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Original Article

Expression of IL-17, IL-17R, and MMP-13 mRNA in spinal tuberculosis and its correlation with lesions

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Abstract: Objective: Expression of IL-17, IL-17R, and MMP-13 in spinal tuberculosis lesions and its mutual correlation in different types of lesions was evaluated. Method: Retrospective analysis was performed on 40 patients with ST that underwent surgery from January 2014 to December 2017, including 22 patients with proliferative lesions and 18 patients with caseous necrotic lesions. Twenty subjects with normal cancellous bones served as the control group. Moreover, mRNA expression of IL-17, IL-17R, and MMP-13 in lesions was detected by qRT-PCR. The relationship was analyzed using Pearson's and Spearman's correlation. Results: Expression of IL-17, IL-17R, and MMP-13 was higher in the necrotic lesion group than in the proliferative lesion and control groups ($P<0.05$). Expression of IL-17, IL-17R, and MMP-13 was higher in the proliferative lesion group than the control group ($P<0.05$). For patients with hyperplasia and patients with caseous necrosis, a positive correlation was found between IL-17 and IL-17R, between IL-17 and MMP-13, and between IL-17R and MMP-13 expression. IL-17, IL-17R, and MMP-13 were higher in the necrotic lesion group than in the proliferative lesion group. Indicators gradually increased with the severity of the disease. IL-17, IL-17R, and MMP-13 in the lesions of proliferative lesion group were positively correlated with each other ($P<0.05$). In the necrotic lesion group, these indicators were also positively correlated ($P<0.05$). Conclusion: IL-17, IL-17R, and MMP-13 are highly expressed in lesions of patients with ST. Expression of IL-17, IL-17R, and MMP-13 is mutually correlated.

Keywords: IL-17, IL-17R, MMP-13, spinal tuberculosis

Introduction

Tuberculosis is the most infectious chronic disease in humans, worldwide. *Mycobacterium tuberculosis* is the causative agent of tuberculosis. One survey revealed that occurrence of tuberculosis is mainly in Asia. The two countries with the highest incidence rates are found in East Asia [1]. China is among the 22 countries with a high burden of tuberculosis, ranking second only to India [2]. In China, about one-third of the total population is infected with tuberculosis. More than 1.4 million new cases are reported, with 130,000 people dying of the disease every year. The number of deaths has increased year by year. Treatment of tuberculosis is, therefore, a great challenge [3].

Spinal tuberculosis (ST) is the most common form of bone and joint tuberculosis. More than 50% of all-body osteoarticular tuberculosis is of the ST type [4], more common in young people. Based on differences in the pathological conditions, ST may be divided into proliferative and caseous necrosis types. As clinical manifestations vary between patients, those with mild lesions may suffer from a lack of medication and patients with severe disease may have severe inflammatory reactions, along with varying degrees of bone destruction and granulation tissue formation [5]. Disease progression is more rapid in patients with caseous necrosis, often accompanied with the formation of dead bones and cold abscesses. Patients with multiple vertebral body involvement and vertebral deformities may present with paraplegia and other symptoms, thereby severely affecting quality of life [6].

Interleukin-17 (IL-17), a proinflammatory cytokine, is expressed in activated CD4+ T-cells. Biologically active IL-17 interacts with interleukin-17R (IL-17R) and induces expression of a variety of adhesion factors and cytokines [7]. Studies have shown that IL-17 plays an important role in the process of tuberculosis infec-

