Int J Clin Exp Med 2015;8(2):2147-2155
www.ijcem.com /ISSN:1940-5901/IJCEM0004302

Original Article

Correlation between triggering receptor expressed on myeloid cells-1 and clinical disease activity in Chinese patients with ulcerative colitis

Shulan Zhang[1*], Jing Luo[2*], Bingbing Shen[3,4], Lijun Li[1], Chaojun Hu[1], Ping Li[1], Chuiwen Deng[1], Fengchun Zhang[1], Jiaming Qian[3], Yongzhe Li[1]

[1]Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Key Laboratory of Rheumatology and Clinical Immunology, Ministry of Education, No. 1 Shuai Fu Yuan, Eastern District, Beijing 100730, China; [2]Division of Rheumatology, Department of Medicine, The Second Hospital of Shanxi Medical University, Taiyuan, Shanxi 030001, China; [3]Department of Gastroenterology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, No. 1 Shuai Fu Yuan, Eastern District, Beijing 100730, People's Republic of China; [4]Current address: Peking Union Medical College Press, No. 9 Dong Dan San Tiao, Eastern District, Beijing 100005, People's Republic of China. [*]Equal contributors.

Received November 30, 2014; Accepted January 29, 2015; Epub February 15, 2015; Published February 28, 2015

Abstract: The need for reliable biomarkers for monitoring disease activity in patients with ulcerative colitis (UC) is increasing. This study aimed at characterizing the correlation between serum sTREM-1 levels and diseases activity in Chinese patients with UC. Consecutive 76 patients with UC and 20 healthy subjects were prospectively enrolled. The disease activity of UC was assessed according to Mayo Score. Expression levels of TREM-1 in peripheral blood mononuclear cells (PBMCs) and serum sTREM-1 levels were evaluated at the time when the disease activity was determined. Other laboratory parameters, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were also determined. Both TREM-1 expression levels in PBMCs and serum sTREM-1 levels from patients with UC were significantly increased compared to healthy subjects. In addition, the levels of TREM-1 expression and serum sTREM-1 were significantly elevated in UC patients with moderate or severe disease compared to the patients with quiescent or mild disease. More importantly, both levels of TREM-1 expression in PBMCs and serum sTREM-1 levels were significantly correlated with disease activity. The correlation between sTREM-1 and disease activity was higher than the correlations between CRP and disease activity or ESR and disease activity. Our findings suggest that serum sTREM-1 could be a potential serum biomarker for monitoring disease activity in Chinese patients with UC, and could be a promising surrogate for CRP and ESR.

Keywords: Ulcerative colitis (UC), triggering receptor expressed on myeloid cells-1 (TREM-1), sTREM-1, disease activity, Chinese patients

Introduction

Inflammatory bowel disease (IBD), which is characterized by recurrent episodes of relapse (active disease) and remission (quiescent disease), is a chronic inflammatory disease that affects colon with unknown etiology. Crohn's disease (CD) and Ulcerative colitis (UC) are the two main entities [1]. CD and UC differentially affect the gastrointestinal tract (GI tract). Generally, CD affects any part of the GI, while UC only affects large intestine. In addition, the lesions in CD localize in the entire bowel wall, while the lesions in UC are restricted to the epithelial lining of the gut [2]. The difference in lesion location suggests that CD and UC might have different pathogenic mechanisms [2].

Increasing evidence indicates significant increase of the incidence of IBD in Asia, especially the incidence of UC [3]. The ratio of incidence of UC to CD in Asia was four times higher than that in Australia (2.0 vs. 0.5) [4]. Assessment of disease activity is crucial for tailoring the therapies [5]. However, traditional assessments of disease activity, such as Clinical Disease Activity

Table 1. The Characteristics of health control and patients with ulcerative colitis

Demographic properties	HC (n = 20)	Quiescent (n = 19)	Mild (n = 23)	Moderate (n = 18)	Severe (n = 16)	*P*-value (Overall)
Age (yrs, mean ± SD)	38.3 ± 11.8	43.8 ± 16.3	42.3 ± 13.1	44.8 ± 15.0	34.3 ± 12.7	0.152
Gender (M/F)	9/11	11/8	9/14	10/8	6/10	0.467
Body Mass Index (mean ± SD)	23.0 ± 2.2	23.9± 1.4	23.2 ± 1.5	22.7 ± 1.1	23.3 ± 1.5	0.238
Duration (yrs, mean ± SD)	NA	7.4 ± 6.8	8.2 ± 5.2	8.0 ± 6.3	5.3 ± 4.3	0.454
Smoking	3	5	5	4	2	0.794*
Alcohol Consumption (>5 drinks per week)	2	3	4	4	1	0.642*
TREM-1 mRNA ($2^{-\Delta\Delta Ct}$, mean ± SD)	1.04 ± 0.07	1.25 ± 0.20	3.58 ± 0.38	10.16 ± 1.06	22.38 ± 4.25	< 0.001
sTREM-1 (pg/ml, mean ± SD)	106 ± 30	139 ± 35	175 ± 38	239 ± 67	296 ± 79	< 0.001
ESR (mm/hr, mean ± SD)	6.15 ± 3.41	6.32 ± 5.95	13.26 ± 10.19	19.00 ± 13.42	19.19 ± 11.37	0.001
CRP (ng/dl, mean ± SD)	2.86 ± 1.30	2.85 ± 5.34	10.58 ± 18.98	12.36 ± 16.68	11.92 ± 11.09	0.152
Hb (g/L, mean ± SD)	127.3 ± 7.4	137.1 ± 16.6	132.1 ± 43.3	128.4 ± 18.6	119.0 ± 26.3	0.328

