ORIGINAL RESEARCH

Triggering Receptor Expressed on Myeloid Cells 2 Mediates the Involvement of M2-Type Macrophages in Pulmonary Tuberculosis Infection

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Background: Macrophage play a significant work in the development of tuberculosis. This study aims to investigate the relationship between TREM2 and macrophage polarization, as well as the related cytokines.
Methods: This study involved 43 pulmonary tuberculosis patients and 37 healthy controls. Enzyme-linked immunosorbent assay (ELISA) was used to detect the expression levels of M1/M2 macrophage-related cytokines IL-10 and IL-12 in the peripheral blood of pulmonary tuberculosis patients. The relative mRNA expression levels of TREM2, IL-10 and IL-12 were detected using quantitative real-time PCR (qRT-PCR). Additionally, Spearman rank correlation analysis was used to preliminarily assess the correlation between TREM2 and M1 / M2 macrophages. Hematoxylin-eosin (HE) staining was performed to observe the pathological manifestations of pulmonary tuberculosis lesions. Immunohistochemical (IHC) staining was used to observe the localization of the macrophage-specific molecule CD68, the M1 specific molecule iNOS, the M2 specific molecule CD163, and TREM2.
Results: The lesions of pulmonary tuberculosis patients showed Langhans multinucleated macrophages and tuberculous granulomas. The ELISA results indicated that the expression levels of IL-10 and IL-12 were significantly increased in peripheral blood of pulmonary tuberculosis patients. Additionally, the relative mRNA expression levels of TREM2, IL-10 and IL-12 were also significantly higher in the pulmonary tuberculosis group. Furthermore, a positive correlation was observed between TREM2 and IL-10, which are secreted by M2 macrophages. IHC revealed significant positivity of TREM2 and macrophage-related markers in tuberculous granuloma. Specifically, TREM2 and M2 macrophage marker CD163 were significantly expressed in the cytoplasm and membrane of Langhans multinucleated macrophages.
Conclusion: The role of macrophage polarization in pulmonary tuberculosis is significant, and further investigation is needed to understand relationship between TREM2 and M2 macrophages.
Keywords: tuberculosis, TREM2, macrophage

Introduce

Tuberculosis (TB) is considered one of the world's most devastating infectious diseases globally, having evolved in humans over the past 70,000 years. Caused by infection with *Mycobacterium tuberculosis* (*Mtb*), it can colonize multiple organs throughout the body. Tuberculosis is responsible for approximately 1.5 million deaths per year.[1] Under the pandemic trend of the Coronavirus disease (COVID-19), although the highly infectious and high mortality rate of the

COVID-19 has attracted people's attention, tuberculosis should not be ignored.[2] In recent years, with the efforts of the Chinese government, the burden of TB epidemic has shown a downward trend throughout the country, but it's still the top priority in the western region of China.[3] Therefore, the research of tuberculosis still needs the efforts of more scholars.

Mtb invades the body through the respiratory tract and spreads to multiple systems via the bloodstream. It can colonize in various organs,[4] leading to subsequent clinical symptoms. *Mtb* infection often manifests as a latent infection. Due to individual differences, about 5% to 10% of infected patients will progress to active pulmonary TB and develop clinical manifestations, such as low-grade fever, night sweats, and fatigue.[4,5] Firstly, Mtb enters the lungs, and the alveolar macrophages (AMs) are among the first cells to come into contact with Mtb. Studies have shown that *Mtb* possesses unique cell surface lipids and secreted protein effectors that can escape the killing of innate immune cells.[6] The heterogeneity and plasticity of macrophages can help limit the spread of *Mtb*. However, virulence factors of *Mtb* can affect the steady state of macrophages and thus influence the progression of the disease.[6,7]

Macrophages are a complex population with high plasticity. Currently, macrophages activated through the classical and alternative pathways are considered the two extremes of macrophage function plasticity modulation.[8] Some studies have found that M1-type macrophages (M1) aid in the killing of *Mtb* by granuloma tissue, and promote the formation of granulomas. During Mtb infection, macrophages undergo foaming changes, and M2-type macrophages (M2) are thought to significantly promote the formation of foamy macrophages, leading to *Mtb* latent infections.[9,10] Therefore, macrophages are considered key in responding to the *Mtb* infection process.

