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Original Article

Streptococcus may aggravate inflammatory damage in chronic nephritis via the chemotaxis of Th22 cells

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Abstract: Background: Infection can induce and aggravate chronic kidney disease (CKD), and the chemotaxis of Th22 cells may aggravate CKD. However, the mechanism underlying group A Streptococcus (GAS) infections in CKD through the chemotaxis of Th22 cells remains unknown. Methods: The experiment was divided into a normal control group, an IgAN model group, a GAS-treated normal group, a GAS-treated IgAN group and an anti-CCL intervention group. An IgA nephropathy model was established, and after the success of the IgA nephropathy model was confirmed, *Streptococcus haemolyticus* A was inoculated intranasally and compared with treatment with anti-CCL to detect changes in Th22 cells, related chemotaxis factors and kidney pathology before and after intervention. Results: An immunoglobulin A nephropathy model was successfully established. Streptococcus was successfully inoculated into the nasal cavity of the normal group and the IgA nephropathy infection control group. After intervention, pulmonary inflammatory cell infiltration was more obvious in the IgA nephropathy group than in the normal control group after Streptococcus infection. Th22 cells were detected more frequently in IgA nephropathy; after streptococcal infection, the percentage of Th22 cells in the IgAN group was higher than that in the normal group but decreased significantly when chemotaxis was blocked, the expression of CCL27, CCR10 and IL-22 declined simultaneously, and improvements in pathological changes were observed. Conclusion: Streptococcus may cause the chemotaxis of Th22 cells to kidney tissue, leading to or aggravating nephritis injury.

Keywords: Streptococcus, IgA nephropathy, Th22 cells, CCR10, CCL27

Introduction

Chronic kidney disease (CKD) is a global public health problem that affects more than 10% of the world's population [1]. In China, IgA nephropathy is the leading type of glomerulosclerosis among primary glomerular diseases that result in end-stage renal disease (ESRD) [2], and more than one-third of patients with a biopsy-proven diagnosis of IgA nephropathy will progress to ESRD within 20 years [3]. At present, scholars believe that genetic, environmental and immune factors together determine the occurrence and development of IgA nephropathy [4]. The clinical presentation is highly variable. Some patients develop hematuria within days of upper respiratory tract infection, and a "multi-hit" hypothesis has been proposed. The inflammatory response induced by immune stimulation is an important step in the development of chronic nephritis.

In clinical practice, infection may cause or aggravate acute and chronic kidney disease, and respiratory tract streptococcal infection has become the most common infection [5]. Mucosal infection is closely related to the occurrence and development of IgA nephropathy. Reducing and controlling the infection in a timely manner is important for patients. However, the specific mechanism is not yet fully clear [6].

Mucosal infection can cause mucosal immune abnormalities. Hemolytic Streptococcus is one of the main pathogens of clinical upper respiratory tract infections. Upper respiratory tract infections can induce and aggravate IgA nephropathy. This phenomenon has been confirmed by research [7]. Previous researchers have injected pathogenic microorganisms, such as Haemophilus Parainfluenzae and Sendai virus, into the respiratory tract to establish IgA nephropathy models, and the successful induction of an IgA nephropathy model by bovine serum albumin, which we used in the modeling process, provided strong experimental evidence from another perspective. Humoral immune

responses may be present throughout a portion of or all subsequent pathophysiological processes.

Th22 cells are an emerging Th cell subset that links the immune response to tissue inflammation. IL-22 is a member of the IL-10 cytokine family, and studies have shown that IL-22 expression is dysregulated in certain human diseases, including mucosa-associated infections and inflammatory disorders of the intestine, skin, and joints [8]. Chemokines, a group of small proteins, serve as key regulators of directional T cell trafficking under inflammatory conditions, achieved by the differential expression of corresponding chemokine receptors on the surface of leukocyte subsets. Th22-polarized cells preferentially express CCR4, CCR6, and CCR10; the highly specific ligands for these receptors are CCL22, CCL20, and CCL27, respectively. It can be argued that these chemokines play critical roles in both B and T cell development. At present, accumulating data have shown that T lymphocyte-mediated tissue damage plays an important role in renal inflammatory diseases and that chemokines can inhibit the infiltration of injured T cells in glomerular diseases. Therefore, by promoting selective chemotaxis of renal-protective lymphocytes or regulating the proportion of T lymphocyte subsets to treat glomerulonephritis, regulating the function of T lymphocytes may be a new treatment direction for glomerulonephritis in the future, but the study of Th22 cells in nephropathy is still rare.