*Exact r × c contingency table. NA, not applicable; TREM-1, triggering receptor expressed on myeloid cells-1; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

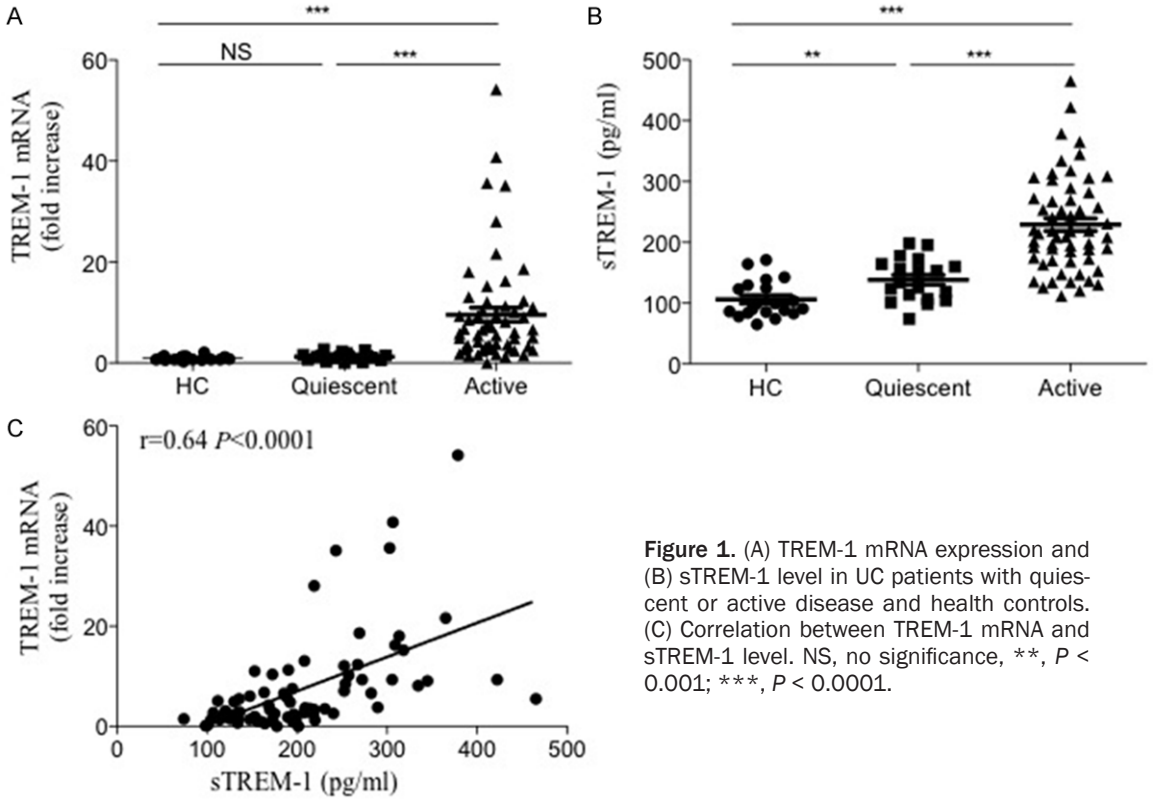

Figure 1. (A) TREM-1 mRNA expression and (B) sTREM-1 level in UC patients with quiescent or active disease and health controls. (C) Correlation between TREM-1 mRNA and sTREM-1 level. NS, no significance, **, $P < 0.001$; ***, $P < 0.0001$.

Index (CDAI) are subjective and may not accurately reflect the true disease status. Moreover, histopathological or endoscopic examinations are invasive and time consuming, and are unsuitable for routine practice [6]. Serum biomarkers, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), are routinely checked in IBD patients to assess disease activity and predict disease progression. It is now appreciated that there is a remarkable heterogeneity in CRP levels between CD and UC [7-9]. CRP levels correlate less well with disease activity in patients with UC compared to CD [7-9]. Therefore, there has been a strong need for reliable biomarkers to reflect disease severity and predict disease progression in UC.