Macrophages detect the invasion of *Mtb* pathogens through various surface receptors. These receptors are critical for pathogen defense because they act as sentinels for *Mtb,* which can then transmit favorable signals intracellularly and trigger a powerful immune response. Current studies have shown that triggering receptor expressed oil myeloid cells (TREM) is a family of immunoglobulin receptors, expressed on the surface of myeloid cells, they play an important role in the activation of macrophages.[11,12] TREM-1 amplifies inflammation through the synergistic effect of Toll-like receptor (TLR) and NOD-like receptor (NLR) signaling reaction, increasing the production of inflammatory cytokines, such as TNF-α, IL-1 and IL-6.[13] TREM2 can stimulate the production of inflammatory factors, contributing to the progression of chronic inflammation and immune response. It is also related to various functions of cell maturation, such as survival, proliferation, activation, and phagocytosis.[14]

Recent studies have shown that patients with multiple sclerosis and other inflammatory nervous systems have a high expression level of soluble TREM2 in their cerebrospinal fluid.[15,16] Additionally, increased TREM2 expression in monocytes from Alzheimer's disease patients has been found to play an important role in the progression of the disease.[17] Some scholars believe that TREM2 plays a key role in promoting the inflammatory Th1 response when infected with *Mtb*.[18] This study aims to explore the expression level of TREM2 in pulmonary tuberculosis patients and its relationship with macrophage polarization. The results of this research may provide new insights and targets for understanding the TB infection mechanism.

Method
Research Objects

43 active pulmonary tuberculosis patients were collected; among them, 23 were male and 21 were female, with an average age of 49:51 ± 11:90 years old. They were diagnosed at the First Affiliated Hospital of Xinjiang Medical University from December 2018 to December 2020, and 5 mL EDTA anticoagulated whole blood was drawn during the active period. At the same time, a total of 37 cases of healthy control group were collected, including 21 males and 16 females, with an average age of 40:27 ± 13:61 years old, collected 5 mL EDTA anticoagulated whole blood. The healthy subjects in the control group had no infectious diseases; liver function, kidney function, and chest imaging examinations were normal; the sputum tuberculosis smear microscopy report was negative, and there was no history of tuberculosis. At the same time, 40 cases of pulmonary tuberculosis patients were treated in the First Affiliated Hospital of Xinjiang Medical University, and they undergo surgical treatment from June 2018 to June 2021; their surrounding lungs and lung stumps were collected.

The "WS288-2017 Pulmonary Tuberculosis Diagnosis" formulated from China in 2018,[19] provides diagnostic criteria, inclusion and exclusion criteria for this study: There are clinical manifestations and signs of typical TB such as low fever, night sweats, and force, and at least in line with one of the following three: 1) sputum smear

microscopy or sputum culture is positive for *Mtb*; 2) sputum examination is negative, but chest imaging examination shows typical active pulmonary TB; 3) sputum examination is negative, disease physically diagnosed TB granulomatous structural samples of lung lesions, or pleural effusion and bronchoalveolar lavage fluid were reported as TB lesions. Patients with other immune diseases, neoplastic diseases, pulmonary infection, and HIV infection were excluded.

HE Staining

Paraffin embedded tissue sections were dewaxed, stained with hematoxylin for 1 min, stained with eosin for 3 min and 1% hydrochloric acid ethanol for 1 s, and returned to blue with PBS. Dehydrated, dried, and sealed with neutral gum, and the pathological manifestations of the lesions were observed under a microscope.

IHC Staining

In this study, the lesion tissues of 43 patients with pulmonary TB were collected. The expression and localization of TREM2, CD68, iNOS and CD163 were observed by IHC, for initial clarification the relationship between TREM2 and M1/M2 macrophages was preliminarily determined. After dewaxing, the tissue sections were repaired with sodium citrate solution for 15 min and endogenous peroxidase blocker to avoid light conditions at 37°C for 10 minutes. Goat serum was sealed for 20 min and incubated with primary antibody in refrigerator at 4°C for 14 h (Table 1). Combined with secondary antibody at 37°C for 90 min, the staining was performed with diaminobenzidine in peroxide substrate solution for 2.5 min ± 10s. Image-Pro Plus version 8.0.1 is used to process the collected images of immunohistochemistry results; after quantitative processing (IOD (sum)/Area(sum)), the positive rate is calculated.