Table 1. Primer sequences

Gene	Upstream primer	Downstream primer
IL-17	5'-CAACCTGAACATCCATAACC-3'	5'-GTCGGCTCTCCATAGTCT-3
IL-17R	5'-CCTGTGGTGATGCCTCAGTT-3'	5'-ATGGACACTGCAGACAGACG-3
MMP-13	5'-GCTAAGACACAGCAAGCCAGA-3'	5'-CGCTAAGGAAAGCAGAGAGG-3
β-actin	5'-CGAGCACAGAGCCTCGCCTT-3'	5'-ATGCCGTGCTCGATGGGGTA-3'

tion, showing differential expression in serum and thoracic edema in patients with tuberculous pleurisy [8]. Matrix metalloproteinase-13 (MMP-13), also known as collagenase-3, is a member of the matrix metalloproteinase family. It exhibits a strong type II collagen degradation ability [9]. Studies have shown that high expression of MMP-13 is conducive for the destruction and degradation of the extracellular matrix in tuberculosis and is closely related to the spread, metastasis, and prognosis of tuberculosis [10]. However, few reports have been published regarding IL-17, IL-17R, and MMP-13 expression in ST disease.

Therefore, this study explored changes in IL-17, IL-17R and MMP-13 expression in ST lesions, examining mutual correlations in different types of lesions.

Materials and methods

In this study, 40 patients with ST that underwent surgical treatment, from January 2014 to December 2017, were retrospectively analyzed. Patients with ST were diagnosed according to clinical manifestations, pathological examinations, acid-fast staining, and imaging examinations. Of these, 22 patients with proliferative lesions were included. There were 12 male and 10 female patients, with an age range of 20-65 years. In addition, 18 patients with necrotic lesions, including 8 males and 10 females, aged 19-70 years, were included. Another 20 subjects with normal cancellous bones served as the control group, including 10 males and 10 females, between 21 and 69 years of age. The study was approved by the Medical Ethics Committee of Ningxia People's Hospital. All family members and patients provided informed consent.

Inclusion and exclusion criteria for patients with tuberculosis

Inclusion criteria: Age > 18 years old, no other hereditary diseases, no autism, no memory impairment and hearing impairment, no blood relationship between the groups, availability for follow-up, and availability of complete clinical information.

Exclusion criteria: Patients with immune complex disease, malignant tumors, and history of cancer and rheumatoid immune system disease.

Main reagents and instruments

RNA reversing transcription and real-time polymerase chain reaction (PCR) kits were purchased from TransGen Biotech, China. TRIzol Reagent was obtained from Invitrogen, USA, while the ABI 7500 PCR amplification instrument was procured from ABI, USA. Primers were designed and synthesized by Shanghai Biotech Co., Ltd. (**Table 1**).

Quantitative reverse-transcription polymerase chain reaction (qRT-PCR) analysis

During the operation, lesion tissues were excised from patients (5 mm × 5 mm) and stored in liquid nitrogen for 1 hour. Total RNA was extracted using TRIzol. Ehe extracted RNA was detected by agarose gel electrophoresis and ultraviolet spectrophotometer for purity, concentration, and integrity. Total RNA was reverse transcribed using a reverse transcription kit. Recombinant cDNA was collected and stored for use, in strict accordance with manufacturer instructions. PCR reaction system included the following reagents: 10 μL of 2 × TransStart® Top Green qPCR SuperMix, 0.6 μL of each of the upstream and downstream primers, and 2.0 μL of cDNA supplemented to 20 μL of nuclease-free water. ABI 7500 was used for amplification. PCR reaction conditions were as follows: Pre-denaturation at 95°C for 10 minutes and 40 cycles of 94°C for 30 seconds, 55°C for 30 seconds, and 72°C for 60 seconds. This was followed by 55°C for 30 seconds and 72°C for 60 seconds. In this study, β-actin was used as an internal reference. Data were analyzed using 2-Δct method. The experiment was performed three times.