Triggering receptor expressed on myeloid cells-1 (TREM-1), a member of the immunoglobulin superfamily, expressed on neutrophils and mo-

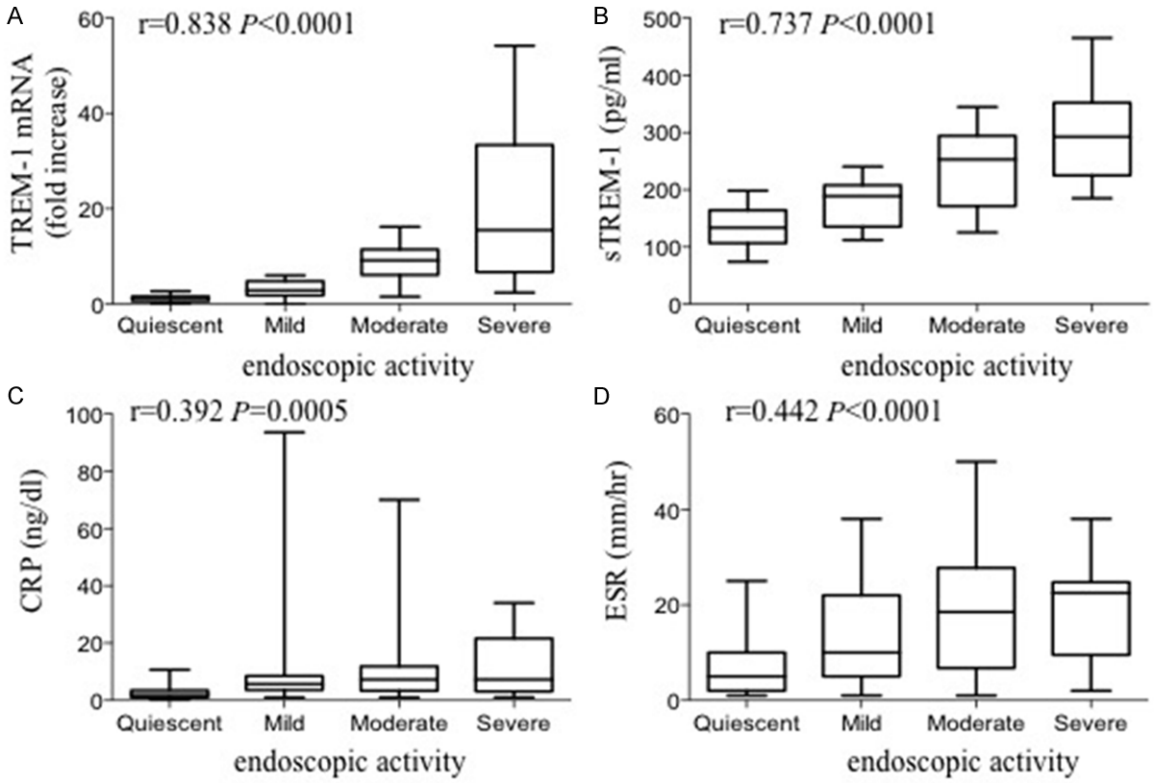

Figure 2. Correlations between various biological markers and endoscopic activity indexes. Correlation between endoscopic activity and TREM-1 mRNA expression (A), endoscopic activity and sTREM-1 (B), endoscopic activity and CRP (C), and endoscopic activity and ESR level. (D) The correlations between variables were assessed using Spearman's rank correlation coefficient.

nocyte/macrophages, has been identified upregulated in various inflammatory conditions [10]. TREM-1 can be secreted as soluble form (sTREM-1), and sTREM-1 has been utilized as indicative of microbial infections [11]. Interestingly, it has been suggested that TREM-1 is involved in the pathogenesis of IBD, as TREM-1 expression in the intestine was upregulated and correlated with disease activity in a mouse model of colitis and in patients with IBD [12]. However, it still remains controversial whether TREM-1 could be used as a biomarker for assessing disease activity in patients with UC. One group from Switzerland reported that serum sTREM-1 levels were weakly correlated with disease activity in patients with UC [13], while other studies from South Korea and Greece showed that serum sTREM-1 levels were highly correlated with disease activity in patients with UC [14, 15]. Given that different genetic or environmental factors may influence the epidemiology and clinical characteristics of UC among different racial groups, it is important to evaluate the potential of TREM-1 as a biomarker for monitor disease activity in Chinese patients with UC.

Materials and methods

Subjects and specimen collection

A total of 76 patients with UC and 20 healthy controls (HC) were enrolled prospectively in the study. All patients were diagnosed and managed at the Department of Gastroenterology, Peking Union Medical College Hospital (PUMCH) between March 2008 and February 2009. All subjects are unrelated. All UC diagnoses were confirmed by established international criteria based on clinical, endoscopic, histological and radiological findings. Individuals with malignancy, infectious or ischemic colitis, liver cirrhosis and other localized or systemic infection were excluded. Healthy subjects without any signs of infection or inflammation or other significant illnesses were considered as control. The Ethical Committee of PUMCH approved this study and informed consent was obtained from all participants.

