopsy; (3) with no repeated history of tonsil infection or current antiadoncus. The exclusion criteria are (1) having acute infection; (2) having tonsil infection; (3) underwent glucocorticoid or immunosuppressant treatments; (4) having other immune-related diseases or complications. For IgAN patient with tonsillitis (IgAN + tonsillitis group), the inclusion criteria are those for IgAN group, plus throat swab culture proved infection. For healthy controls (HC groups), the inclusion criteria are: no renal pathology and coexisting tonsillitis, and the exclusion criteria are having any perceptible diseases, including immune disease, renal disease, infection. All patients were receiving valsartan.

Table 1 Demographic, clinical, and biochemical characteristics and pathology of patients with IgAN ($n = 60$)

	HC group ($N = 16$)	IgAN group ($N = 30$)	IgAN + tonsillitis group ($N = 14$)
Male (n, n%)	5 (31.25%)	10 (33.33%)	5 (35.71%)
Age (years)	26.69 ± 1.35	30.33 ± 9.69	30.79 ± 8.47
SBP (mmHg)	119.75 ± 9.09	121.53 ± 19.35	119.14 ± 13.52
DBP (mmHg)	77.75 ± 2.62	80.13 ± 13.10	76.36 ± 11.28
Proteinuria (g/24 h)	Negative	1.03 ± 1.23*	0.81 ± 0.95*
Hematuria (n, n%)	Negative	20 (66.67%)*#	13 (92.86%)*
Serum albumin (g/L)	43.26 ± 3.21	38.70 ± 4.69*	39.09 ± 7.11*
Blood urea nitrogen (mmol/L)	4.78 ± 0.84	6.37 ± 6.21	6.78 ± 5.79
Serum creatinine (umol/L)	81.38 ± 13.74	93.49 ± 26.75	81.27 ± 21.53
Uric acid (umol/L)	312.56 ± 55.82	355.48 ± 126.44	319.16 ± 62.34
Total cholesterol (mmol/L)	4.70 ± 0.73	4.91 ± 1.14	4.96 ± 0.98
Triglyceride (mmol/L)	1.04 ± 0.41	1.67 ± 1.19	1.34 ± 0.73
Peripheral blood lymphocytes (10^9/L)	1.42 ± 0.44	1.99 ± 0.65*	2.03 ± 0.71*
Pathological lesions (n, n%)			
Mesangial hypercellularity (M1)		30 (100%)	14 (100%)
Endocapillary hypercellularity (E1)		15 (50%)#	8 (57.14%)
Segmental glomerulosclerosis (S1)		13 (43.33%)#	13 (92.86%)
Tubular atrophy/interstitial fibrosis (T1-2)		1 (3.33%)#	3 (21.43%)

#$P < 0.05$ when IgAN group compared with IgAN + tonsillitis group

*$P < 0.05$ compared with control group

Flow cytometry

Peripheral blood mononuclear cells from subjects were isolated using ficoll purchased from GE Healthcare Life Sciences. The cells were then stained for CD3 (PerCP-Cyanine5.5; eBioscience), CD4 (FITC; eBioscience), INF-γ (APC, eBioscience), IL-17 (PE-Cyanine7, eBioscience), IL-22 (PE or Pacific blue, eBioscience), and CCR10 (PE-Cyanine7, BioLegend). Th1 cells ($CD3^+CD4^+INF\text{-}\gamma^+$), Th17 cells ($CD3^+CD4^+IL17^+$), and Th22 cells ($CD3^+CD4^+INF\text{-}\gamma^-IL\text{-}17^-Th22^+$) [9] were isolated and quantified by flow cytometry. Flow cytometry was conducted, using Becton Dickinson FACScalibur system in Central Lab of Xiangya Hospital.

Enzyme-linked immunosorbent assay (ELISA)

The serum IL-6, IL-1β, TNF-α, CCL20, CCL22, and CCL27 of patients and healthy controls were quantified by ELISA according to the manufacturer's recommendations (RayBiotech, USA).

Renal histopathology

The renal tissues were stained with hematoxylin and eosin (HE) and periodic acid-Schiff reagents and then analyzed by a renal pathologist under a light microscope according to Oxford Classification of IgA nephropathy 2016 [10].