Statistical analysis

SPSS 20.0 software package (Guangzhou Bomai) was used to perform statistical analysis

Table 2. Comparison of baseline clinical data among the three groups of patients

Group	Proliferative lesion group (n=22)	Caseous lesion group (n=18)	Control group (n=20)	F/X^2	*P* value
Sex					
Male	12 (54.55)	8 (44.44)	10 (50.00)	0.404	0.817
Female	10 (45.45)	10 (55.56)	10 (50.00)		
Age (years)	45.52±14.13	47.31±12.54	43.96±15.12	0.270	0.764
BMI (kg/m^2)	22.58±1.84	22.12±1.70	21.89±1.77	0.825	0.443
Hypertension				1.473	0.479
Yes	8 (36.36)	8 (44.44)	9 (45.00)		
No	14 (63.64)	10 (55.55)	11 (55.00)		
Diabetes mellitus				1.161	0.560
Yes	9 (40.91)	10 (55.56)	8 (40.00)		
No	13 (59.09)	8 (44.44)	12 (60.00)		
Smoking history				0.116	0.944
Yes	12 (55.55)	9 (50.00)	11 (55.00)		
No	10 (45.45)	9 (50.00)	9 (45.00)		
A history of alcoholism				0.904	0.637
Yes	3 (13.64)	2 (11.11)	1 (5.00)		
No	19 (86.36)	16 (88.89)	19 (95.00)		
Other tuberculosis				0.058	0.810
Yes	3 (13.64)	2 (11.11)			
No	19 (86.36)	16 (88.89)			
History of tuberculosis treatment				0.178	0.673
Yes	2	1			
No	20	17			
Tuberculosis course (year)	8.47±6.25	9.62±6.88		0.553	0.583

on collected data. Data were plotted using GraphPad Prism 7 (Shanghai Beka), wherein count data usage rates (%) were expressed. Chi-squared test was also used. Measurement data are expressed as mean ± standard deviation (means ± SD). Three groups were tested using one-way ANOVA, indicated by F values. LSD was used for pairwise comparisons. Analysis of variance was used for comparisons between groups. Correlation coefficients of IL-17, IL-17R, and MMP-13 were calculated by Pearson's correlation analysis. Correlations between IL-17, IL-17R, MMP-13, and lesion types were investigated by Spearman's correlation. Statistical differences are indicated by $P<0.05$.

Results

Baseline characteristics

Comparison of the clinical data of the three groups of patients revealed no statistical differences between proliferative lesions, caseous necrotic lesions, and control groups in gender, age, body mass index (BMI), hypertension, diabetes, smoking history, history of tuberculosis, and alcohol abuse history ($P > 0.05$) (**Table 2**).

Expression of IL-17, IL-17R, and MMP-13 in tissues from three groups of patients

Relative expression levels of IL-17, IL-17R, and MMP-13 were detected in the tissues from proliferative lesions, caseous necrosis, and control groups of patients. IL-17, IL-17R, and MMP-13 expression was significantly higher in the necrotic lesion group than in the proliferative lesion and control groups ($P<0.05$). Expression of IL-17, IL-17R, and MMP-13 was higher in the proliferative lesion group than in the control group ($P<0.05$) (**Figure 1** and **Table 3**).

Correlation between IL-17, IL-17R, and MMP-13 expression in patients with proliferative lesions and caseous necrotic lesions

The current study found that IL-17, IL-17R and MMP-13 were higher in the necrotic lesion