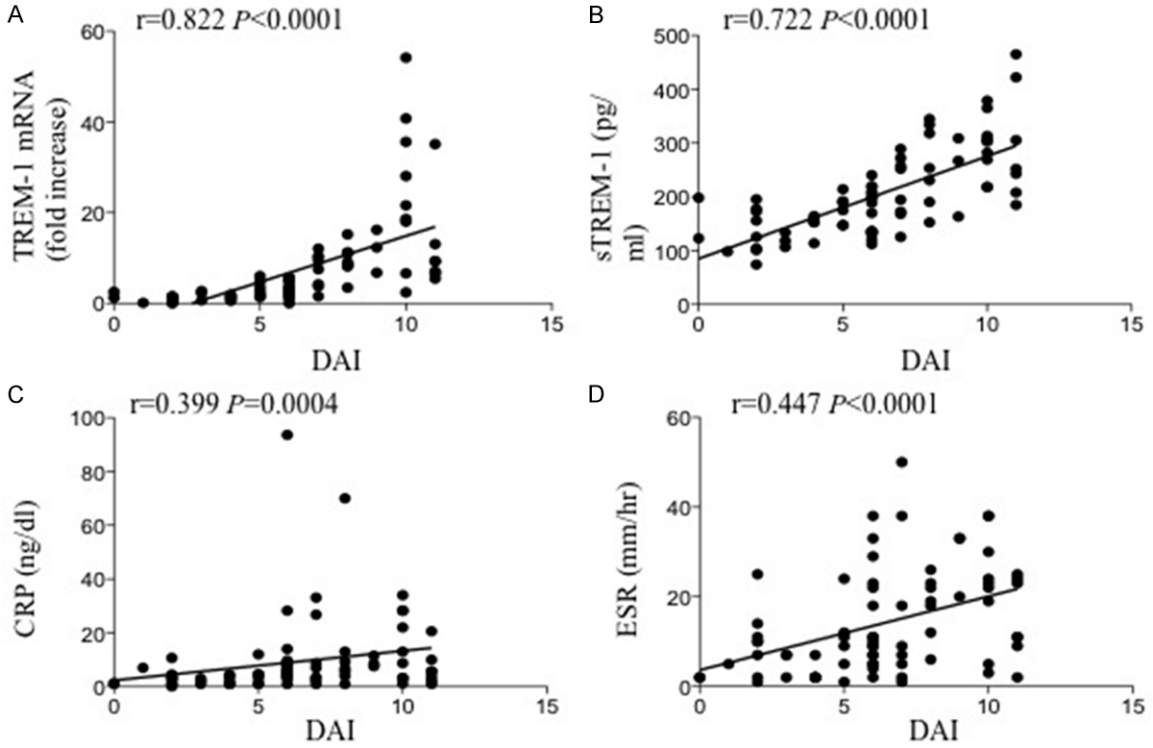

Figure 3. Correlations between various biological markers and the DAI score. Correlation between DAI and TREM-1 mRNA expression (A), DAI and sTREM-1 (B), DAI and CRP (C), and DAI and ESR level. (D) The correlations between variables were assessed using Spearman's rank correlation coefficient. DAI, disease activity index for Ulcerative Colitis.

Disease activity determination

Disease activity was assessed according to Mayo Score/disease active index (DAI), which included number of bowel movements per day, the presence or absence of blood, endoscopy scoring, and physician's global assessment [16]. The endoscopic findings for UC were grouped as follows: quiescent, mild disease (erythema, decreased vascular pattern, mild friability), moderate disease (marked erythema, lack of vascular pattern, friability, erosions), or severe disease (spontaneous bleeding, ulceration). For each patient, the clinical severity of UC was scored at the time of colonoscopy by a single gastroenterologist unaware of the endoscopic results and biological makers.

RNA isolation

Heparinized venous blood sample (3 ml) was obtained from individual subject. The peripheral blood mononuclear cells (PBMCs) were isolated within 2 hours post collection, then suspended in Trizol (Invetrogen, USA) and stored at -80°C. RNA was isolated using the Qiagen RNeasy Mini kit (Qiagen Germany) and following the manufacturers' instructions.

Quantitative RT-PCR for TREM-1 mRNA

cDNA was generated with PrimeScript™ RT-PCR Kit (Takara, Japan) from the extracted RNA (10 μg). Expression of TREM-1 mRNA was analyzed on a Light Cycler 2.0 Real-time PCR System (Roche Diagnostics, Switzerland) using SYBR® Premix Ex Taq™ (Takara, Japan). The housekeeping gene β-actin was used for normalization of TREM-1 mRNA expression. The primers utilized were as follows. For Trem-1 (221 bp): sense primer 5'-CTTGGTGGTGACCAAGGGTTTTTC-3' and antisense primer 5'-ACACCGGAACCCTGATGATATCTGTC-3'. For β-actin (123 bp): sense primer 5'-TGTACGCCAACACAGTGCTG-3' and antisense primer 5'-TCAGGAGGAGCAATGATCTTG-3'. The copy number was calculated from cycle threshold values using the $2^{-\Delta\Delta Ct}$ values of healthy subjects as 1.