Immunohistochemistry

Healthy renal tissues obtained from renal carcinoma patients without glomerulonephritis were taken as control group (HTC group). The renal expressions of CCL20, CCL22, and CCL27 were analyzed by immunohistochemistry. Image-Pro Plus 6.0 was used for quantitative calculation. Anti-human CCL27 antibody (Ab), anti-human CCL20Ab, and anti-human CCL22Ab were bought from Abcam.

Coculture assay

Experiments were independent biological repeats. $CD4^+$ T lymphocytes of IgAN patients were isolated and purified using a $CD4^+$ T cell isolation kit based on the manufacturer's instructions (Miltenyi Biotec, Germany). LD columns with manual separators were used for magnetic separation. $CD4^-$ cells were excluded. Purified $CD4^+$ T lymphocytes of patients with IgAN were not pooled. Purified $CD4^+$ T lymphocytes drawn from one patient with IgAN at a single time point were divided into different treatment groups in one repeat experiment. The purified $CD4^+$ T lymphocytes were then cocultured with human mesangial cells (HMC; purchased from Central South University Advanced Research Center) at a ratio of 5:1 for 5 days [11, 12]. Inactive HS ($1x10^8$ CFU/ml) was used to induce mesangial cell injury and Th22 cell disorder. HS was isolated from human tonsils, purified, and diluted to 1×10^{10} CFU/ml in sterile phosphate-buffered saline. All bacteria were formalin inactivated. The vaccine did not contain any viable microorganisms, as confirmed by sterility test [8].

IL-1, TNF-α, and IL-6 in the supernatant of cocultures were quantified by ELISA (RayBiotech, USA). Th22 cells in cocultures were harvest and determined by flow cytometry.

Th22 cell chemotaxis assay

Before transwell assay, HMC was first stimulated with or without inactivated HS (1×10^8 CFU/ml) for 96 h. $CD4^+$ T lymphocytes (1×10^7) were added to the upper chambers of transwell plate (Corning Costar, USA) in RPMI-1640 supernatant with 0.5% FBS in a final volume of 100 µl, and the lower chambers were filled with 600 µl of the supernatant of cultured HMC. HS group and antibody groups were stimulated with inactive α-HS, while supernatant used in control group was from cultured HMC without HS stimulation. The transwell chambers were incubated at 37 °C in 5% CO_2. Blocking experiments were performed by mixing HMC culture supernatant with 100 ng/ml anti-CCL20, anti-CCL22, and anti-CCL27 mAbs (Abcam; USA). Blank group represents the migration of T lymphocytes that responded to only supernatant. The Th22 cells in the lower chamber were assigned a chemotaxis index (chemotaxis index = number of migrated Th22 cells in each experiment group ÷ number of migrated Th22 cells in Blank group) and analyzed by flow cytometry.

Statistical analysis

Data were expressed as the mean ± standard deviation (SD) or median with minimum and maximum values. Comparison between groups was analyzed by using one-way analysis of variance (ANOVA), Kruskal–Wallis *H* test, or the Mann–Whitney *U* test. Correlations among variables were determined by calculating the Spearman or Pearson rank correlation coefficients. $P < 0.05$ was defined as statistically significant. Statistical analyses were performed using SPSS 19.0 software (Chicago, USA). The exact *P* values were expressed as $P < 0.001$ if the *P* value was less than 1×10^{-3}.

