European Review for Medical and Pharmacological Sciences 2021; 25: 1242-1249

TIPE2 and PCNP expression abnormalities in peripheral blood mononuclear cells associated with disease activity in rheumatoid arthritis: a meta-analysis

Z.-P. HAN[1], Y. YANG[1], H.-Y. CHEN[1], M.-Y. ZHONG[1], G.-H. ZHUANG[1,2]

[1]Cancer Research Center, School of Medicine, Xiamen University, Xiamen, Fujian, China
[2]Organ Transplantation Institute of Xiamen University, Fujian Provincial Key Laboratory of Organ and Tissue Regeneration, School of Medicine, Xiamen University, Xiamen, Fujian, China

Zhaopu Han and Yan Yang contributed equally to this work

Abstract. – OBJECTIVE: Rheumatoid arthritis (RA) is a prevalent chronic autoimmune disease posing a considerable burden on both individuals and society. Tumor necrosis induced protein 8-like 2 (TIPE2), closely related to PEST-containing nuclear protein (PCNP) expression, is an immune-related protein potentially involved in the pathogenesis of autoimmune diseases. In this study, we aimed to assess differential expressions of TIPE2 and PCNP in peripheral blood mononuclear cells (PBMCs) between active and inactive RA patients.

MATERIALS AND METHODS: Relevant studies were selected from Medline, Google Scholar, Web of Science, and China National Knowledge Infrastructure (CNKI). Only observational studies (irrespective of publication status, language, or blinding), which compared patients in high disease activity, irrespective of the sample size, with patients in low disease activity of RA were evaluated.

RESULTS: Four studies were included with 248 patients, 138 in the active group and 110 in the inactive group. Three studies provided data on TIPE2 expression levels, where 106 patients were divided into the active group and 88 patients were divided into the inactive group. The pooled analysis revealed a statistically significant difference between the two groups (WMD: 5.60; 95% CI: 5.02-6.18). Two studies provided data on PCNP expression levels, where 64 patients were divided into the active group and 44 patients were divided into the inactive group. The pooled analysis revealed a statistically significant difference between the two groups (WMD: 7.76; 95% CI: 3.09-12.43).

CONCLUSIONS: The expression levels of TIPE2 and PCNP are significantly increased in PBMCs of active RA patients.

Key Words:
Rheumatoid arthritis, TIPE2, PCNP, PBMCs, Meta-analysis.

Abbreviations

RA: Rheumatoid arthritis; TIPE2: Tumor necrosis induced protein 8-like 2; PCNP: PEST-containing nuclear protein.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by joint swelling and synovial joint destruction[1]. Through inflammatory damage of synovial tissue, it can lead to progressive destruction of cartilage and bone in peripheral joints and even severe disabilities. A variety of cytokines, inflammatory factors and autoantibodies like rheumatoid factor (RF) have been shown to be linked with the pathogenesis of RA, but the precise molecular mechanisms remain unknown[2]. Therefore, it is of great practical significance for RA to continuously identify potential molecular factors, summarize the most current evidence of the pathogenesis, and develop novel therapeutic targets.

Tumor necrosis induced protein 8-like 2 (TIPE2) is an intracellular molecule discovered in 2002[3]. As a member of TIPE family, it has been found to play an essential role in the maintenance of immune homeostasis[4]. Specifically, TIPE2 serves as a negative regulator of macrophages and T cells via regulating the expression

Corresponding Authors: Guohong Zhuang, MD; e-mail: zhgh@xmu.edu.cn
Zhaopu Han; e-mail: xmu_zghzp@126.com

and function of toll-like receptor (TLR) and T cell receptor (TCR)[5]. Furthermore, TIPE2 has been confirmed to inhibit the mitogen-activated protein kinase (MAPK) and nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) signaling pathways, which are implicated in the pathogenesis of many autoimmune diseases like RA and systemic lupus erythematosus (SLE)[6,7]. PEST-containing nuclear protein (PCNP) is a protein mainly located in the nucleus. Shi-Bai et al[8] showed a positive correlation between TIPE2 and PCNP expression, which suggests the reference value of PCNP in assessing TIPE2-related diseases.