Our previous studies have found that the proportion of Th22 cells in IgA nephropathy is significantly higher than that in the normal control group. The overexpression of Th22 cells in IgA nephropathy may be attributed to the differentiation and chemotaxis of Th22 cells, which are stimulated by proinflammatory cytokines and the recruitment of Th22 cells to peripheral tissues [9]. In this study, we intend to clarify the possible mechanism of Th22 cells in streptococcal infection and inflammatory injury during IgA nephropathy.

Materials and methods

Reagents and antibodies

Flow cytometry antibodies and reagents related to flow analysis were purchased from BD, kidney pathology-related reagents were obtained from Sigma, animal model-related reagents were purchased from Cell Signaling Technology, and other reagents were purchased from Sigma unless specifically indicated.

HS intervention and treatment

Female BALB/c mice (19±2 g, N=20, 5/treatment group) were obtained from the Experimental Animal Center of Central South University (Changsha, Hunan, China) at 6 weeks of age. The IgAN model was induced by administering BSA (Roche, USA) in acidified water, CCl_4, and castor oil combined with LPS (Sigma, USA) (50 μg) at different time points for two months after adaptive feeding for one week [10].

The mice were randomly separated into a normal control group, an IgAN model group, a GAS-treated normal group, a GAS-treated IgAN group and an anti-CCL intervention group. The GAS-treated group was subjected to intranasal infection with live GAS during the 10th week. GAS was isolated from human tonsils and inoculated intranasally at a dose of $2*10^8$ CFUs in 10 ml of PBS/mouse (5 ml/nostril). The anti-CCL intervention group was sensitized by the combined intraperitoneal injection of anti-CCL antibodies (Abcam, USA) (100 μg/mouse). The controls received equal amounts of distilled water. All mice were terminated at the 11th week after the administration of GAS and/or CCL antibody [11].

Sample collection and processing

Samples of approximately 1 milliliter of whole blood were collected from each mouse in heparin-treated tubes and then centrifuged at 500 g for 10 min. After absorbing the plasma and diluting with PBS at a ratio of 1:1, mononuclear cells were isolated by Ficoll gradient centrifugation (GE, USA) within 1 h to evaluate T cell subsets.

Flow cytometry

The expression of T cell markers in the blood was determined via flow cytometry after the cells were stained for surface or intracellular markers with specific anti-mouse antibodies conjugated to APC/Cy7, FITC or PE. These mouse Abs included anti-CD3, anti-CD4, and anti-IL-22 antibodies. Intracellular staining for

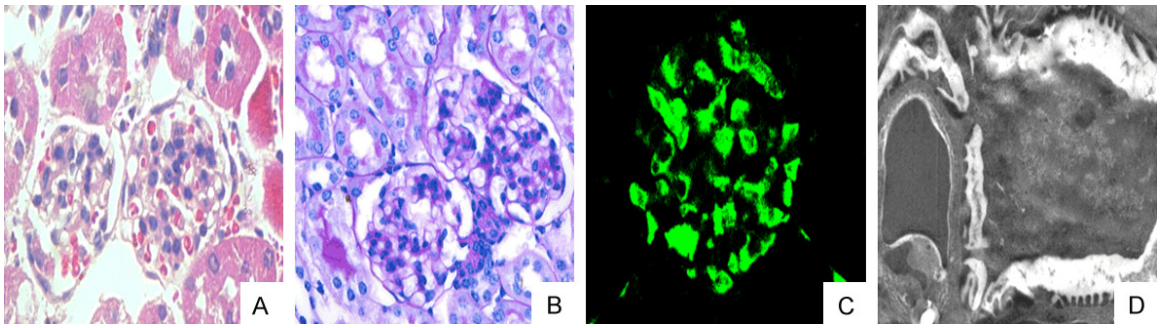

Figure 1. Main kidney pathological features of IgA nephropathy in the chronic nephritis mice model. Mesangial cells proliferated significantly (A, B, ×400), IgA was deposited in the mesangial area (C, immunofluorescence, ×400), and podocytes fused extensively under D-electron microscopy (D, ×2000).