Determination of sTREM-1 and other biomarkers in the sera

Serum sTREM-1 was measured with Human TREM-1 Quantikine ELISA Kit (R&D systems, USA) according to the manufacturer's protocol. The levels of serum C-reactive protein (CRP) were assessed by a nephelometric method

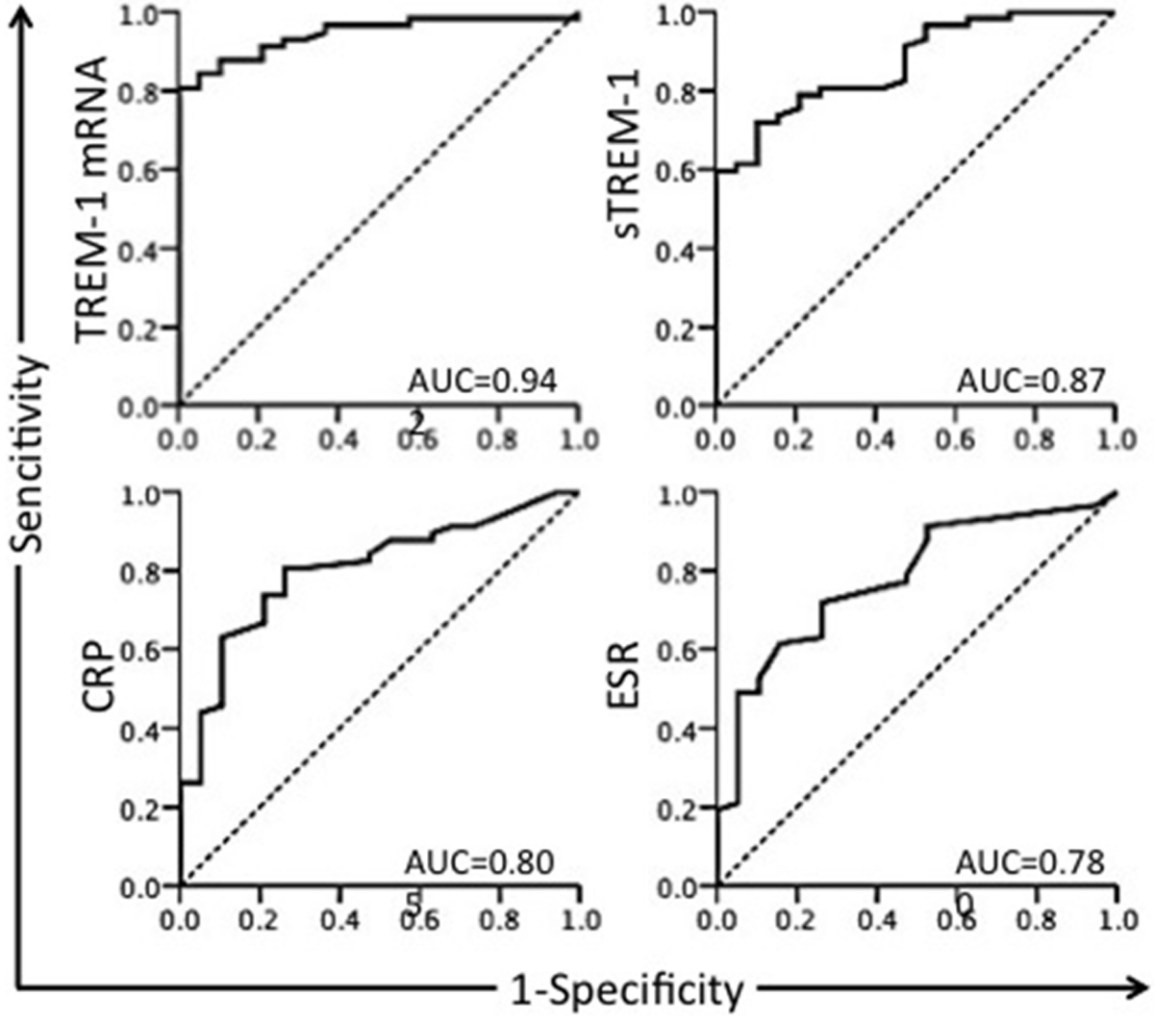

Figure 4. ROC curves for various biological markers to differentiate UC patients with active and quiescent disease. AUC, area under the curve.

(Beckman Coulter, USA). The erythrocyte sedimentation rate (ESR) and the contents of blood plasma hemoglobin (Hb) were determined by Westergren method (Greiner, Austria) and measured by an automated hematology analyzer XE-5000 (Sysmex, Japan), respectively.