As an autoimmune disease, RA has been reported to be associated with the aberrant expression of TIPE2. Although there have been some researches about abnormalities of TIPE2 expression in joint effusion or fibroblast-like synoviocytes (FLSs) of patients with RA[9-11], studies on TIPE2 in peripheral blood mononuclear cells (PBMCs) are rare. There is no evidence-based medicine (EBM) study to evaluate the available clinical information. Given the potential position of TIPE2 in the pathogenesis of RA[9,12], it will be of interest to review current studies in this field and make a convincing conclusion. Moreover, based on the TIPE2-PCNP correlation, to identify the abnormal expression of PCNP with EBM methods will be a beneficial supplement to TIPE2-related assessment on RA progression.

This review aimed to compare the expression of TIPE2 and PCNP in PBMCs between active and inactive RA patients, and thus to define laboratory abnormalities of new indexes reflecting the disease activity of RA.

Materials and Methods

The inclusion criteria of primary researches met the requirements of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) recommendations[13].

Types of Studies

Observational studies (irrespective of publication status, language, or blinding), which compared patients in high disease activity, irrespective of the sample size, with patients in low disease activity of RA were evaluated. Any other type of comparative study (experimental studies, cohort studies, or case-control studies), as well as case reports were excluded.

Types of Outcome Measures

The primary outcome of selected researches was the sample mean and standard deviation of TIPE2 expression levels. The secondary outcome was the sample mean and standard deviation of PCNP expression levels.

Literature Search

We conducted an electronic search in Medline, Google Scholar, Web of Science, and China National Knowledge Infrastructure (CNKI), using the following combination of keywords (MeSH and not MeSH medical terms): "rheumatoid arthritis" AND "TIPE2" AND "peripheral blood mononuclear cell". The strings retrieved in PubMed were ("rheumatoid arthritis"[All Fields] OR "RA"[All Fields] OR "Arthritis, Rheumatoid"[Mesh Terms]) AND ("TIPE2"[All Fields] OR "TNFAIP8L2"[All Fields] OR "Tumor necrosis induced protein 8-like 2[All Fields]" OR "TIPE2 protein, human" [Supplementary Concept]) AND ("peripheral blood mononuclear cell"[All Fields] OR "PBMC"[All Fields] OR "peripheral blood lymphocytes"[All Fields]), between 1966 and present time. All studies listed as references and similar articles beneath the directly searched researches on retrieval platforms were scrutinized to extend the range of searching. No language or date restrictions were imposed. To recognize additional eligible researches, we also performed a search on identified relevant books.

Data Extraction

All data were independently extracted from the selected studies by three reviewers (ZPH, YY, and HYC), after which a fourth author (GHZ) would check the accuracy of data. The collected information included: authors, study design, publication year, definition of outcomes, and laboratory values (sample size, mean and standard deviation). The disease activity of RA was defined in conformity with DAS28 score[14]. Patients in high disease activity (DAS28>3.2) were divided into the active group, while patients in low disease activity (DAS28≤2.6) were divided into the inactive group.

Assessment of Risk of Bias

The methodology quality of the included studies was independently assessed by two reviewers (MYZ and HYC) in compliance with the Cochrane Collaboration guidelines[15]. A third author (GHZ) was in charge of arbitration if any discrepancies arose.

Statistical Analysis

The quantitative analysis was performed with Review Manager, software Version 5.3 (Cochrane Collaboration). For continuous variables, we calculated the weighted mean difference (WMD) with 95% confidence interval (95% CI). The Inverse Variance method was applied to calculate the weighted summary WMD. In terms of heterogeneity among the primary studies, the I^2 statistic was used to give an assessment. If I^2 was less than 50%, which represented low heterogeneity, the fixed-effects model would be used; otherwise, we would perform an analysis with the random-effects model and investigate the possible sources of high heterogeneity. As for the significance level of outcomes, a *p*-value less than 5% was considered to be significant.