IL-22 was performed on T cells that had been stimulated with Leukocyte Activation Cocktail (2 μl/ml, BD Biosciences) for 5 h at 37°C in 5% CO_2. Then, the T cells were stained with a PE-conjugated anti-IL-22 monoclonal Ab. Appropriate species-matched Abs served as isotype controls. Flow cytometry was performed using a FACS Can to II flow cytometer (BD Biosciences), and the data were analyzed using BD FACS and FlowJo software.

Histological analysis of the kidneys

The lungs and kidneys were fixed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin (HE). The stained sections were analyzed via light microscopy; sections from healthy age-matched female BALB/c mice were used as controls. Light microscopy and immunohistochemistry were performed using routine procedures.

Statistical analyses

The data were expressed as the mean ± standard deviation. The data from different groups were compared using the Mann-Whitney U test. Statistical analyses were performed using SPSS version 19.0 statistical software, and *p* values of less than 0.05 were considered statistically significant.

Results

Animal model of chronic kidney disease

We established an IgA nephrology model and HS infection model. In the ninth week, two mice were randomly selected to validate the model by collecting urine using metabolic cages and examining kidney pathology. Urine sediment microscopy showed 6-8 RBCs/hpf in urine. The pathological analysis showed mesangial cell proliferation and mesangial IgA deposition based on immunofluorescence microscopy, as well as electron-dense deposits in the mesangium based on electron microscopy, as shown in **Figure 1**.

Inflammatory cell infiltration into the lungs of mice with IgA nephropathy increased significantly after HS infection

In the 10th week of the experiment, we used Streptococcus A to intervene in the IgA nephropathy group. We isolated and proliferated Streptococcus A in vitro and inoculated mice via the nasal cavity. After 2 weeks of antibody intervention, the results showed that HE staining of lung tissues was worse in the treatment group than in the control group. The lungs of IgA nephropathy mice treated with Streptococcus haemolyticus A had obvious inflammatory cell infiltration. The infection with Streptococcus haemolyticus A was successful, as shown in **Figure 2**.

After streptococcal infection, the percentage of Th22 cells in the IgAN group was higher than that in the normal group but decreased significantly when chemotaxis was blocked

The proportion of Th22 cells in the IgA nephropathy model was significantly higher than that in the normal control group, especially after Streptococcus haemolyticus A infection. Flow cytometry was used to detect the proportion of Th22 cells in the plasma. First, $CD3^+$ and $CD4^+$ cells were gated by flow cytometry. Then, the

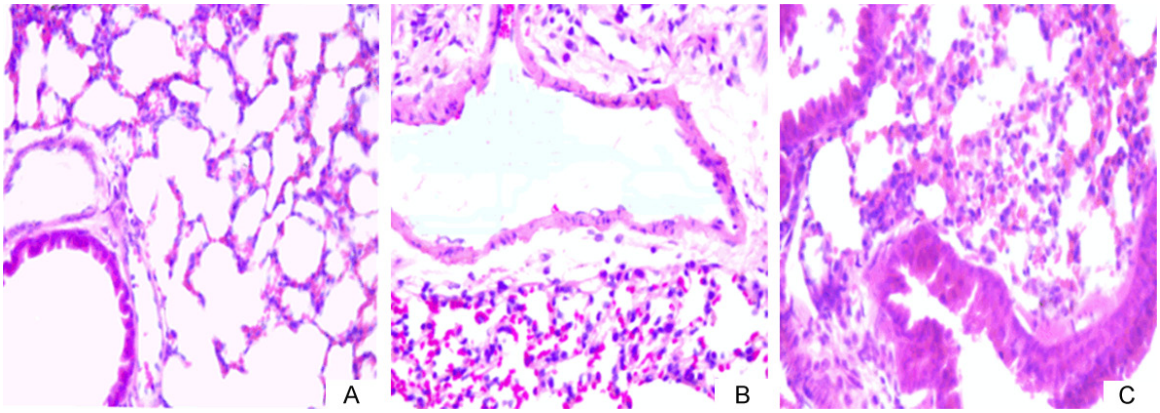

Figure 2. Inflammatory cell infiltration was more obvious in the lungs of mice with IgA nephropathy that were infected with hemolytic Streptococcus A than in the lungs of normal mice. In the infection of isodose streptococcus, the inflammatory cell infiltration of the lungs in the IgA nephropathy group increased significantly, indicating that patients with IgA nephropathy may be more susceptible to infection and once infected, the condition is also heavier. A. Normal control group; B. Normal group with Streptococcus A infection; C. IgA nephropathy with Streptococcus A infection (HE, ×400).