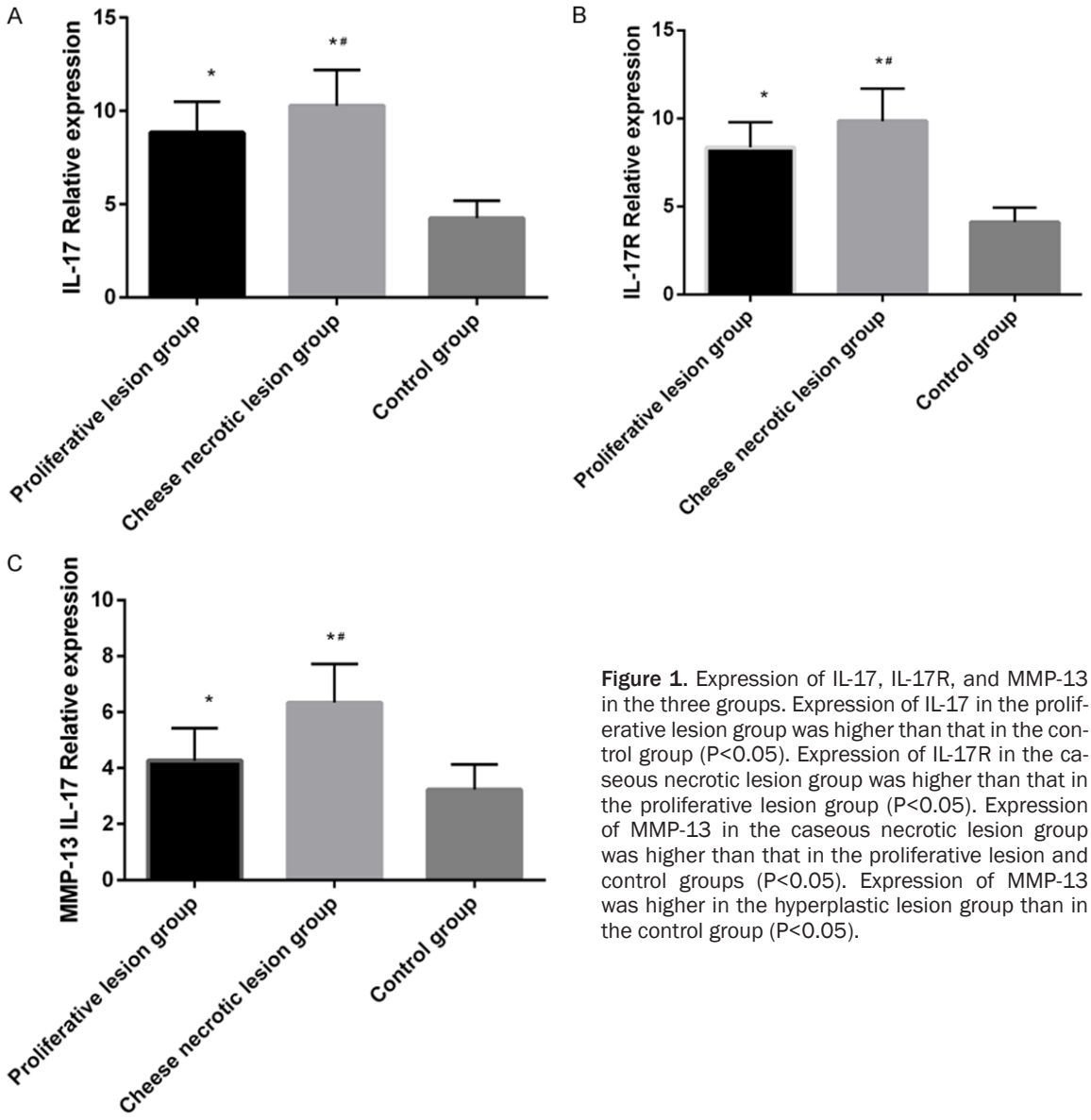

Figure 1. Expression of IL-17, IL-17R, and MMP-13 in the three groups. Expression of IL-17 in the proliferative lesion group was higher than that in the control group (P<0.05). Expression of IL-17R in the caseous necrotic lesion group was higher than that in the proliferative lesion group (P<0.05). Expression of MMP-13 in the caseous necrotic lesion group was higher than that in the proliferative lesion and control groups (P<0.05). Expression of MMP-13 was higher in the hyperplastic lesion group than in the control group (P<0.05).

Table 3. Expression of IL-17, IL-17, IL-17, and MMP-13 in lesions of the three groups of patients

Group	Proliferative lesion group (n=22)	Caseous lesion group (n=18)	Control group (n=20)	F-number	*P* value
IL-17	8.84±1.65*	10.28±1.92*,**	4.25±0.95	80.379	<0.001
IL-17R	8.35±1.44*	9.84±1.86*,**	4.11±0.83	84.794	<0.001
MMP-13	4.27±1.15*	6.34±1.38*,**	3.24±0.89	35.520	<0.001

Note: *P<0.05 compared with the control group; **P<0.05 when proliferative lesion group compared with caseous lesion group.

group than in the proliferative lesion group. Indicators gradually increased with the severity of the disease (P<0.05). Relative expression levels of IL-17, IL-17R, and MMP-13 in patients with proliferative lesions showed a positive correlation (P<0.05). Furthermore, a positive correlation was observed between relative expression levels of IL-17, IL-17R, and MMP-13 and degree of patient conditions (P<0.05) (**Figure 2**, **Tables 4**, **5**).