Statistical analysis

Statistical analysis was performed with GraphPad Prism software version 5.0c. Results are expressed as means ± standard deviation (SD). Continuous variables were compared using either the independent t-test or Mann-Whitney U test and categorical variables were compared with a chi-square test or Fisher's exact test. The correlation between variables was evaluated with Spearman's rank of order. Serial receiver operating characteristic (ROC) curves (± 95% confidence interval [CI]) were used to calculate the area under the ROC (AUC) and define optimal cutoff values of sTREM-1 according to endoscopic severity grade. $P < 0.05$ was considered as significant.

Results

Clinical characteristics

Clinical characteristics and laboratory findings of patients with UC and healthy controls are shown in **Table 1**. No significant differences within the groups regarding demographic properties such as age, sex, duration, smoking and alcohol usage were identified. Of the 76 UC patients, 19 (25%) patients exhibited quiescent

Table 2. Cutoff values of sTREM-1 according to endoscopic severity grade

Endoscopic findings	Cutoff (pg/ml)	AUC of ROC Curve	Confidential Interval	Sensitivity	Specificity
Quiescent					
	183.2	0.761	0.617-0.904	52.2%	89.5%
Mild					
	225.5	0.768	0.612-0.924	61.1%	97.5%
Moderate					
	296.5	0.682	0.503-0.862	50%	77.8%
Severe					

sTREM-1, soluble triggering receptor expressed on myeloid cells-1; AUC, area under the curve; ROC, receiver operating characteristic.

disease activity, 23 (30.3%) exhibited mild activity, 18 (23.7%) exhibited moderate activity, and 16 (21%) exhibited severe disease activity.

TREM-1 mRNA expression in PBMCs and serum sTREM-1 levels in patients with UC and healthy controls

TREM-1 mRNA expression in PBMCs was increased in UC patients with active disease compared to those in patients with quiescent disease or healthy controls ($P < 0.001$) (**Figure 1A**). The levels of serum sTREM-1 in patients with active disease were significantly higher than those in patients with quiescent disease and healthy controls ($P < 0.001$) (**Figure 1B**). In addition, serum sTREM-1 levels were significantly higher in patients with quiescent diseases than in healthy controls (**Figure 1A** and **1B**). In patients with active disease, there was significant correlation between PBMCs TREM-1 mRNA expression and serum sTREM-1 levels ($r = 0.64$ $P < 0.0001$) (**Figure 1C**).

Correlations among various biological markers and endoscopic activity grade as well as disease activity index (DAI)

In patients with UC, all the three serum biomarkers (sTREM-1, ESR and CRP) as well as TREM-1 mRNA levels were significantly correlated with endoscopic activity indexes. TREM-1 mRNA expression had the strongest correlation with endoscopic activity ($r = 0.838$, $P < 0.001$), followed by serum sTREM-1 levels ($r = 0.737$, $P < 0.001$), ESR ($r = 0.442$, $P < 0.001$) and CRP ($r = 0.392$, $P < 0.001$) (**Figure 2**). Correlations between TREM-1 mRNA expression ($r = 0.822$, $P < 0.001$) or serum sTREM-1 level ($r = 0.722$, $P < 0.001$) with disease activity index (DAI) were higher than ESR ($r = 0.447$, $P < 0.001$) or CRP ($r = 0.399$, $P < 0.001$) (**Figure 3**).

Receiver operator characteristic (ROC) curves of various biological markers and the cutoff values of serum sTREM-1 for monitoring disease activity

Receiver operator characteristic (ROC) curves of various biological markers for differentiating between active disease and quiescent disease in patients with UC are shown in **Figure 4**. The area under the ROC (AUC) of TREM-1 mRNA expression (0.94) and serum sTREM-1 levels (0.87) were higher than ESR (0.78) and CRP (0.80), indicating a better performance of TREM-1 mRNA expression and serum sTREM-1 levels in identifying active versus quiescent disease in patients with UC. The cutoff values of serum sTREM-1 level were determined by ROC curves for differentiating among the quiescent, mild, moderate, and severe disease activities. The optimal cutoff values of serum sTREM-1 level for differentiating between the quiescent and mild, mild and moderate, and moderate and severe disease activity were 183.2, 225.5, and 296.5, respectively (**Table 2**).

Discussion

In this study, we showed that the levels of TREM-1 in PBMCs as well as the levels of serum sTREM-1 correlated with disease activity in Chinese patients with UC, indicating the potential role of TREM-1 as a biomarker for monitoring disease activity in UC.

TREM-1 was first identified as a critical pro-inflammatory mediator in sepsis by amplification of inflammation [10]. The levels of sTREM-1 in the serum have appeared to be a valuable marker for early diagnosis of sepsis [11]. Recently, elevated levels of sTREM-1 have been reported in autoimmune diseases and inflammatory diseases. In patients with rheumatoid

arthritis (RA), increased levels of sTREM-1 were observed in serum [17] or in synovial fluid [18]. Intervention of TREM-1 pathway ameliorated the disease in collagen-induced arthritis (CIA) model [19]. In addition, serum sTREM-1 levels were found increased in intestinal Behcet's disease, and the level of sTREM-1 correlated with clinical disease activity [20].