proportion of Th22 cells was calculated on the basis of $CD4^+$ staining. The results showed that the proportion of Th22 cells in whole blood from IgA nephropathy mice was significantly different from that in whole blood from normal mice. Infection with Streptococcus haemolyticus A aggravated the abnormality of T lymphocytes, and the CCL antibody blocked this effect. After treatment, the percentage of Th22 cells decreased significantly (0.13±0.02%, 2.73±0.13%, 3.69±0.20%, 6.71±0.43%, and 2.97±0.09%, n=5; $P<0.01$). Homotypic controls were used for each corresponding antibody, as shown in **Figure 3**.

Histopathological analysis showed that CCL27 and CCR10 were expressed more strongly in IgA nephropathy mice than in normal controls, aggravated in the Streptococcus haemolyticus A group, and expressed weakly after CCL intervention

The expression of CCL27 and CCR10 was detected by immunohistochemistry. The expression of CCL27 and CCR10 in various groups was observed under a microscope at a 400× magnification. No CCL27 or CCR10 was found in the normal group. CCL27 and CCR10 were expressed in the renal tubules and glomeruli in the IgA nephropathy group and further enhanced after infection with *Streptococcus haemolyticus* A. After intervention with the CCL antibody, the expression of CCL27 and CCR10 decreased, as shown in **Figure 4**.

Inhibition of chemotaxis reduced Th22 cell infiltration

To further determine the role of Th22 cells in renal injury, in addition to immunohistochemistry, we also detected the expression of CCL27 and IL-22 in renal tissue and plasma by ELISA. The expression of CCL27 and IL-22 in each group was repeated three times, which was consistent with the results of immunohistochemistry. Compared with the normal group, the expression of IL-22 in the IgA nephropathy group was significantly increased. After Streptococcus haemolyticus A infection, the expression of IL-22 was further increased. After the intervention with the CCL antibody, the expression of IL-22 decreased significantly. Similarly, the expression of CCL27 was significantly higher than that of the normal group. The expression of CCL27 in IgA nephropathy mice infected with Streptococcus A increased significantly but decreased after intervention with the CCL27 antibody, especially in the combined intervention group, as shown in **Figure 5**.

Discussion

Mucosal immunity-related immunological mechanisms have become a hot topic in recent years [12], the relationship between IgA nephropathy and mucosal immunity has been studied [12-14]. At present, IgA nephropathy studies mainly concentrate on two large sites of mucosal immunity in the digestive tract and