Discussion

A chronic skeletal joint disease, ST is a type of secondary tissue injury disease caused by *M. tuberculosis* in patients with tuberculosis via blood circulation into the spine [11]. Statistics have shown that ST is mainly a type of vertebral

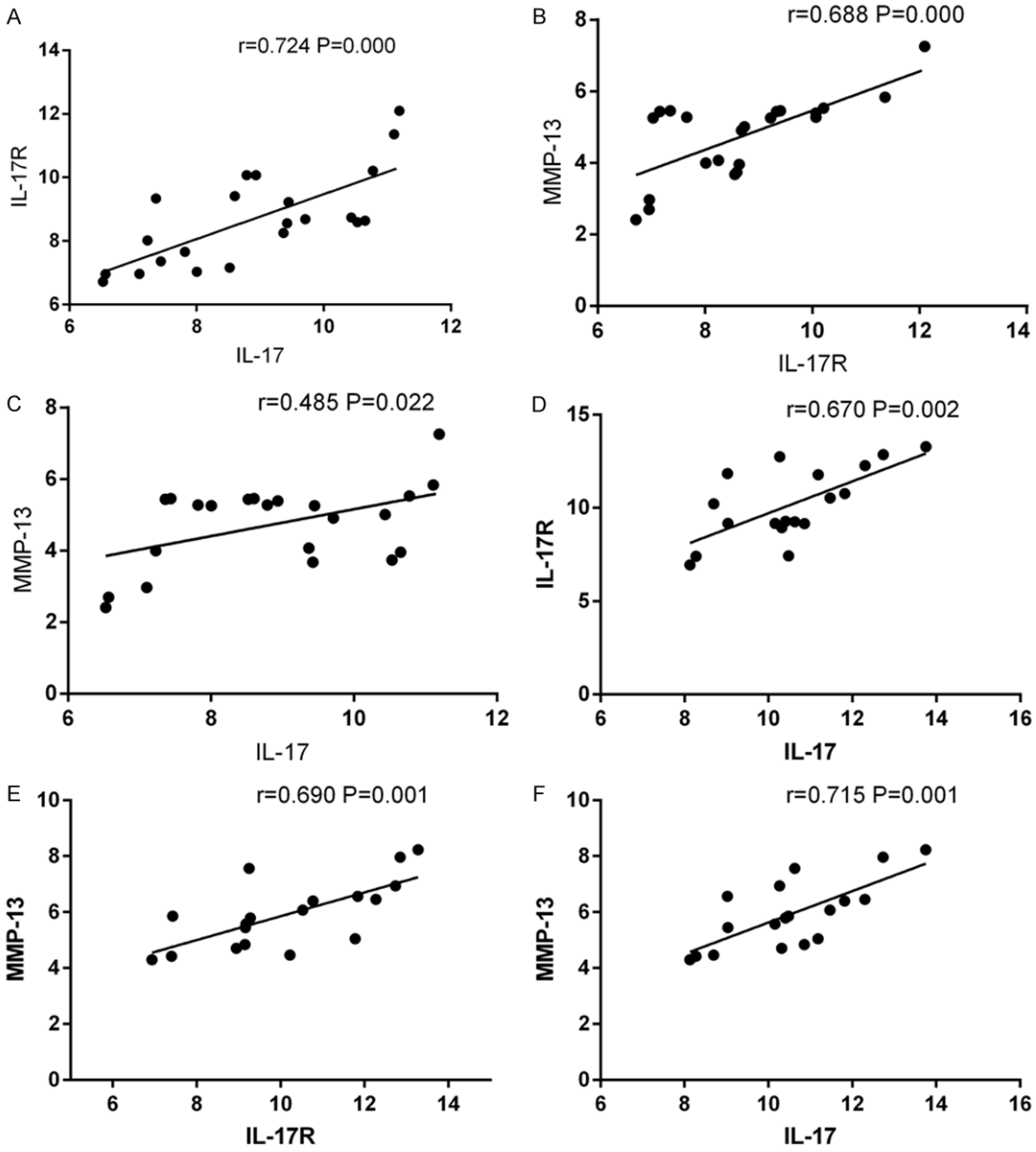

Figure 2. Correlation between IL-17, IL-17R, and MMP-13 expression levels in patients with proliferative lesions and caseous necrotic lesions. A. Proliferative lesions (r=-0.724). B. Hyperplastic lesion group shows a positive correlation between expression of IL-17R and MMP-13 (r=-0.668). C. Proliferative type group shows a positive correlation between expression of IL-17 and MMP-13 (r=0.485 and P=0.022). D. Caseous necrotic type group shows a positive correlation between expression of IL-17 and IL-17R in the lesion tissues (r=0.670 and P=0.002). E. Proliferative type group shows a positive correlation between expression of IL-17R and MMP-13 (r=0.690 and P=0.001). F. Caseous necrotic type group shows a positive correlation between expression of IL-17 and MMP-13 (r=0.715 and P=0.001).

tuberculosis, with a large number of cases are reported in adolescents [12]. ST may be misdiagnosed in clinic, causing patients to miss the best treatment opportunity. Patients with severe disease may also have spinal cord injuries and paraplegia. Like other types tuberculosis, ST also has three pathological forms of exudation, hyperplasia, and necrosis. The exudative type of lesions mainly manifests as serous and fibrous inflammation. There are no clinical

Table 4. Correlation analysis of IL-17, IL-17, and MMP-13 between the two groups