Results

Figure 1 shows the PRISMA flow chart for study identification and selection. In the first place, we obtained 46 records through database searching and 3 records in the reference lists. After removing duplicate records, a total number of 32 articles were identified for initial records screening. Of these, 22 studies were excluded after title and abstract review and 10 remained for full-text examination. Assessing for the final eligibility, two studies were excluded for a lack of group control, and one study was excluded because the classification criterion dividing RA patients was not generally used to match other researches[9,16,17]. Moreover, lacking quantitative data of mean or standard deviation, we excluded three studies unavailable[18-20]. Four studies met the inclusion criteria and were finally included in the pooled analysis[8,21-23].

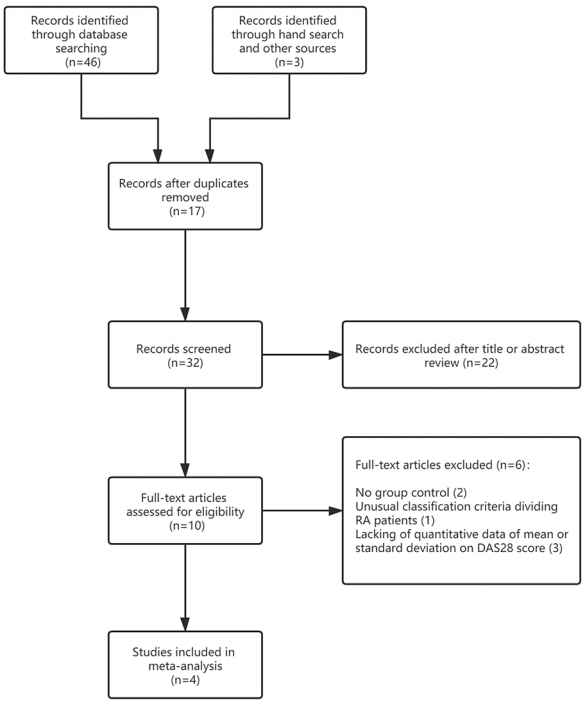

Figure 1. Study flow chart.

Characteristics of the Included Studies

Four included cross-sectional trials have been all published in full. The characteristics of these studies are tabulated in Table I.

Analysis of Data

Three studies with a total sample of 194 confirmed RA patients provided data on TIPE2 expression levels, where 106 patients were divided into the active group and 88 patients were divided into the inactive group. The pooled analysis revealed a statistically significant difference between the two groups (WMD: 5.60; 95% CI: 5.02-6.18; Figure 2). Heterogeneity was not significant (I^2=0%, *p*=0.40).

Two studies with a total sample of 108 confirmed RA patients provided data on TIPE2 expression levels, where 64 patients were divided into the active group and 44 patients were divided into the inactive group. The pooled analysis revealed a statistically significant difference between the two groups (WMD: 7.76; 95% CI: 3.09-12.43; Figure 3). There was heterogeneity between the included studies. Due to the scarcity of other evidence in this field, sub-group and sensitivity analyses were inaccessible. We could only speculate from the raw data that the heterogeneity derived from a few outliers existing in one or both trials, leading to a considerable impact on the weighted summary.

Risk of Bias

The Agency for Healthcare Research and Quality (AHQR) Scale for assessing the risk of bias of cross-sectional studies is shown in Table II[24]. As displayed, all four trials were of moderate quality.

Discussion

RA is a prevalent chronic autoimmune disease associated with pain, joint swelling, and bone damage[25]. With an incidence of 0.5% to 1%, it

Table I. Summary of characteristics of the included studies.