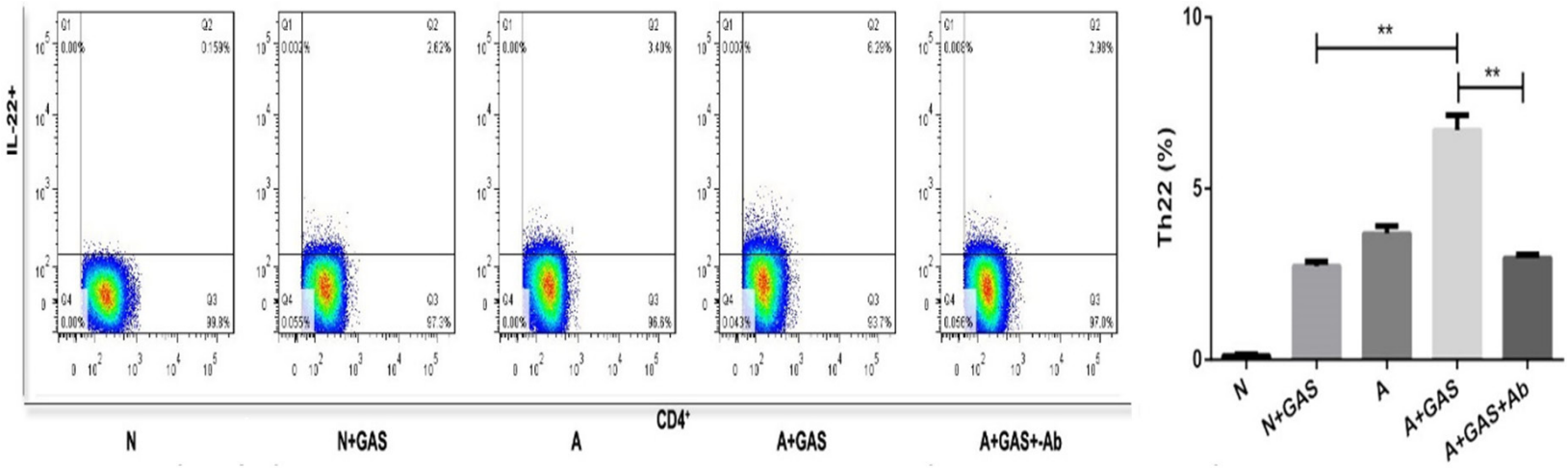

Figure 3. Th22 cells were increased more prominently in the streptococcal infection group. After GAS infection in the chronic glomerulonephritis group, the proportion of Th22 cells was higher. After intervention with anti-Th22 chemokine antibody, the number of Th22 cells decreased significantly. N, normal; N+GAS, normal control group infected with GAS; A, IgAN group; IgAN+GAS, IgAN group with GAS infection; A+GAS+Ab, IgAN group with GAS infection and with chemokine interference.

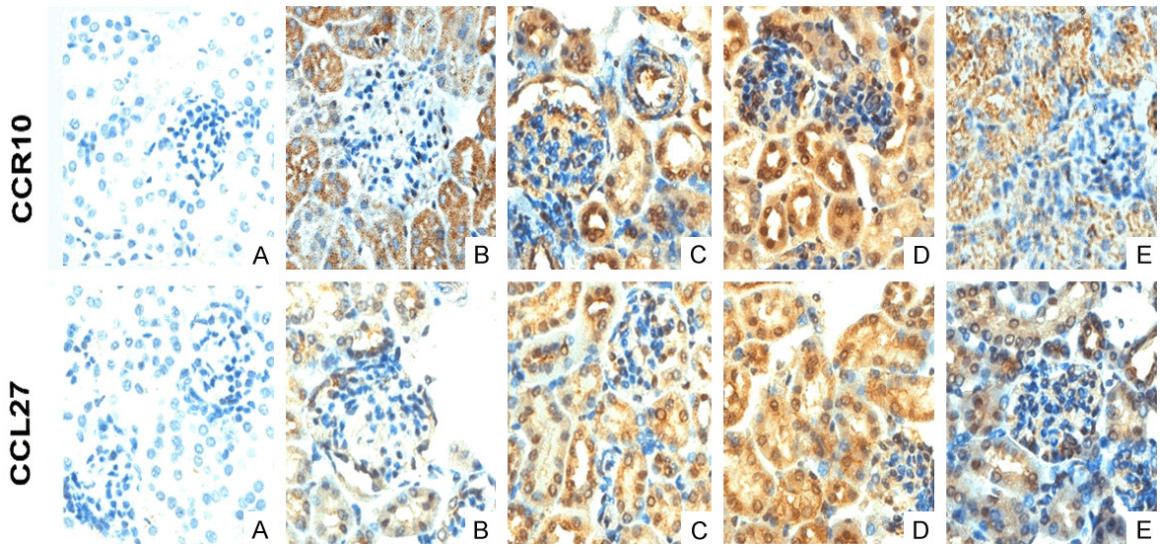

Figure 4. Streptococcus can promote the expression of CCL27 and CCR10 in the kidney. Immunohistochemical staining analysis of renal tissue samples with a CCL27 immunohistochemical antibody showed that the positive site was brown. CCL27 and CCR10, a specific chemokine of Th22 cells, were expressed in the glomeruli. Compared with the control group, CCL27 was more expressed in IgA nephropathy mice, and this expression was stronger after infection with Streptococcus haemolyticus A. The difference was more obvious, and the expression of CCL27 and CCER10 decreased significantly after anti-CCL27 antibody intervention. A. Norma control group; B. Normal group with GAS infection; C. IgAN group; D. IgAN with GAS infection group; E. IgAN with CCL-Ab intervention group.