Group	ρ	P
Proliferative lesion group VS Cheese necrotic lesion group (IL-17)	0.499	0.035
Proliferative lesion group VS Cheese necrotic lesion group (IL-17R)	0.496	0.036
Proliferative lesion group VS Cheese necrotic lesion group (MMP-13)	0.472	0.048

Table 5. Correlation analysis of IL-17, IL-17R, and MMP-13 between the groups

Proliferative lesion group	R	*P* value	Cheese necrotic lesion group	R	*P* value
IL-17 vs IL-17R	0.724	<0.001	IL-17 vs IL-17R	0.670	0.002
IL-17R vs MMP-13	0.688	<0.001	IL-17R vs MMP-13	0.690	0.001
IL-17 vs MMP-13	0.485	0.022	IL-17 vs MMP-13	0.715	0.001

manifestations of clinically exudative ST patients, thus it is rarely diagnosed and treated [13].

Interleukin, a type of cytokine that regulates cell growth and differentiation, is secreted by leukocytes. The main role of this cytokine is to mediate T-cell and B-cell activation and proliferation, regulate immune cell differentiation and activation, and fight against inflammatory reactions [14]. IL-17 is a class of ILs that is not well-studied. Recent studies have shown that IL-17 secretes pro-inflammatory cytokines through CD4+ memory T lymphocytes and monocytes [15]. IL-17 and its receptors are widely expressed in the tissues. It mainly functions by binding to IL-17R, promoting inflammatory response and recruiting central granulocytes. It has been shown that IL-17 upregulates MMP and IL-6 expression during cell activation and stimulates chondrocytes to produce nitric oxide and nitric oxide synthase [16]. High concentrations of oxidative nitrogen stimulate the activity of MMP and promote the degradation of chondrocytes.