The association between TREM-1 and inflammatory bowel disease (IBD) was first described in 2007 by Schenk M, et al [12]. They showed higher levels of TREM-1 positive macrophages in the lamina propria of patients with IBD as well as increased levels of TREM-1 mRNA and protein in the colonic tissue of mouse models of colitis. Furthermore, administration of TREM-1 antagonists had therapeutic effect in established colonic inflammation. More importantly, elevated levels of sTREM-1 were identified in the serum of patients with IBD [13-15]. Consistent with these studies, we found greatly enhanced levels of TREM-1 mRNA in the PBMCs and sTREM-1 in the serum in patients with UC compared to healthy controls. Moreover, we observed significantly elevated levels of TREM-1 mRNA and sTREM-1 in UC patients with active disease compared with UC patients with quiescent disease. Taken together, these findings reveal a critical role for TREM-1 in the pathogenesis of UC, and indicate targeting TREM-1 could bring therapeutic beneficial for patients suffering from UC.

More importantly, we found a strong correlation between serum sTREM-1 levels and disease activity in patients with UC. The correlation between serum sTREM-1 levels and disease activity was higher than the correlations between CRP and disease activity (0.737 vs. 0.392) or ESR and disease activity (0.737 vs. 0.442). Currently, it remains controversial whether serum sTREM-1 should be used as a marker for monitoring disease activity. Studies from Switzerland showed that levels of sTREM-1 was significantly increased in UC patients with active disease compared to UC patients with quiescent disease, but this increase was not observed in CD patients with active disease compared to CD patients with quiescent disease. Interestingly, they did not find significant correlation between intestinal TREM-1 mRNA expression and serum sTREM-1 levels in either UC patients or CD patients, suggesting that serum sTREM-1 may not be an accurate marker for disease activity in IBD patients [13]. In contrast, studies from South Korea showed that sTREM-1 was highly correlated with disease activity in IBD patients, especially in UC patients [14]. In that study, the correlation coefficient between serum sTREM-1 level in UC patients and disease activity is 0.849, which is similar to that in our study ($r = 0.737$). In addition, data from Greece, another European Country, also reported significant correlation between sTREM-1 and endoscopic activity indexes of UC ($p = 0.009$) [15]. Furthermore, they found strong correlation between serum sTREM-1 levels and TNF-α levels [15]. As different genetic, immunologic, and environmental factors are implicated in the pathogenesis of UC, the discrepancy between the findings from Europe and Asia could be explained by the differences of these factors. For example, the genetic risk factor in IBD, NOD2/CARD15 mutations, is much less common in Asian IBD patients compared to those of Caucasians, resulting in less CD prevalence [2-4].

In summary, our data demonstrated significant increase of TREM-1 expression in PBMCs as well as the serum levels of sTREM-1 in Chinese patients with UC. More importantly, our findings suggested sTREM-1 could be used as a potential biomarker for monitoring disease activity in Chinese patients with UC.

Acknowledgements

This work was supported in part by the grants from the National Natural Science Foundation of China (30471617, 30640084, 30872331, 81072486, 81172857, 81302592 and 813-73188), National Science Technology Pillar Program in the Eleventh Five-year Plan (No. 2008BAI59B02, 2008BAI59B03), and the Shanxi Scholarship council of China (No. 2014-079).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yongzhe Li, Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Key Laboratory of Rheumatology and Clinical Immunology, Ministry of Education, No.

1 Shuai Fu Yuan, Eastern District, Beijing 100730, People's Republic of China, E-mail: yongzhelipumch@126.com; Dr. Jiaming Qian, Department of Gastroenterology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, No. 1 Shuai Fu Yuan, Eastern District, Beijing 100730, People's Republic of China. E-mail: qjiaming1957@aliyun.com

References

[1] Abraham C, Cho JH. Inflammatory bowel disease. N Engl J Med 2009; 361: 2066-2078.

[2] Fakhoury M, Negrulj R, Mooranian A, Al-Salami H. Inflammatory bowel disease: clinical aspects and treatments. J Inflamm Res 2014; 7: 113-120.

[3] Thia KT, Loftus EV Jr, Sandborn WJ, Yang SK. An update on the epidemiology of inflammatory bowel disease in Asia. Am J Gastroenterol 2008; 103: 3167-3182.