Elisa

The kit used in this experiment was provided by Shanghai Jiang Lai Biotechnology Co., Ltd. According to the instructions of the kit, measure the OD value of the standard and samples, draw the standard curve of the four-parameter logistic function, and detect the expression levels of IL-10 (NOJL19246) and IL-12 (NO.JL18332) in blood serum.

qRT-PCR

RNA was extracted from the peripheral blood of patients, using TransZol Up plus RNA kit (Beijing, China), requiring RNA concentration (>80ng/μL) and purity (OD_{260}/OD_{280}=1.8–2.0). Synthesize cDNA according to the kit (Takara. NO. RR037, Japan), and then prepare the PCR reaction system according to the kit instructions (Takara. NO.RR820, Japan). The above reaction system was mixed thoroughly, centrifuged for 10s, placed in a PCR instrument, and amplified according to the following reaction conditions: pre-denaturation (1 cycle) 95 °C for 30s, PCR reaction (40 cycles) 95 °C for 5 s and 60 °C for 34s. For the obtained Cycle threshold (Ct) value, $2^{-\Delta\Delta t}$ value was represented the relative expression level for every indicator.

Statistical Analysis

The GraphPad Prism (v8.0.1) and SPSS (v26.0) software were used for calculation and visualization. For quantitative data, the mean and standard deviation ($\overline{\chi} \pm$ s) were used for normal distribution data, *t*-test was used to compare the

Table 1 Immunohistochemical Antibody

Antibody	Brand	Concentration
Ag85B	Bioss(bs-6460R), China	1:300
TREM2	Bioss(bs-2723R), China	1:200
CD68	Abcam(ab955), Britain	1:2000
INOS	Bioss(bs-0162R), China	1:300
CD163	Bioss(bs-2527R), China	1:100

differences between the two groups. The median and interquartile range [M (P25, P75)] were used for non-normal distribution data, the Wilcoxon test was used to analyze the differences. Count data with sample number (n) represent, The Chi-square test analysis differences between the two groups. Pearson correlation coefficient was used to evaluate the correlation between numerical variables. P value < 0.05 was considered statistically significant.

Result
Analysis Clinical Data of TB Patients
This study included 43 active tuberculosis patients in TB group, with average age of 49.51±11.90 years old. There were 37 cases in control group, with average age of 40.27±13.61 years old. In TB group, the expression of Albumin (ALB) was 41.76±3.14(u/L), the expression of C-reactive protein (CRP) was 42.70 (9.31, 104.30) (mg/L), and the expression of White blood cells (WBC) was 8.96±2.83 (10^9/L), there are significant differences. Among them, ALB in the peripheral blood of TB patients was significantly lower than control group patients, while CRP and WBC were significantly increased with statistical significance. However, the expressions of Age, Hematocrit (Hct)and Mean corpuscular volume (MCV) were not prompt obvious difference (P>0.05), see Table 2.

Histopathological Manifestations of Lesions
There were typical tuberculous granulomas in the pulmonary tuberculosis after HE staining, caseous necrosis accompanied by Langerhans multinucleated macrophage accumulation. Microscopically, the cytoplasm was pink, and the blue-purple nuclei gathered at the edge of giant macrophage like a horseshoe (Figure 1B). Inflammatory cell infiltration was occasionally seen at distal sites, and no obvious granulomatous structure (Figure 1A).

Ag85B is a unique virulence protein expressed by *Mtb*. After IHC staining, it was dark brown under microscope in the pulmonary tuberculosis lesions, in the cytoplasm and nucleus of Langhans cells were obviously positive (Figure 1D). However, no positive expression area was found in the distal tissue (Figure 1C). There was a statistically significant difference in expression between the lesion site and the distal site (Figure 1E, P < 0.001).

Expression Localization of TREM2 and M1/M2 Type Macrophage
The IHC staining results of TREM2 and M1/M2 type macrophage indicators are shown in the figure (Figure 2). In the pulmonary TB lesion tissue, TREM2 was mainly expressed in the cell membrane and cytoplasm, especially in Langhans multinucleated macrophages, and occasionally in the nucleus in the control group (Figure 2A and B). As a typical marker of macrophages, CD68 was significantly positive expressed in large areas of the lesions, mainly located in the nucleus and cytoplasm. In the control group, scattered brown areas were also seen, mainly only located in the nucleus (Figure 2C and D). However, iNOS and CD163, as markers of M1 and M2 type macrophage, were positively expressed in the cytoplasm of multinucleated macrophages in TB patient's lesions (Figure 2F–H). In the TB lesion tissues and distal side tissues, the expression difference was statistically significant (Figure 2I).