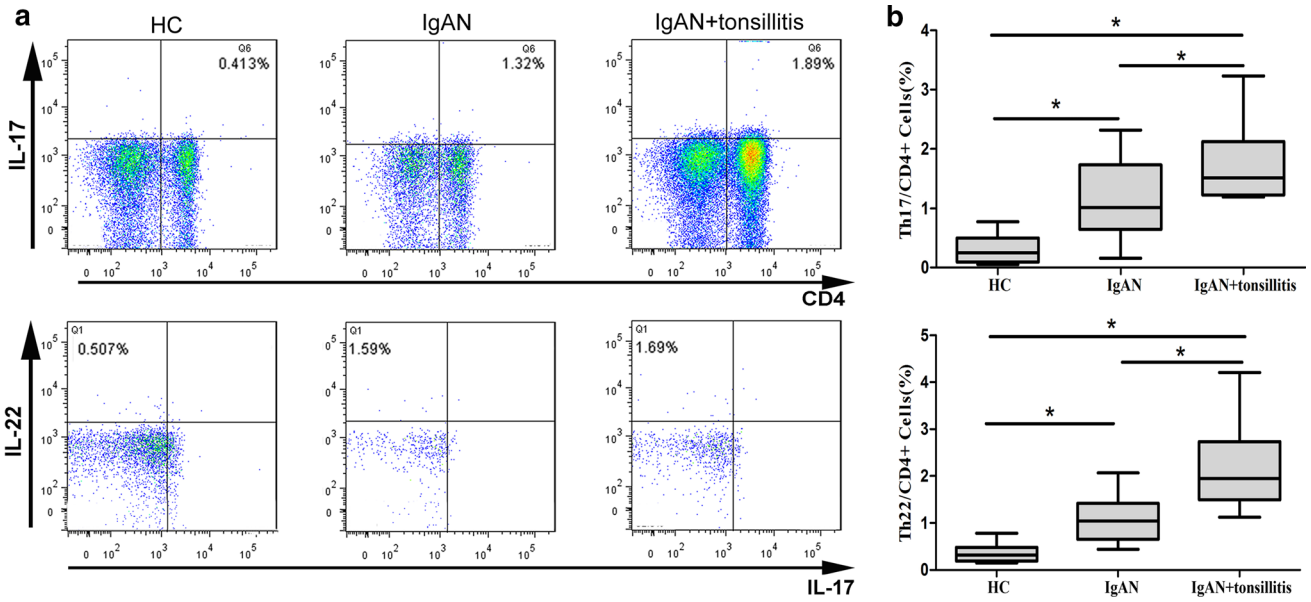

Fig. 1 Expressions of Th17 cells and Th22 cells in IgAN Patients. **a** The frequencies of Th17 cells and Th22 cells within $CD4^+$ T cells from peripheral blood of IgAN patients without tonsillitis (IgAN group), IgAN patients with tonsillitis (IgAN + tonsillitis group), and healthy controls (HC group) were detected by flow cytometry. Th17 cells and Th22 cells were identified based on their expression of $CD4^+IL\text{-}17^+$ and $CD4^+IL\text{-}17^-IL\text{-}22^+$. **b** Comparisons of percentages of Th17 and Th22 cells were determined by flow cytometry. *Represents $P < 0.05$

Results

Tonsillitis promotes Th22 cells lymphocytosis and CC chemokines expression in IgAN

It has been reported that Th22 cell disorder often combined with an imbalance of Th17 and Th1 cells [8]. Thus, flow cytometry was first performed to analyze the peripheral blood percentages of Th1, Th17, and Th22 cells. As shown in Fig. 1, patient with IgAN had higher Th22 cell percentages compared with healthy controls. (The Th22 cell percentages in IgAN group and HC group were 1.07 ± 0.50% vs. 0.35 ± 0.19%; $P < 0.001$.) Significantly increased Th22 cell percentages were observed in IgAN + tonsillitis group compared with IgAN group (2.19 ± 0.91% vs. 1.07 ± 0.50%; $P < 0.001$). Similarly, higher Th17 cell percentages were observed in IgAN and IgAN + tonsillitis groups compared with HC group (1.13 ± 0.61%, 1.46 ± 0.56% vs. 0.28 ± 0.22%). However, there was no significant difference in Th1 cell percentages between IgAN, IgAN + tonsillitis, and HC groups ($P > 0.1$).

We further noticed that over-expressions of CCL20, CCL22, and CCL27 existed in patients with IgAN. Data showed that serum concentrations of CCL20, CCL22, and CCL27 in IgAN group were higher than in healthy controls (16.53 ± 3.28 vs. 5.82 ± 2.88 pg/ml, 34.33 ± 9.77 vs. 5.40 ± 2.35 pg/ml, and 394.34 ± 28.25 vs. 273.66 ± 15.46 pg/ml; $P < 0.001$, respectively), while a more significant increase in serum CCL20, CCL22, and CCL27 was observed in IgAN + tonsillitis group (28.57 ± 1.76, 36.5 ± 4.09, and 455.54 ± 16.12 pg/ml; $P < 0.001$, respectively). Moreover, immunohistochemistry proved that the renal expression of CCL20, CCL22, and CCL27 in IgAN + tonsillitis group was much higher that in IgAN and HC groups (Fig. 2). Our data suggested that tonsillitis promoted the Th22 cells accumulation and the over-expression of CCL20, CCL22, and CCL27 in IgAN.