Primary studies	Methods	Participants	Intervention & Control	Outcomes
Shi-Bai et al[8] 2017	Cross-sectional study	38 women & 16 men with RA (average age: 46 ± 10 years); Disease course ranged from 4 to 10 years	Active group (DAS28 > 3.2, n = 32)[a]; Inactive group (DAS28 ≤ 2.6, n = 22)	The expression levels of TIPE2 and PCNP (Mean ± SD): TIPE2: Active group: $2^{-\Delta\Delta C}$t (9.42 ± 3.01)[b], Inactive group: $^{2-\Delta\Delta C}$t (3.62 ± 1.42); PCNP: Active group: $2^{-\Delta\Delta Ct}$ (9.64 ± 2.55), Inactive group: $2^{-\Delta\Delta Ct}$ (4.13 ± 1.59)
Liu et al[21] 2013[a]	Cross-sectional study	38 women & 16 men with RA (average age: 46 ± 9 years); Disease course ranged from 4 to 11 years	Active group (DAS28 > 3.2, n = 32); Inactive group (DAS28 ≤ 2.6, n = 22)	The expression levels of TIPE2 (mean ± SD): Active group: $2^{-\Delta\Delta Ct}$ (8.80 ± 1.80), Inactive group: $2^{-\Delta\Delta Ct}$ (3.62 ± 1.4)
Zhang et al[22] 2018	Cross-sectional study	72 women & 14 men with RA (average age: 48 ± 11.6 years); Disease course ranged from 8 to 82 months	Active group (DAS28 > 3.2, n = 42); Inactive group (DAS28 ≤ 2.6, n = 44)	The expression levels of TIPE2 (mean ± SD): Active group: $2^{-\Delta\Delta Ct}$ (9.46 ± 3.28), Inactive group: $2^{-\Delta\Delta Ct}$ (3.39 ± 0.98)
Liu et al[23] 2013[b]	Cross-sectional study	38 women & 16 men with RA (average age: 46 ± 10 years); Disease course ranged from 4 to 10 years	Active group (DAS28 > 3.2, n = 32); Inactive group (DAS28 ≤ 2.6, n = 22)	The expression levels of PCNP (mean ± SD): Active group: $2^{-\Delta\Delta Ct}$ (14.06 ± 7.01), Inactive group: $2^{-\Delta\Delta Ct}$ (3.78 ± 1.24)

[a]The DAS28 score was calculated according to the 2010 ACR-EULAR classification criteria for rheumatoid arthritis14. [b]Ct, cycle threshold.

has imposed a considerable burden on both individuals and society[26]. Although in recent years, the emergence of new classification criteria, novel treatment strategies, and the conception of early therapy has brought about favorable prospects for many patients, there are still a lot responding inefficiently to current methods[25,27,28]. Therefore, it is very critical and meaningful for RA to explore the pathogenesis and seek novel therapeutic targets.

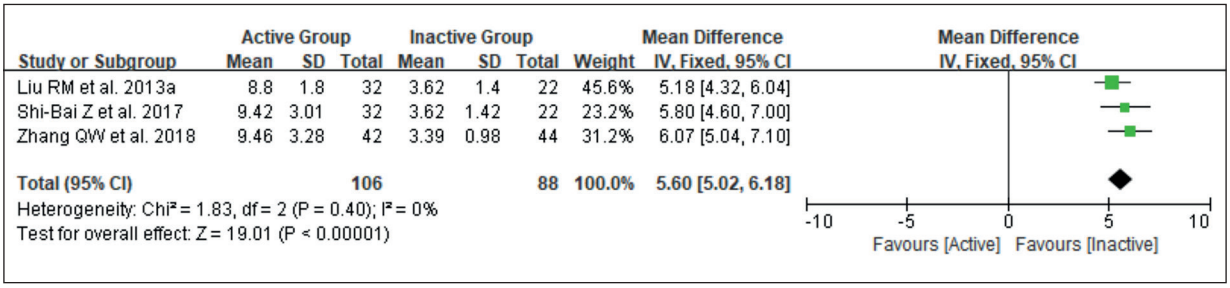

Figure 2. Forest plot analyzing the difference of TIPE2 expression levels in RA patients with different disease activities.