[4] Ng SC, Tang W, Ching JY, Wong M, Chow CM, Hui AJ, Wong TC, Leung VK, Tsang SW, Yu HH, Li MF, Ng KK, Kamm MA, Studd C, Bell S, Leong R, de Silva HJ, Kasturiratne A, Mufeena MN, Ling KL, Ooi CJ, Tan PS, Ong D, Goh KL, Hilmi I, Pisespongsa P, Manatsathit S, Rerknimitr R, Aniwan S, Wang YF, Ouyang Q, Zeng Z, Zhu Z, Chen MH, Hu PJ, Wu K, Wang X, Simadibrata M, Abdullah M, Wu JC, Sung JJ, Chan FK; Asia-Pacific Crohn's and Colitis Epidemiologic Study (ACCESS) Study Group. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-pacific Crohn's and colitis epidemiology study. Gastroenterology 2013; 145: 158-165.

[5] Nielsen OH, Vainer B, Madsen SM, Seidelin JB, Heegaard NH. Established and emerging biological activity markers of inflammatory bowel disease. Am J Gastroenterol 2000; 95: 359-367.

[6] Vilela EG, Torres HO, Martins FP, Ferrari Mde L, Andrade MM, Cunha AS. Evaluation of inflammatory activity in Crohn's disease and ulcerative colitis. World J Gastroenterol 2012; 18: 872-81.

[7] Saverymuttu SH, Hodgson HJ, Chadwick VS, Pepys MB. Differing acute phase responses in Crohn's disease and ulcerative colitis. Gut 1986; 27: 809-813.

[8] Lewis JD. The utility of biomarkers in the diagnosis and therapy of inflammatory bowel disease. Gastroenterology 2011; 140: 1817-1826.

[9] Vermeire S, Van Assche G, Rutgeerts P. Laboratory markers in IBD: useful, magic, or unnecessary toys? Gut 2006; 55: 426-431.

[10] Bouchon A, Facchetti F, Weigand MA, Colonna M. TREM-1 amplifies inflammation and is a crucial mediator of septic shock. Nature 2001; 410: 1103-1107.

[11] Gibot S, Kolopp-Sarda MN, Béné MC, Cravoisy A, Levy B, Faure GC, Bollaert PE. Plasma level of a triggering receptor expressed on myeloid cells-1: its diagnostic accuracy in patients with suspected sepsis. Ann Intern Med 2004; 141: 9-15.

[12] Schenk M, Bouchon A, Seibold F, Mueller C. TREM-1-expressing intestinal macrophages crucially amplify chronic inflammation in experimental colitis and inflammatory bowel diseases. J Clin Invest 2007; 117: 3097-3106.

[13] Saurer L, Rihs S, Birrer M, Saxer-Seculic N, Radsak M, Mueller C; Swiss IBD Cohort Study. Elevated levels of serum-soluble triggering receptor expressed on myeloid cells-1 in patients with IBD do not correlate with intestinal TREM-1 mRNA expression and endoscopic disease activity. J Crohns Colitis 2012; 6: 913-923.

[14] Park JJ, Cheon JH, Kim BY, Kim DH, Kim ES, Kim TI, Lee KR, Kim WH. Correlation of serum-soluble triggering receptor expressed on myeloid cells-1 with clinical disease activity in inflammatory bowel disease. Dig Dis Sci 2009; 54: 1525-1531.

[15] Tzivras M, Koussoulas V, Giamarellos-Bourboulis EJ, Tzivras D, Tsaganos T, Koutoukas P, Giamarellou H, Archimandritis A. Role of soluble triggering receptor expressed on myeloid cells in inflammatory bowel disease. World J Gastroenterol 2006; 12: 3416-3419.

[16] Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005; 353: 2462-2476.

[17] Kuai J, Gregory B, Hill A, Pittman DD, Feldman JL, Brown T, Carito B, O'Toole M, Ramsey R, Adolfsson O, Shields KM, Dower K, Hall JP, Kurdi Y, Beech JT, Nanchahal J, Feldmann M, Foxwell BM, Brennan FM, Winkler DG, Lin LL. TREM-1 expression is increased in the synovium of rheumatoid arthritis patients and induces the expression of pro-inflammatory cytokines. Rheumatology (Oxford) 2009; 48: 1352-1358.

[18] Collins CE, La DT, Yang HT, Massin F, Gibot S, Faure G, Stohl W. Elevated synovial expression of triggering receptor expressed on myeloid cells 1 in patients with septic arthritis or rheumatoid arthritis. Ann Rheum Dis 2009; 68: 1768-1774.

[19] Murakami Y, Akahoshi T, Aoki N, Toyomoto M, Miyasaka N, Kohsaka H. Intervention of an in-

flammation amplifier, triggering receptor expressed on myeloid cells 1, for treatment of autoimmune arthritis. Arthritis Rheum 2009; 60: 1615-1623.

[20] Jung YS, Kim SW, Yoon JY, Lee JH, Jeon SM, Hong SP, Kim TI, Kim WH, Cheon JH. Expression of a soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) correlates with clinical disease activity in intestinal Behcet's disease. Inflamm Bowel Dis 2011; 17: 2130-2137.