Tonsillitis promotes Th22 cell-related inflammatory response in IgAN

IL-1β, IL-6, and TNF-α are proinflammatory factors which participate in the progression of IgAN [8]. Meanwhile, they are also known as accelerators of Th22 cell proliferation [9]. Since Th22 cells accumulation was observed in IgAN with tonsillitis, we further explored the IL-1β, IL-6, and TNF-α secretion. Increased secretions of IL-1β, IL-6, and TNF-α were observed in IgAN group (21.49 ± 0.23, 105.07 ± 3.07, and 295.34 ± 13.05 pg/ml), while IgAN + tonsillitis group had a much higher levels of IL-1β, IL-6, and TNF-α (31.36 ± 0.18, 134.11 ± 2.37, and 366.19 ± 24.55 pg/ml; $P < 0.001$, respectively). Our data suggested that tonsillitis promoted the Th22 cell-related inflammatory response in IgAN.

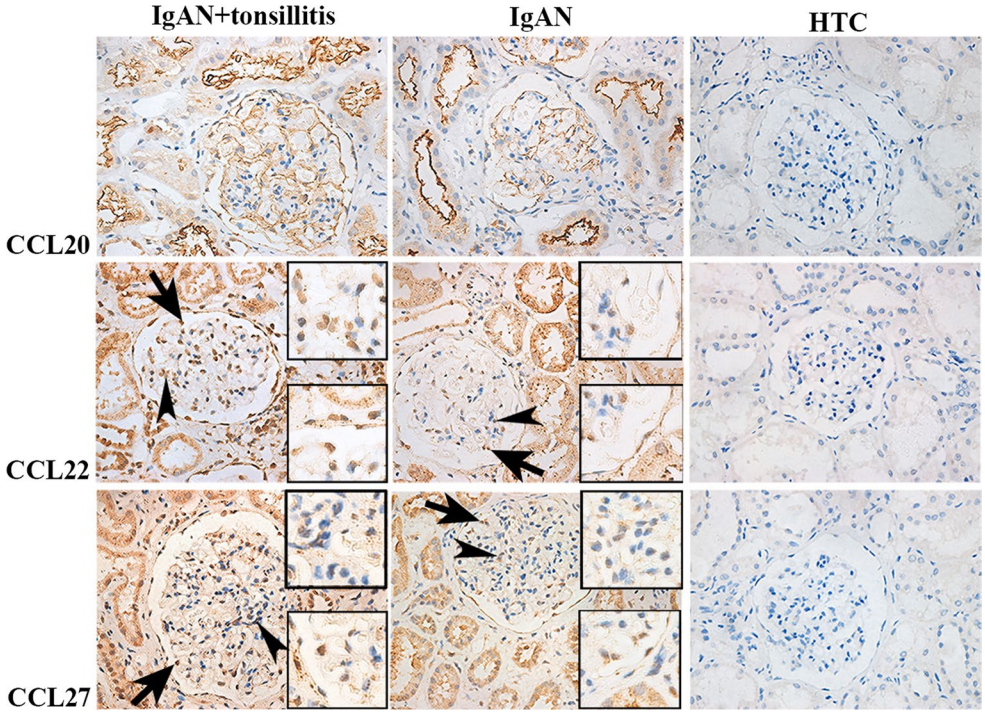

Fig. 2 Renal expressions of CCL20, CCL22, and CCL27 in IgAN patients (400X). Representative images of immunohistochemistry staining (brown) of anti-CCL20, anti-CCL22, and anti-CCL27 in renal tissue from IgAN patients with tonsillitis (IgAN + tonsillitis) and IgAN patients without tonsillitis (IgAN), and healthy tissues from renal carcinoma patient without glomerulonephritis (HTC)