Table 2 Basic Clinical Data

	TB group(*n*=43)	Control group(*n*=37)	*P* value
Age (year)	49.51±11.90	40.27±13.61	0.422
Gender (Male/ Female)	23/20	21/16	0.77
ALB (u/L)	41.76±3.14*	45.64±1.64	0.002
CRP (mg/L)	42.70(9.31, 104.30)**	2.56(1.70, 4.74)	<0.001
WBC (10^9/L)	8.96±2.83*	7.05±1.57	0.001
Hb (g/L)	124.25±21.81*	120.97±13.72	0.036
Hct (%)	38.24±4.23	40.29±3.51	0.396
MCV(Fl)	83.90±7.32	87.56±7.98	0.913

Notes: *P<0.05, **P<0.01.
Abbreviations: ALB, Albumin; CRP, C-reactive protein; WBC: White blood cells; Hb, hemoglobin; Hct, Hematocrit; MCV, Mean corpuscular volume.
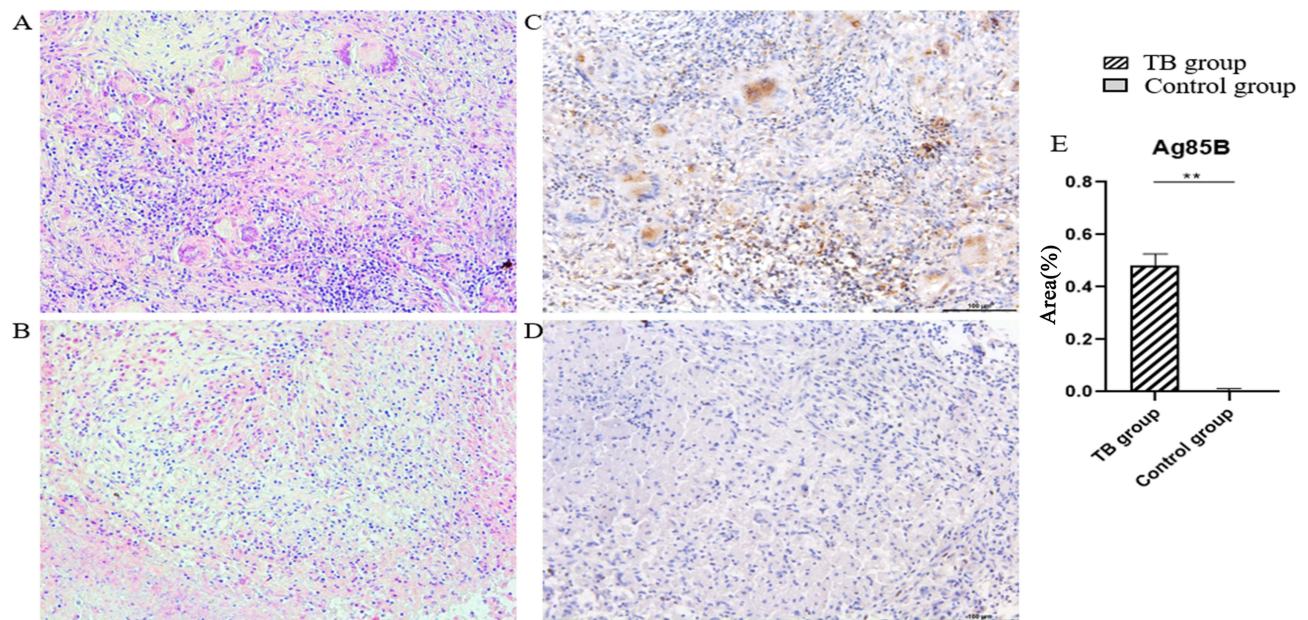
Figure 1 Pulmonary tuberculosis pathological staining. (**A** and **B**) Distal side control group and TB group hematoxylin and eosin staining (×200). (**C** and **D**) Ag85B IHC staining of distal side control and TB group (×200). (**E**) Ag85B IHC staining results statistical analysis.(****** P < 0.01).

Expression of TREM2, IL-10 and IL-12 in Peripheral Blood

The expression levels of IL-10 and IL-12 in the peripheral serum of research objects were detected by ELISA. The expression level of IL-12 was 105.80(65.36, 230.51) (pg/mL), and the expression level of IL-12 was 25.35(12.52, 110.08) (pg/mL), the difference was statistically significant. Table 3, Figure 3.