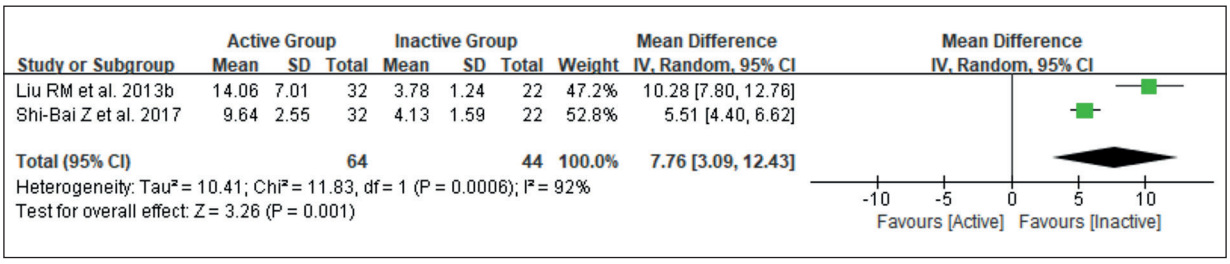

Figure 3. Forest plot analyzing the difference of PCNP expression levels in RA patients with different disease activities.

TIPE2 is an immune-related protein discovered in 2002. It has been known in recent years for the maintenance of immune homeostasis. Li et al[29] have revealed the aberrant expression of TIPE2 in PBMCs of patients with SLE, relative to normal controls. Moreover, Wang et al[30] have confirmed that TIPE2 expression is increased in patients with ulcerative colitis. These studies suggest that TIPE2 expression abnormalities may be implicated in the pathogenesis of autoimmune diseases. Together with the necessity to assess new targets of RA, we decided to summarize available data to analyze the potential role of TIPE2 in RA.

In our pooled analysis, the increase of TIPE2 and PCNP expression in PBMCs could be found in active RA patients. To our knowledge, this study is the first meta-analysis comparing TIPE2 and PCNP expression levels between RA patients with different disease activities.

To explain the result, there is a need to elaborate on the characteristic of TIPE2 in immune homeostasis. When the disease activity of RA increases, many immune cells including PBMC are activated to proliferate and upregulate the expression of many cytokines. Serving as a protective mechanism, we surmised that the expression of TIPE2 can be upregulated to attenuate and limit inflammatory responses through MAPK, NF-κB, and other unknown pathways[6,7]. Furthermore, some researchers have confirmed that TIPE2

Table II. Risk of bias of the included studies (AHQR Scale).

Item	Shi-Bai et al[8] 2017	Liu et al[21] 2013[a]	Zhang et al[22] 2018	Liu et al[23] 2013[b]
1) Define the source of information (survey, record review)	Yes	Yes	Yes	Yes
2) List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications	Yes	Yes	Yes	Yes
3) Indicate time period used for identifying patients	Unclear	Unclear	Unclear	Unclear
4) Indicate whether or not subjects were consecutive if not population-based	Yes	Yes	Yes	Unclear
5) Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants	Unclear	Unclear	Unclear	Unclear
6) Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements)	Yes	Yes	Yes	Yes
7) Explain any patient exclusions from analysis	Unclear	Unclear	Unclear	Unclear
8) Describe how confounding was assessed and/or controlled.	Yes	Unclear	Yes	Unclear
9) If applicable, explain how missing data were handled in the analysis	Unclear	Unclear	Unclear	Unclear
10) Summarize patient response rates and completeness of data collection	Yes	Yes	Yes	Yes
11) Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained	Unclear	Unclear	Unclear	Unclear

overexpression can enhance both the intrinsic and extrinsic apoptosis in fibroblast-like synoviocytes of Adjuvant Arthritis Model, which supports the hypothetical mechanism underlying the results[9,12,31]. Being reported to relate to cell-cycle regulation and the ubiquitination pathway of protein degradation, the overexpression of PCNP may participate in the proliferation and apoptosis of inflammatory cells[29,32].