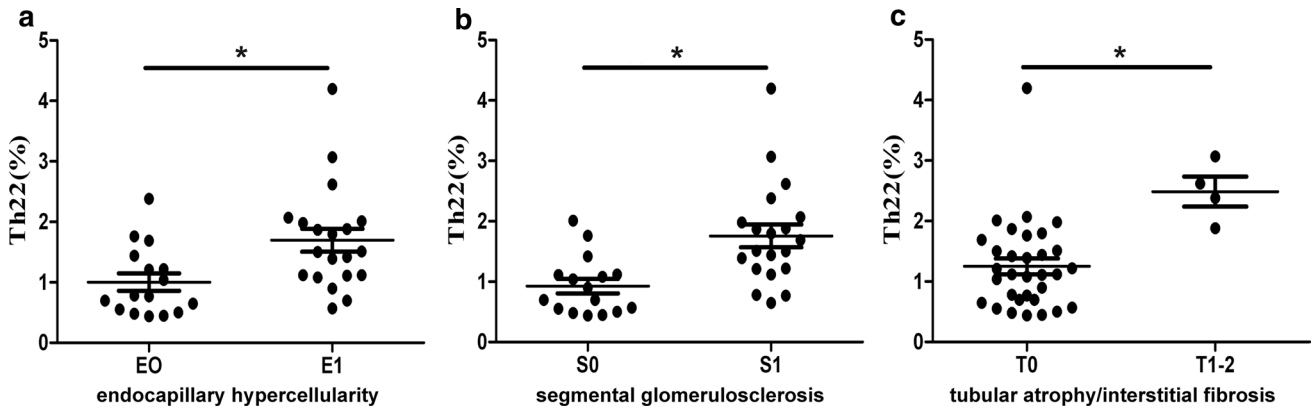

Fig. 3 Correlationship between Th22 cells and renal lesions in IgAN. The renal pathological lesions were analyzed to Oxford Classification of IgA nephropathy 2016 (MEST score). **a** Comparisons of Th22 cell percentages between patients with endocapillary hypercellularity absent (E0) or present (E1). **b** Comparisons of Th22 cell percentages between patients with segmental glomerulosclerosis absent (S0) or present (S1). **c** Comparisons of Th22 cell percentages between patients with tubular atrophy/interstitial fibrosis < 25% (T0), > 26% (T1-2). *Represents $P < 0.01$

Tonsillitis aggravates Th22 cell-related renal injury in IgAN

To clarify the role Th22 cells served in IgAN, we further explored the relationship between Th22 cells accumulation and IgAN renal lesions. Data showed that consistent with the increasing Th22 cells, worse renal lesions were observed in IgAN + tonsillitis group compared with IgAN group. (MEST scores were 2.8 (2.0, 3.5) vs. 2.0 (1.7, 2.4), $P = 0.027$.) As shown in Fig. 3, patients with worse pathological lesions had higher percentages of Th22 cell. Moreover, Th22 cell percentages were positively related to MEST scores ($R = 0.686$, $P < 0.001$). This indicated that tonsillitis aggravated renal injury in IgAN underlying Th22 cell over-expression.

HS-infected mesangial cells induce Th22 cell chemotaxis underlying the effects of CCL20, CCL22, and CCL27

Although researched reported that HS infection may induce lymphocytes accumulation in local renal tissues of mice with