The Relative Expression and Correlation Analysis of TREM2, IL-10 and IL-12 mRNA

We used qRT-PCR to detect the mRNA relative expressions of TREM2, IL-10 and IL-12. The results showed that TB group relative expression levels were significantly higher than control group. In the TB group, the TREM2 mRNA was 5.49 (4.01, 6.33), IL-10 mRNA was 32.43 (22.56, 36.73), the two subunits mRNA of IL-12 were 15.52 (13.74, 17.26) and 23.56±6.42. Table 4, Figure 4.

Subsequently, to further explore the relationship between TREM2 and macrophages in TB group, the results of Spearman correlation analysis indicated that there was a significant positive correlation between TREM2 and IL-10, and the correlation coefficient R value was 0.444, but there was no correlation between TREM2 and the two subunits of IL-12. Figure 5.

Discussion

Mycobacterium tuberculosis (*Mtb*) is an intracellular parasite that poses a significant threat to global public health. Tuberculosis caused by Mtb is a highly infectious disease with a high mortality rate in infected hosts.[20] When *Mtb* infects the host, alveolar macrophages are the primary innate immune cells that phagocytose the droplets entering the alveolar space in the lung tissue. This leads to the early inflammation and the formation of granuloma-like structures in the lung tissue[4,21]。 Simultaneously, it provides a site for *Mtb* retention and pathogenic effect, regulates the initiation of adaptive immune responses, and ultimately enables the immune system suppress or clear *Mtb* infection.[22–24] Both M1 and M2 macrophages play an important roles in the body's resistance to *Mtb*. M1 is believed to primarily kill Mtb and promote the formation of granulomas, while M2 is mainly involved in the formation of TB granulomas and promotes macrophage foaming changes.[6,25]

M1 macrophages are triggered and activated by IFN-γ or Lipopolysaccharide (LPS). They are characterized by the high expression of iNOS and the secretion of various pro-inflammatory cytokines, including TNF-α, IL-12, CXCL10, and others. Under the induction of IL-4, IL-13 and other cytokines, macrophages can be activated to M2, with high expression CD206 and CDl63, secrete high levels of cytokines, such as IL-6, IL-10 and CXCLl7 and others.[26] In this
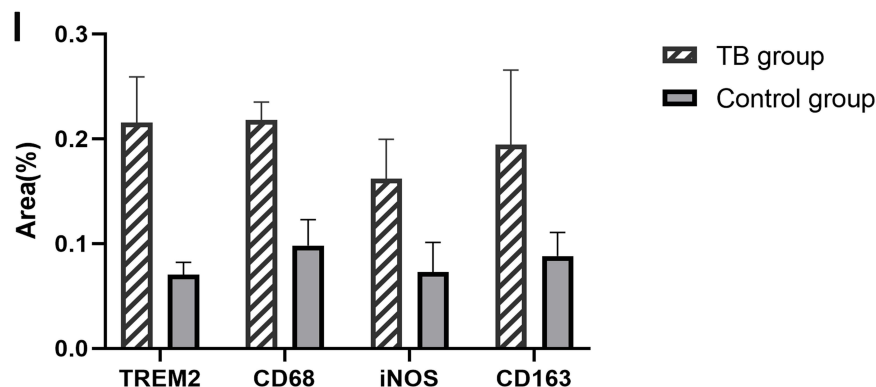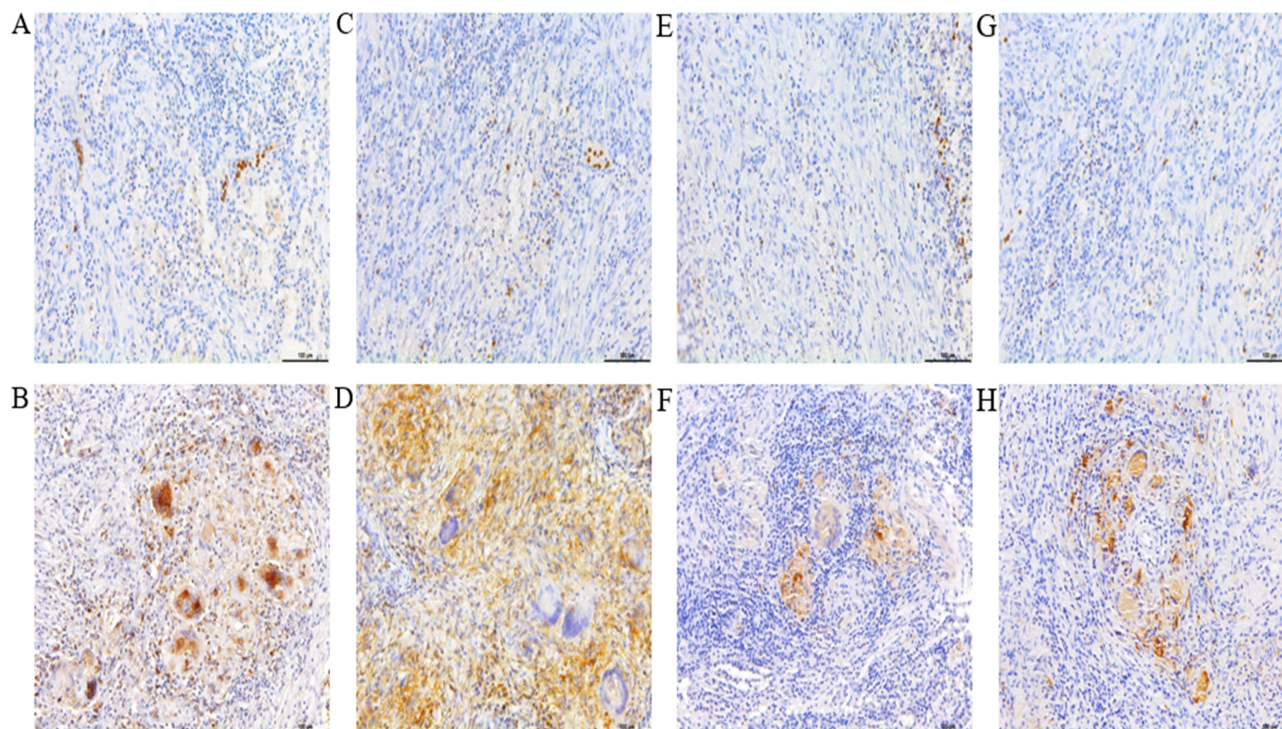
Figure 2 Pulmonary tuberculosis IHC results. (**A** and **B**) Distal side control and TB group TREM2 IHC staining (×200). (**C** and **D**) Distal side control group and TB group CD68 IHC staining (×200). (**E** and **F**) Distal side control group and TB group iNOS IHCstaining (×200). (**G** and **H**) Distal side control group and TB group CD163 IHC staining (×200). (**I**) TREM2,CD68,iNOS and CD163 immunohistochemistry staining statistical analysis.