However, some limitations of our study should be noted. First, the number of included studies is relatively small. This may be explained by the fact that both TIPE2 and PCNP are newly discovered proteins related to RA, thus have not received enough attention by investigators. Another explanation can be a lack of uniform criteria to evaluate the disease activity of RA and record the expression levels of molecules, which directly contributes to the difficulty in summarizing enough homogeneous trials. During the full-text screening, we excluded one trial setting an abnormal critical value (DAS= 2.6) to divide RA patients, which was not in conformity with the 2010 ACR-EULAR classification criteria[14,16]. We also found a few articles where Δ Ct, $2^{-\Delta Ct}$, or some other relevant variables rather than $2^{-\Delta\Delta Ct}$, the appropriate marker, were applied to evaluate the expression levels of target proteins[19,20]. Since we failed to get in touch with the authors and could not transform the primary data into the available form, these articles were excluded.

The second limitation is the relatively small group size, which could exaggerate the difference of molecular expression levels between different groups.

Another limitation is that the methodological quality of the included studies is of moderate quality, which caused difficulties for us to assess the risk of bias. As is shown in Figure 2, none of these articles explicitly mentioned whether confounding factors, other than disease activity, would have an impact on grouping patients. The criteria for patients screening and exclusion of selected trials are also ambiguous, thus the possibilities of overestimating or underestimating the difference between the two groups have to be taken into account. Besides, the results of many primary researches are underdeveloped. Of all included studies, only one further explored the correlation between DAS28 score and TIPE2 expression in RA patients, while others were confined to the simple comparisons between groups, lower the availability of data. Based on the limitations mentioned above, we find it advisable to enroll larger populations and establish uniform criteria on disease activity in further studies. Beyond this, a quantitative analysis of the correlation between TIPE2 expression and the activity of RA should be required. Overcoming these limitations, the roles of TIPE2 and PCNP expression abnormalities in PBMCs of RA patients are expected to be elucidated.

Conclusions

Summarily, we have identified that TIPE2 expression is significantly increased in PBMCs of active RA patients, as well as PCNP. That is, RA patients with higher disease activity have higher expression levels of TIPE2 and PCNP.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

This study was supported by National Natural Scientific Foundation of China (No. 81272720), Natural Science Foundation of Fujian Province (Grant No. 2018J01138), the joint research project of Health and Education of Fujian Province (WKJ2016-2-17), and XMU Undergraduate Innovation and Entrepreneurship Training Programs (Grant No. 201810384226).

Authors' Contribution

Zhaopu Han, Yan Yang: study design; Guohong Zhuang, Huiyu Chen, Mengya Zhong, Zhaopu Han, Yan Yang: data extraction or analysis, drawing diagrams, drafting or revising the article, and approval of the manuscript to be submitted.

References

1) Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, Combe B, Costenbader KH, Dougados M, Emery P, Ferraccioli G, Hazes JM, Hobbs K, Huizinga TW, Kavanaugh A, Kay J, Kvien TK, Laing T, Mease P, Ménard HA, Moreland LW, Naden RL, Pincus T, Smolen JS, Stanislawska-Biernat E, Symmons D, Tak PP, Upchurch KS, Vencovský J, Wolfe F, Hawker G. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010; 62: 2569-2581.
2) Goekoop-Ruiterman YP, Huizinga TW. Rheumatoid arthritis: can we achieve true drug-free remission in patients with RA? Nat Rev Rheumatol 2010; 6: 68-70.