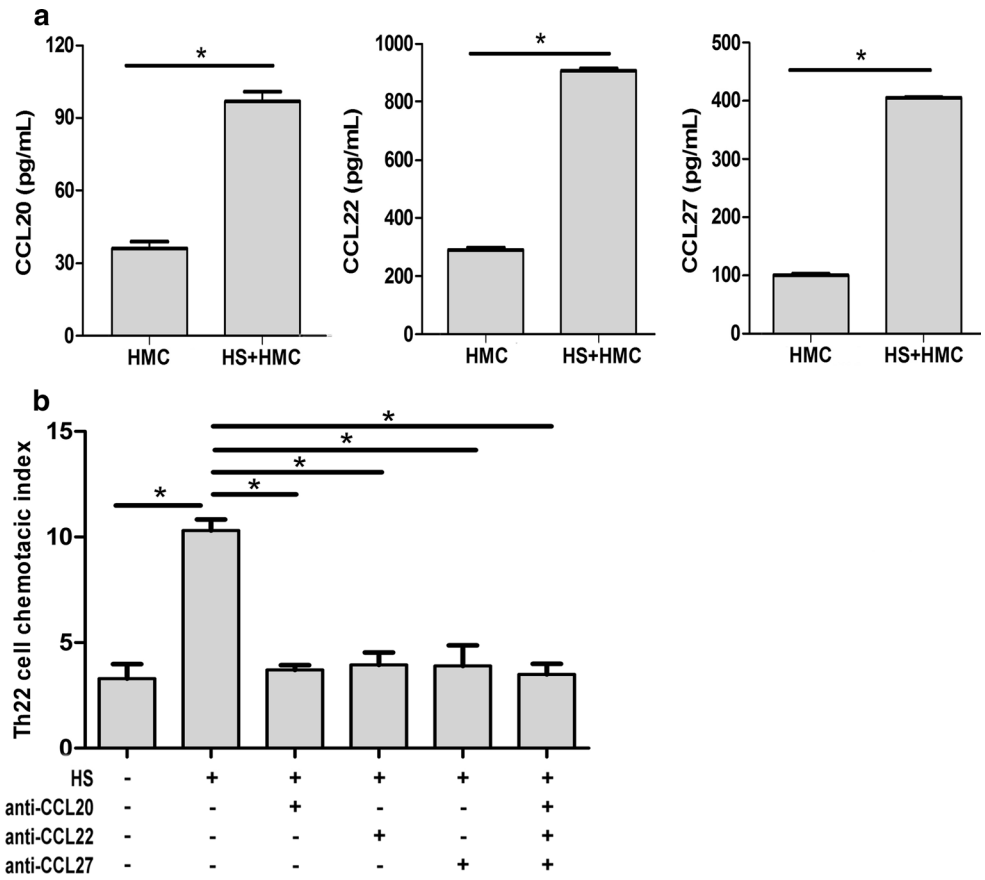

Fig. 4 Effects of HS on mesangial cells to induce Th22 cells chemotaxis. **a** HMCs were incubated for 96 h with or without inactivated HS treatment. The concentrations of CCL20, CCL22, and CCL27 in the culture supernatant were analyzed by ELISA ($n = 4$). **b** Supernatant of cultured HMC with/without inactivated HS treatment was used to induce the chemotaxis of $CD4^+$ T lymphocytes from patients with IgAN in transwell assay. Blockage experiment was performed by using anti-CCL20, anti-CCL22, and anti-CCL27 mAbs. Bars represents the chemotactic index of Th22 cell ($n = 4$). *Represents $P < 0.01$

IgAN, it is unsure whether human renal tissues can recruit Th cells in IgAN with tonsillitis. To explore the mechanism of Th22 cell lymphocytosis in IgAN, transwell assay was further performed by using the supernatant of HMC to induce the chemotaxis of $CD4^+$ T lymphocytes from IgAN patients. As shown in Fig. 4, significantly increased CCL20, CCL22, and CCL27 were observed in the supernatant of HS-stimulated HMC group (96.71 ± 4.20, 907.18 ± 6.28, and 404.70 ± 2.59 pg/ml) compared with controls (36.20 ± 2.81, 292.17 ± 8.42, and 100.12 ± 1.99 pg/ml). Accordingly, an increased Th22 cell chemotactic index was observed in HS group (10.31 ± 0.52) compared with controls (3.29 ± 0.52, $P < 0.001$). However, when the effects of chemokines were blocked by anti-CCL20, anti-CCL22, and anti-CCL27, the Th22 cell chemotactic index significantly reduced (3.70 ± 0.22, 3.94 ± 0.59, and 3.89 ± 0.98). Our data suggested that HMC was chemotactic for Th22 cells by secreting CCL20, CCL22, and CCL27.

HS infection aggravates Th22 cell over-expression-related inflammatory response

In order to further understand the collaboration between human mesangial cells and Th22 cell underlying HS infection, coculture assay of HMC and $CD4^+$ T lymphocytes from IgAN patients was performed. We found that Th22 cell percentages significantly increased in cocultures stimulated with HS (1.17 ± 0.63%) compared to controls without HS simulation (4.57 ± 0.45%, $P < 0.001$). Similarly, the secretion of IL-1β, IL-6, and TNF-α in cocultures stimulated with HS significantly increased compared with controls (93.50 ± 5.45 vs. 171.72 ± 6.18 pg/ml, 35.97 ± 0.42 vs. 66.73 ± 1.79 pg/ml, and 102.59 ± 1.26 vs. 301.58 ± 1.01 pg/ml; $P < 0.001$, respectively). Moreover, the Th22 cell percentages was positively correlated with IL-1β, IL-6, and TNF-α levels (R were 0.853, 0.829, and 0.747; $P < 0.001$, respectively).

Discussion

Tonsillitis is involved in the progression of IgAN [13]. The mechanism of IgAN with tonsillitis is unclear. Here, we tried to clarify the mechanism of IgAN with tonsillitis underlying Th22 cell chemotaxis response to the effects of CCL20, CCL22, and CCL27.

Although not extensively studied, it is clear that Th cell disorder participates in IgAN with tonsillitis. Our results indicate that abundant Th22 and Th17 cells were observed in IgAN patients. This increase in Th22 cells was positively correlated with renal lesions in IgAN. Tonsillitis could aggravate this overrepresentation of Th22 and Th17 cells and had an adverse effect on clinical remission. This suggested that Th22 and Th17 cells disorder was involved in the mechanism of IgAN with tonsillitis.