study, IL-12 and IL-10 were used in subsequent studies as cytokines secreted by M1 and M2, respectively. And iNOS and CD163 were explored as M1/M2 cell surface markers, respectively. TREM2 expression is regulated by various pathogens and disease conditions to modulate host-triggered innate immune responses.[27] TREM2 senses bacterial or fungal infections and suppresses the secretion of induced pro-inflammatory factors.[28] Recently, myeloid cells have been

Table 3 Cytokine IL-10 and IL-12 Expression Levels(Pg/Ml)

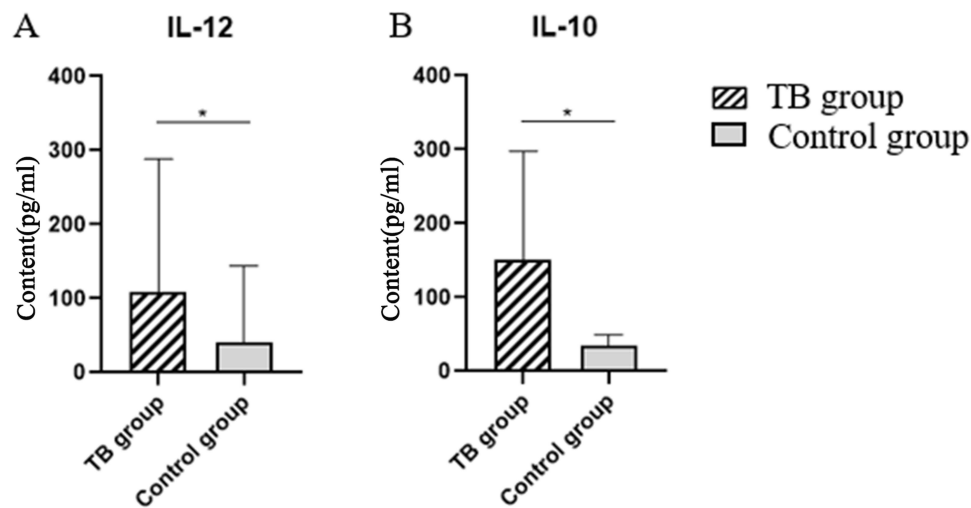|	TB group	Control group	P value
IL-10	105.80(65.36,230.51)*	30.13(30.01,30.18)	0.008
IL-12	25.35(12.52,110.08)*	9.11(2.32,19.36)	0.006

Notes: *$P < 0.05$.