3) Strausberg RL, Feingold EA, Grouse LH, Derge JG, Klausner RD, Collins FS, Wagner L, Shenmen CM, Schuler GD, Altschul SF, Zeeberg B, Buetow KH, Schaefer CF, Bhat NK, Hopkins RF, Jordan H, Moore T, Max SI, Wang J, Hsieh F, Diatchenko L, Marusina K, Farmer AA, Rubin GM, Hong L, Stapleton M, Soares MB, Bonaldo MF, Casavant TL, Scheetz TE, Brownstein MJ, Usdin TB, Toshiyuki S, Carninci P, Prange C, Raha SS, Loquellano NA, Peters GJ, Abramson RD, Mullahy SJ, Bosak SA, McEwan PJ, McKernan KJ, Malek JA, Gunaratne PH, Richards S, Worley KC, Hale S, Garcia AM, Gay LJ, Hulyk SW, Villalon DK, Muzny DM, Sodergren EJ, Lu X, Gibbs RA, Fahey J, Helton E, Ketteman M, Madan A, Rodrigues S, Sanchez A, Whiting M, Madan A, Young AC, Shevchenko Y, Bouffard GG, Blakesley RW, Touchman JW, Green ED, Dickson MC, Rodriguez AC, Grimwood J, Schmutz J, Myers RM, Butterfield YS, Krzywinski MI, Skalska U, Smailus DE, Schnerch A, Schein JE, Jones SJ, Marra MA; Mammalian Gene Collection Program Team. Generation and initial analysis of more than 15,000 full-length human and mouse cDNA sequences. Proc Natl Acad Sci U S A 2002; 99: 16899-16903.

4) Bordoloi D, Banik K, Shabnam B, Padmavathi G, Monisha J, Arfuso F, Dharmarajan A, Mao X, Lim LHK, Wang L, Fan L, Hui KM, Kumar AP, Sethi G, Kunnumakkara AB. TIPE family of proteins and its implications in different chronic diseases. Int J Mol Sci 2018; 19(10): 2974.

5) Sun H, Gong S, Carmody RJ, Hilliard A, Li L, Sun J, Kong L, Xu L, Hilliard B, Hu S, Shen H, Yang X, Chen YH. TIPE2, a negative regulator of innate and adaptive immunity that maintains immune homeostasis. Cell 2008; 133: 415-426.

6) Shao Y, Chen H, Lv M, Li C, Zhang, W, Li Y, Zhao X, Bao Y. A novel TNFAIP8 gene mediates l-arginine metabolism in Apostichopus japonicus. Fish Shellfish Immunol 2017; 69: 26–34.

7) Zhang YH, Yan HQ, Wang F, Wang YY, Jiang YN, Wang YN, Gao FG. TIPE2 inhibits TNF-α-induced hepatocellular carcinoma cell metastasis via Erk1/2 downregulation and NF-κB activation. Int J Oncol 2015; 46: 254-264.

8) Shi-Bai Z, Rui-Min L, Ying-Chuan S, Jie Z, Chao J, Can-Hua Y, Xi C, Wen-Wei Q. TIPE2 expression is increased in peripheral blood mononuclear cells from patients with rheumatoid arthritis. Oncotarget 2017; 8: 87472-87479.

9) Shi C, Zhang S, Hong S, Pang J, Yesibulati Y, Yin P, Zhuang G. The pro-apoptotic effects of TIPE2 on AA rat fibroblast-like synoviocytes via regulation of the DR5-caspase-NF-κB pathway in vitro. Onco Targets Ther 2016; 9: 993-1000.

10) Bottini N, Firestein GS. Duality of fibroblast-like synoviocytes in RA: passive responders and imprinted aggressors. Nat Rev Rheumatol 2013; 9: 24-33.

11) Nakano K, Boyle D, Firestein GS. Regulation of DNA methylation in rheumatoid arthritis synoviocytes. J Immunol 2013; 190: 1297-1303.

12) Shi C, Wang Y, Zhuang G, Qi Z, Li Y, Yin P. Tumor necrosis factor α induced protein 8 like 2 regulates lipopolysaccharide induced rat rheumatoid arthritis immune responses and is associated with Rac activation and interferon regulatory factor 3 phosphorylation. Mol Med Rep 2017; 16: 6346-6353.

13) Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009; 151: W65-W94.