respiratory tract. T lymphocytes and B lymphocytes are involved in mucosal immunity. The transformation of B lymphocytes into antibody-secreting cells requires induction of the cytokine IL-21 [15]. In clinical work, patients with IgA nephropathy often suffer from upper respiratory tract infection in the course of onset, recurrence and aggravation. Mucosal infection is closely related to the onset of IgA nephropathy. Mucosal immune dysfunction is an important mechanism in the pathogenesis of IgA nephropathy, which has been widely recognized by the academic community [16]. The typical clinical symptoms of IgA nephropathy, hematuria and proteinuria often occur after upper respiratory tract infection. IgA is also a mucosal immune-related immunoglobulin [17], and Streptococcus haemolyticus A is the main pathogen in the tonsils of patients with IgA nephropathy [18]. IgA deposited in the mesangial area of the kidney mainly comes from the bone marrow. Abnormal IgA1 produced by the tonsils is a possible source of low glycosylated IgA1 in the serum of patients with IgA nephropathy [19]. Recently, accumulating data have shown that T lymphocyte-mediated tissue damage plays an important role in renal inflammatory diseases, and chemokines can inhibit the infiltration of injured T cells in glomerular diseases [20]. Therefore, selective chemotaxis can protect kidney lymphocytes or regulate the proportion of T lymphocyte subsets to treat nephritis. Regulating the function of T lymphocytes may be a new treatment direction for nephritis in the future [13]. Some studies have found that there is an increase in IL-22 in the primary focus and serum of patients with non-small cell lung cancer, and the increase in IL-22 is related to the occurrence and progression of lung cancer [21].

It is clear that Th22 cells participate in the occurrence and development of IgA nephropathy and that IL-22 can promote mesangial cell proliferation and inflammatory cell chemotaxis to affect renal function. In the field of cancer research, it has been found that there is an increase in IL-22 in the primary focus and serum of patients with non-small cell lung cancer [22]. Our previous studies found that the proportion of Th22 cells in IgA nephropathy was significantly increased. The probability and severity of infection in patients with chronic nephritis are often higher than those in normal controls, but the specific mechanism is not fully understood, and no relevant pathological analysis has verified this observation. In this study, we detected Th22 cells in IgA nephropathy

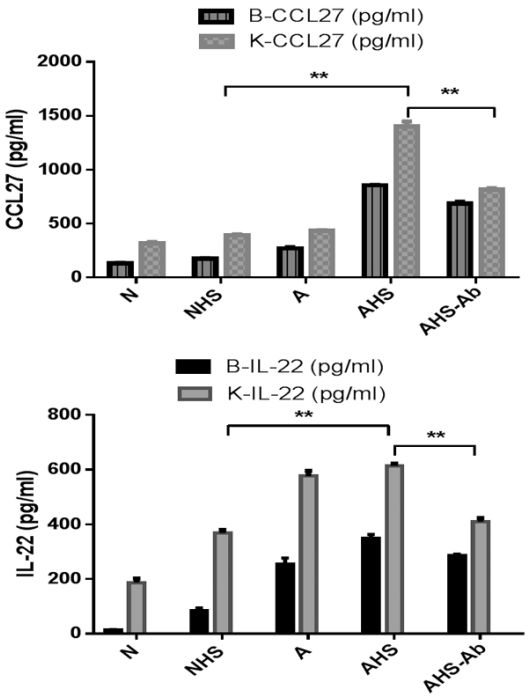

Figure 5. Main effector of Th22 cells in renal homogenate and plasma. After streptococcal infection, the expression of the major effector IL-22 and chemokine CCL27 also increased simultaneously. The above figure shows the concentration changes in CCL27 and IL-22 in kidney tissue and plasma (n=5). The horizontal line in the figure indicates the mean (x+s). The concentration of chemokines in kidney homogenate and plasma was detected by ELISA. The data for each group were analyzed by the Wilcoxon rank sum test, *P<0.05, **P<0.01.

mice, as well as their surface-specific chemokine receptor CCR10 and the chemotaxis factor CCL27. The expression of the factor CCL27 changed, and infection with Streptococcus haemolyticus A could aggravate the injury. After intervention with anti-CCL antibody, the injury was reduced, and renal protection could be achieved. In our previous experiments in vitro, we found that IL-1β, IL-6, TNF-α and IL-21 could promote the differentiation of initial $CD4^+$ T cells into Th22 cells independently. It was recently shown that chemokines, a group of small proteins, serve as key regulators of directional T cell trafficking under inflammatory conditions, achieved by the differential expression of corresponding chemokine receptors on the surface of leukocyte subsets. It can be argued that these chemokines play critical roles in both B and T cell development [23]. The expression of these receptors may change depending on the activation status of the T cell [24]. IL-22, an effector molecule of Th22 cells, has multiple roles in immune regulation. IL-22 is named for its homology with IL-10. It has biological functions of enhancing congenital immunity, protecting against injury and promoting regeneration. IL-22 can regulate cell growth, proliferation and the cell cycle [25] in tumor immunity. Recent studies have shown that the expression of IL-22 in the early stage of lung cancer is significantly increased, and the overexpression of IL-22 is associated with the occurrence and progression of lung cancer. IL-22 can activate erk, c-Jun, N-terminal enzyme and p38 mitogen-activated protein kinase [22].