Figure 3 ELISA results. (**A**) IL-10 expression levels. (**B**) IL-12 expression levels.(*$P < 0.05$).

recognized as playing a central role in various diseases, with TREM2 being a major immune signaling hub induced by pathology. This study aims to investigate the relationship between TREM2 and macrophage polarization.

Immunohistochemical experiments were conducted to clarify the relationship between TREM-2 and macrophages of different polarization types. The expression levels of IL-10 and IL-12 in the peripheral blood of patients were detected using ELISA. Finally, qRT-PCR was used to count the mRNA relative expression levels of TREM2, IL-10 and IL-12. Statistical analysis was then performed to investigate the correlation between TREM2 and the macrophage polarization index, revealing the relationship between TREM2 and macrophage polarization.

TREM2 expression was initially discovered on monocyte-derived dendritic cells (MODCs) and later on the surface of various myeloid cells, Such as osteoclasts, microglia, neutrophils, and macrophages.[29,30] TREM2 is a novel immunor-egulatory receptor that has been implicated in the pathophysiology of inflammatory reactions, such as sepsis and inflammatory bowel disease, by regulating cytokine secretion by macrophages.[31,32] In this study, IHC results showed that TREM2 was mainly expressed in the cell membrane and cytoplasm, especially in the TB granulomas formed by Langhans multinucleated macrophages, where it exhibits significant positive expression. CD68, as a typical marker of macrophages, was significantly positive expressed in large areas of the lesions, which once again to verifies the important role of macrophages in resistance to Mtb. In addition, iNOS and CD163 were used as markers for M1 and M2 type macrophages, respectively. Both markers showed positive expression. It is noteworthy that CD163 expression was more prominent in the cytoplasm and membrane of multinucleated macrophages, which is more consistent with the expression localization of TREM2. This suggests that TREM2 may be involved in the process of promoting the foaming process of macrophages near granuloma in M2 macrophages. Therefore, we further explored the expression levels of TREM2 and macrophage-related factors, in the peripheral blood. The relative expression levels of TREM2 mRNA were significantly higher in the TB group than in the control group, indicating an important biological role for TREM2 in both the lesion site and in the peripheral blood circulation system. The experimental results of the qRT-PCR and ELISA experiments showed significant expression of IL-12 and IL-10 in the TB group. Additionally, the cytokine IL-10 secreted by M2 appeared to have higher expression levels in the peripheral blood of TB patients. Further statistical analysis indicated

Table 4 TREM2, IL-10 and IL-12 mRNA Expression Levels

	TB group	Control group	P value
TREM2	5.49(4.01,6.33)**	0.95±0.95	<0.001
IL-10	32.43(22.56,36.73)**	1.31(0.61,1.62)	<0.001
IL-12A	15.52(13.74,17.26)**	1.54±1.02	<0.001
IL-12B	23.56±6.42**	1.01(0.66,1.52)	<0.001

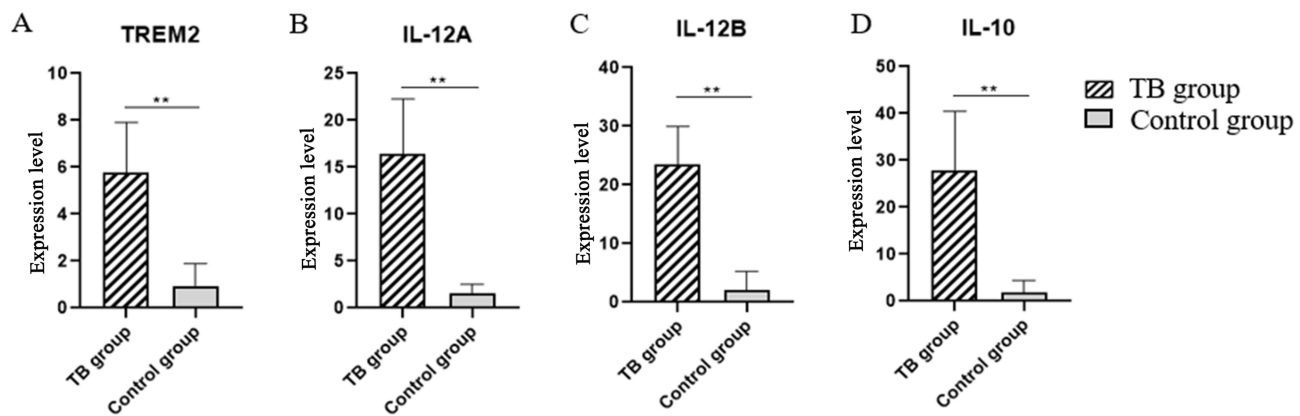**Notes**: **$P<0.01$.