Th17 cells are recently discovered as a subset of Th cell which are strong inducers of local tissue inflammation [14]. The persistent and uncontrollable inflammation triggered by Th17 cells severs as a major stimulator in the pathogenesis chronic disease which includes IgAN. Meng T et al. set forth that Th17 cells were involved in the pathogenesis of hemolytic streptococcus infection-related IgAN [8]. The Th17 cell lymphocytosis was observed in IgAN rats and IgAN patients and positively correlated with lower renal function, greater proteinuria, and more severe tubulointerstitial damage [15–17]. Yang L et al. set forth that the increase in Th17 cells in IgAN may attribute to the disorder of mmiR-155. They found that the imbalance of Th cells, i.e., the up-regulation of Th2 and Th17 along with the down-regulation of Th1 and Treg, was due to the decreased expression of peripheral lymphocyte miR-155, which inhibited Cosmc gene expression and worsened the aberrant glycosylation of IgA1 in IgAN patients [18].

As the cross-regulations between Th17, Th2, Treg, and Th1 cells [19], cross talk exists between Th17 and Th22 in the pathology of IgAN. A significantly positive correlation between Th22 and Th17 cells in IgAN patients was observed in Peng et al. research, and the increasing Th22 and Th17 cells were correlated with worse proteinuria [20]. This was in agreement with our results, which indicated that Th22 cells as well were involved in the pathology of IgAN.

Our research demonstrated that tonsillitis may exacerbate kidney damage in IgAN through CCL20, CCL22, and CCL27 response to the effect of Th22 cells. In vitro experiments showed that HS infection induced a significantly increased CCL20, CCL22, and CCL27 secretion in HMC, leading to the up-regulation of Th22 cell chemotaxis. Blockage experiment further confirmed that anti-CCL20, anti-CCL22, and anti-CCL27 mAbs successfully alleviated Th22 cell infiltration. Taken together, our research demonstrated that tonsillitis may accelerate the progress of IgAN underlying Th22 accumulation through promoting renal expressions of CCL20, CCL22, and CCL27.

Several studies have proved that Th22 cell has an adverse effect on kidney regeneration. Suh JH et al. demonstrated that polymorphisms in the IL-22R are associated with development of nephropathy [21]. Weber GF et al. suggested that blockade the activity of IL-22 can help reduce kidney injury in polymicrobial peritonitis [22]. In conclusion, the over-expression of Th22 cells may lead to kidney damage.

CCL20, CCL22, and CCL27 are Th22 cell attracting chemokines, which can mediate Th22 cell chemotaxis and local accumulation. CC chemokines can be classified into two categories according to their different effector cells: one is inflammation regulator, and the other is homeostasis regulator. CCL27 is mainly associated with the maintenance of homeostasis, while CCL20 and CCL22 are involved in the regulation of inflammatory response and homeostasis at the same time [23]. Our results that human mesangial cell over-expressed CCL20, CCL22, and CCL27 in IgAN with tonsillitis are consistent with Kanapathippillai P et al. research, which demonstrated that mesangial cells can overproduce CCL20 and CCL22 in lupus nephritis, and resulted in lymphocytes chemotaxis [7]. Besides, Paust et al. also demonstrated that renal tissue can recruit Th cells through CCL20-CCR6 axe, thus inducing inflammation and renal injury in mice crescentic glomerulonephritis [24, 25]. Xiao et al. research on mice IgAN proved that Losartan could suppress the inflammatory responses in mice with IgAN by inhibiting Th22 cells chemotaxis. Taken together, it is clear that the over-expression of CC chemokines exists in IgAN and contributed to local inflammatory injury by inducing lymphocytes infiltration and accumulation [26].

Conclusions

This study was the first to demonstrate that an over-expression of Th22 cells responded to the effect of CCL20, CCL22 and CCL27 exists in IgAN patients. This Th22 cell disorder is correlated with the aggravation of inflammatory response and pathology lesions in IgAN. Tonsil infection may aggravate the disease progression by exacerbating accumulation of Th22 cells.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All patients were recruited and examined in the Xiangya Hospital, Central South University. This study was carried out according to the Declaration of Helsinki and approved by the Medical Ethics Committee of the Xiangya Hospital of Central South University for Human Studies (approval number 201403270).

Informed consent Informed consent was obtained from all individual participants included in the study.

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