Chemokines play an important role in the inflammatory response. In human defense and the clearance of pathogens and other foreign bodies, chemokines play a guiding role [26]. Inflammatory cells migrate to target tissues according to the signals provided by chemokines. At the same time, chemokine release can stimulate the production of inflammatory factors. The main role of inflammatory chemokines is chemotaxis of inflammatory cells from the blood circulation to infection or tissue damage sites. Chemokines can also promote wound healing. The Th1-based immune response can promote the formation of the crescent body, the deposition of local fibrin mediated by cellular immunity, the delayed high-sensitivity-like mechanism, the activation of cells in the kidney through MHCII molecules and costimulatory molecules and the production of chemokines and cytokines, the recruitment and damage of white blood cells, and the T-cell-mediated response mechanism in crescent glomerulonephritis [7]. T lymphocyte subsets differ by secreting different cytokines but share common antigens. Even in the same patient, unused T lymphocyte dominance can lead to different diseases, leading to different prognoses. The number, function and proportion of T lymphocytes change throughout the course of disease evolution. The outcomes are also different. The number of T lymphocytes changes, and functional deficiencies may occur. Sex also has an effect and may increase the activity of B cells [27].

In chronic glomerular diseases mediated by immune inflammation, innate renal cells (including mesangial cells, endothelial cells, podocytes and tubular epithelial cells, etc.) have receptors for multiple inflammatory mediators

[1, 28], and they can secrete a variety of inflammatory mediators and chemokines, thus making innate renal cells not only passive victims of glomerular immune-mediated inflammation but also active participants in the immune response [29]. Renal capillary endothelial cells and tubular epithelial cells are nonprofessional APCs, while podocytes and mesangial cells have helpful antigen-presenting effects due to MHCII molecules, CD80 and CD86, which can provide T cell activating signals [30]. IL-22 can play a dual role in pathogenicity and protection in participating organs and tissues as well as in different stages of disease. With the in-depth study of cytokines, new cytokines have been found, and IL-22 has become a hotspot in immunology.

Our previous studies explored the mechanism of differentiation and chemotaxis of Th22 cells in the pathogenesis of nephritis [9], and Cordyceps sinensis or dexamethasone may modulate the chemotaxis of Th22 cells to suppress inflammatory responses in IgA nephropathy [10, 31]. This study further explored the possible mechanism of Streptococcus in the pathogenesis and development of chronic nephritis. In renal autoimmune diseases, the chemokine-chemokine receptor interaction is a possible target for the treatment of renal diseases. However, there is no unified theory to describe how microorganisms cause asthma and mucosal inflammation. The respiratory mucosa is the key microbial defense barrier. Respiratory mucosal epithelial cells and dendritic cells can interact with a series of lymphocytes with different functions. Then, lymphoid cells control a series of natural and specific pathways of the host mucosal immune response. This theory provides new, specific therapies that can be evaluated in clinical trials. Based on these new ideas, specific host biomarkers may allow personalized therapy to become a new treatment strategy for patients with IgA nephropathy. The results of our study were consistent with a possible role for Th22 cells in IgA nephropathy, and we explored one of the possible pathogenic mechanisms of Streptococcal infection in CKD. However, there are several limitations of this study. For instance, the examination period of the experiments was limited and did not explore the mechanism of pulmonary involvement at the same time. Future studies will explore the role of Th22 cells in glomerulonephritis.

Conclusions

In this study, we found that streptococcus may aggravate inflammatory damage in chronic nephritis through the chemotaxis of Th22 cells.

Acknowledgements

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This study adhered to the principles of the Declaration of Helsinki II and was approved by the medical ethics committee of Xiangya Hospital, Central South University (Ethical Code: 20150003). Written informed consent was obtained from all the study participants.

Disclosure of conflict of interest

None.

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