Figure 4 qRT-PCR results. (**A**) TREM2 mRNA relative expression. (**B** and **C**) IL-12 mRNA relative expression. (**D**) IL-10 mRNA relative expression.(**P < 0.01).
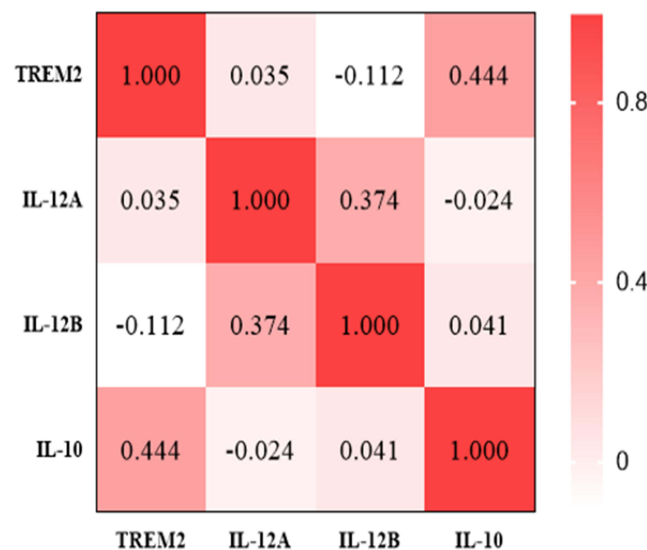

Figure 5 Spearman correlation analysis results.

a higher positive correlation between TREM2 and IL - 10. Therefore, we speculation that TREM2, as a kind of transmembrane receptor, may mediated the process of M2 type macrophages during *Mtb* infection to exert biological effects.

Recent studies have found that TREM2 specifically binds to *Mtb* infection and plays a role in defending against it by disabling the antimicrobial response of macrophages. Turnbull et al reported that the binding of TREM-2 to its ligand inhibits macrophage activation and the secretion of pro-inflammatory cytokines, such as TNF-α and IL-6. The expression of TREM-2 was significantly increased on the membrane surface of M2-type macrophages and was almost absent on the membrane surface of M1-type macrophages, which is consistent with the results of the present study.[33] This is basically consistent with our research results. TREM2 and CD163 were positively expressed in the cytoplasm and membrane of Langhans multinucleated macrophages, and the expression patterns are very similar. TREM2 suppresses the macrophage inflammatory response by inhibiting the TLR signaling pathway.[34,35] In addition, some studies have shown that macrophages overexpressing TREM2 can produce more IL-10 after exposure to LPS.[36] This was also verified in this study, the expression levels of both IL-10 and IL-12 were significantly increased, while the expression level of IL-10 was a little higher when the TB group expressed more TREM2. Especially, in our further correlation analysis, the statistical results suggest that the relative expression levels of TREM2 and IL-10 have a higher correlation, showing a significant positive correlation. In fact, some scholars have proposed that, when *Mtb* infects macrophages, TREM2 acts as a gatekeeper, which can block the production of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and

reactive oxygen species (ROS), at the same time, it can enhance the expression of interferon-β (IFN-β) and IL-10.[37] This is consistent with our findings. In tuberculosis, the positive relationship between TREM2 and M2 is more closely, which lays a foundation for us to further reveal the action mechanism of TREM2 on M2 type macrophages surface, and we hope to provide new ideas for other scholars' research.

Conclusion

In conclusion, the present study has shown a positive correlation between TREM2 and M2 macrophage-specific cytokines. This suggests that TREM2 may play a critical role in mediating macrophage polarization to M2 during the development of TB.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics Statement

This study was approved by the Ethics Committee of First Affiliated Hospital of Xinjiang Medical University and the trial conformed to the principles outlined in the Declaration of Helsinki. All adult subjects provided written informed consent, and no children were included in the study. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for Publication

Informed consent for publication was obtained from all participants.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships.

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