Matrix metalloproteinases are a class of calcium-dependent zinc-containing endopeptidases. Studies have shown that MMPs play a key role in tissue remodeling and are involved in various pathological processes, including angiogenesis, tissue repair, and arthritis [17]. An important member of the MMP family, MMP-13 has a specific cleavage effects on helicase enzymes. The ability of MMP-13 to degrade type II collagen is 5-10 times higher than that of MMP-1, the highest among all MMPs [18]. Studies have shown that high expression of MMP-13 may promote the degradation of damaged outer matrix of tuberculosis-infected tissue and is associated with tuberculosis metastasis [19]. In the study by González-Avila G et al. [17], *M. tuberculosis* was thought to promote expression of MMP-13 in lung fibroblasts and participate in the formation and decomposition of various collagens. However, very little is known about these two factors in ST. Whether IL-17, IL-17R, and MMP-13 play any roles in the development of ST remains unclear. Therefore, this study explored the relationship between these factors and the extent of lesions by evaluating expression levels of IL-17, IL-17R, and MMP-13 in the lesions of patients with ST, aiming to provide clinical reference.

The current study detected expression levels of IL-17 and IL-17R in patients with proliferative lesions and necrotic lesions. Expression of MMP-13 was higher in these groups than in the control group. Expression of IL-17, IL-17R, and MMP-13 in the lesions of patients with caseous necrosis was higher than in the lesions of patients with proliferative lesions. This observation indicates that IL-17, IL-17R, and MMP-13 are differentially expressed in ST and that expression levels vary in different pathological lesion tissues. These biomarkers may be potentially useful for ST pathological typing. It has been shown that IL-17 expression was higher in patients with tuberculosis potential and active infections than in normal subjects [20]. It was found that IL-17 mediates immune-protection from *M. tuberculosis* (MtbHN 878) by IL-17 receptor signaling in non-hematopoietic cells [21]. These effects are mainly induced by the chemokine CXCL-13. CXCL-13 is an important B lymphocyte chemokine. Its expression may be related to the pathogenesis of various diseases, such as autoimmune and inflammatory dis-

eases. Ong [22] showed that high expression of MMP-13 in patients with tuberculosis was closely related to clinical and radiological markers of lung tissue destruction.

The current study examined expression of IL-17, IL-17R, and MMP-13 in patients with different pathological types of ST, finding that IL-17, IL-17R, and MMP-13 are involved in the development of ST. At the end of the study, the correlation between IL-17, IL-17R, and MMP-13 expression was analyzed. Results showed a positive correlation between each indicator, suggesting the presence of a regulatory relationship between IL-17, IL-17R, and MMP-13. In the study by Koenders M, IL-17 was shown to enhance expression of MMP-13 in chondrocytes and synovial fibroblasts, thereby promoting a reduction in cartilage proteoglycans and collagen [23]. Another study showed that IL-17 regulates the activity of MMP-13 [24]. Therefore, it was speculated that, due to long-term infection in patients, Th17 cells are activated to secrete IL-17 and IL-17 binds to its receptor (IL-17R, etc.). This promotes the secretion of various inflammatory factors and MMP-13 protein. Secretion is involved in the development of the disease. However, more *in vitro* experiments and animal experiments should be conducted to verify the specific mechanisms.

Present results and previous studies indicate that differential expression of IL-17, IL-17R, and MMP-13 in ST lesions may serve as a potential observation index.

The present study had a few limitations, however. First, the sample size was small and whether the results may have caused errors is unclear. Second, this study failed to follow-up with patients to observe whether differential expression of each index had an impact on patient survival. Present experiments have not been thoroughly studied. How to regulate the relationship between IL-17, IL-17R, and MMP-13 expression has not been proven. Moreover, the study did not determine protein levels and did not observe the relationship between the above factors and clinical symptoms. These should be examined in the future.

In summary, IL-17, IL-17R, and MMP-13 are highly expressed in lesions of patients with ST. These markers showed differential expression in lesions of patients with different degrees of disease. Expression levels of IL-17, IL-17R, and MMP-13 are correlated, serving as potential observation indicators of ST.

Disclosure of conflict of interest

None.

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