14) Villeneuve E, Nam J, Emery P. 2010 ACR-EULAR classification criteria for rheumatoid arthritis. Rev Bras Reumatol 2010; 50: 481-483.

15) Higgins JPT, Green S. Cochrane handbook for Systematic Reviews of Interventions, version 5.1.0. 2011. The Cochrane Collaboration, 2011.

16) Shi GS, Wu XF, Wang F, Shi XF. Expression of TIPE2 in rheumatoid arthritis patient and its effect on NF-κB signal pathway. China J Modern Med 2014; 24: 34-37.

17) Feng XN, Jiang ZY. Expression and clinical significance of lymphotoxin β receptor, TIPE2 and soluble PD-1 in patients with rheumatoid arthritis. Chin J Immun 2019; 35: 1876-1879.

18) Zhang D. Expression and clinical significance of TIPE2 in peripheral blood mononuclear cell of rheumatoid arthritis patient. Jinan: Shandong Univ, 2011.

19) Sun YC. Expression and significance of TIPE2 and PCNP in rheumatoid arthritis. Kaifeng: Henan Univ, 2012.

20) Zhou JC, Chen P, Li Z, Zuo Q. Gene delivery of TIPE2 attenuates collagen-induced arthritis by modulating inflammation. Int Immunopharmacol 2020; 79: 106044.

21) Liu RM, Sun YC, Zhang AH, Zhu SB, Bai HL. Expression and clinical significance of TIPE2 in rheumatoid arthritis. Chin J Microbiol Immunol 2013; 3: 212-215.

22) Zhang QW. Clinical values of TNF-α in sera and TIPE2 in peripheral blood lymphocytes for rheumatoid arthritis. J Med Res 2018; 47: 165-168.

23) Liu RM, Wang ML, Sun YC, Zhang AH, Zhu SB. Expression and clinical significance of PCNP in rheumatoid arthritis. Chin J Immun 2013; 29: 499-502.

24) Zhang TS, Zhong WZ, Li B. Practical methodology of evidence-based medicine, 2nd. Changsha: Zhongnan University Publishing, 2014.

25) Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet 2016; 388: 2023-2038.

26) Silman AJ, Pearson JE. Epidemiology and genetics of rheumatoid arthritis. Arthritis Res 2002; 4 (Suppl 3): S265-S272.

27) Smolen JS, Aletaha D. Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges. Nat Rev Rheum 2015; 11: 276-289.

28) Stoffer MA, Schoels MM, Smolen JS, Aletaha D, Breedveld FC, Burmester G, Bykerk V, Dougados M, Emery P, Haraoui B, Gomez-Reino J, Kvien TK, Nash P, Navarro-Compán V, Scholte-Voshaar M, van Vollenhoven R, van der Heijde D, Stamm TA. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update. Ann Rheum Dis 2016; 75: 16-22.

29) Li D, Song L, Fan Y, Li X, Li Y, Chen J, Zhu F, Guo C, Shi Y, Zhang L. Down-regulation of TIPE2 mRNA expression in peripheral blood mononuclear cells from patients with systemic lupus erythematosus. Clin Immunol 2009; 133: 422-427.

30) Wang LY, Fan YC, Zhao J, Gao S, Sun FK, Han J, Yang Y, Wang K. Elevated expression of tumor necrosis factor-alpha-induced protein 8 (TNFAIP8)-like 2 mRNA in peripheral blood mononuclear cells is associated with disease progression of acute-on-chronic hepatitis B liver failure. J Viral Hepat 2014; 21: 64-73.

31) Shi C, He Q, Yang JJ, Zhuang GH. Fibroblast-like synoviocytes from adjuvant arthritis rat were transfected with plasmid over-expressed TIPE2 and its related analysis. Chin J Immun 2013; 29: 1240-1243.

32) Mori T, Li Y, Hata H, Ono K, Kochi H. NIRF, a novel RING finger protein, is involved in cell-cycle regulation. Biochem Biophys Res Commun 2002; 296: 530-536.