Received: 21 September 2021 | Revised: 17 October 2021 | Accepted: 31 October 2021

DOI: 10.1002/jcla.24111

RESEARCH ARTICLE

WILEY

Measurement of synovium and serum dual specificity phosphatase 22 level: Their inter-correlation and potency as biomarkers in rheumatoid arthritis

Chen Qian[1] | Jie Chen[2] | Xiaopeng Xu[1] | Qingyang Liu[3] | Minhong Gu[1] | Sheng Lu[1] | Hongxia Bai[1] | Qiubo Wang[3] | Mingyu Xue[4]

[1]Department of Clinical Laboratory, Xishan People's Hospital of Wuxi City, Wuxi, China

[2]Department of Orthopedics, Huashan Hospital, Fudan University, Shanghai, China

[3]Department of Clinical Laboratory, Wuxi 9th People's Hospital, Wuxi 9th Affiliated Hospital of Soochow University, Wuxi, China

[4]Department of Clinical Orthopaedics, Wuxi 9th People's Hospital, Wuxi 9th Affiliated Hospital of Soochow University, Wuxi, China

Correspondence
Mingyu Xue, Department of Clinical Orthopaedics, Wuxi 9th People's Hospital, Wuxi 9th Affiliated Hospital of Soochow University, No. 999 Liangxi Road, Binhu District, Wuxi 214000, China.
Email: xuemingyu1010@sina.com

Qiubo Wang, Department of Clinical Laboratory, Wuxi 9th People's Hospital, Wuxi 9th Affiliated Hospital of Soochow University, No. 999 Liangxi Road, Binhu District, Wuxi 214000, China.
Email: wangqiubo2020@suda.edu.cn

Funding information
Innovation Project (PhD) of Wuxi 9th Affiliated Hospital of Soochow University, Grant/Award Number: YB202101

Abstract

Background: Dual specificity phosphatase 22 (DUSP22), also named as Jun N-terminal kinase pathway associated phosphatase recently, is reported to be closely engaged in immune and inflammation regulation. This study aimed to investigate the interaction between synovium DUSP22 and serum DUSP22 levels and to explore their correlation with rheumatoid arthritis (RA) risk, inflammation, and disease activity.

Methods: Synovium and serum samples from 42 RA patients with knee involvement underwent arthroscopy, and 20 knee trauma patients were collected. Besides, serum samples from 40 healthy controls were also obtained. Synovium DUSP22 expression was detected by reverse transcription quantitative polymerase chain reaction, while serum DUSP22 level was detected by enzyme-linked immunosorbent assay.

Results: Synovium DUSP22 level was greatly decreased in RA patients compared to trauma controls ($p < 0.001$), and it was negatively correlated with tender joint count (TJC) ($r = -0.318$, $p = 0.040$), C-reactive protein (CRP) ($r = -0.330$, $p = 0.033$), and Lysholm score ($r = -0.423$, $p = 0.005$) in RA patients. Serum DUSP22 level was lowest in RA patients, followed by trauma controls, then highest in healthy controls ($p < 0.001$). Serum DUSP22 level was negatively associated with TJC ($r = -0.438$, $p = 0.004$), swollen joint count (SJC) ($r = -0.372$, $p = 0.015$), CRP ($r = -0.391$, $p = 0.011$), and disease activity score in 28 joints ($DAS28_{ESR}$) score ($r = -0.406$, $p = 0.008$), and it increased after treatment ($p = 0.001$) in RA patients. In addition, serum DUSP22 level positively related to synovium DUSP22 level in RA patients ($r = 0.394$, $p = 0.010$).

Conclusion: Synovium and serum DUSP22 are intercorrelated and insufficiently expressed in RA patients; meanwhile, their deficiency correlates with increased systemic inflammation, disease activity, and joint dysfunction.

KEYWORDS
biomarkers, DUSP22, rheumatoid arthritis, serum, synovium

Chen Qian, Jie Chen, and Xiaopeng Xu contributed equally to this work.

1 | INTRODUCTION

Rheumatoid arthritis (RA), as a chronic and autoimmune disease, is featured by increased systematic autoantibody, inflammation, and synovial hyperplasia, which affects many populations especially females.[1,2] Along with the development of biopharmaceutics (such as tumor necrosis factor inhibitor, interleukin-6 inhibitor, and JAK inhibitor) and more standardized management (such as treat-to-target strategy), the outcome of RA is much improved.[3–6] However, there are still a proportion of RA patients lack response to the current treatment, giving rise to the deeper exploration of RA pathology and biomarkers to improve its management.[7]

Dual specificity phosphatase 22 (DUSP22), also named as Jun N-terminal kinase pathway associated phosphatase (JKAP) recently, is reported to be closely engaged in immune and inflammation regulation.[8–14] DUSP22 could represses Lck mediated T-cell receptor (TCR) signaling to regulate immunity, through which it modifies T-cell activation and differentiation in several autoimmune diseases such as systemic lupus erythematosus (SLE) and inflammatory bowel disease (IBD).[8–11] Besides, serum DUSP22 also correlates with systematic inflammation and Th17 cells in critical ill diseases such as sepsis.[12,13] As to RA, serum DUSP22 relates to disease risk and activity, which also links with treatment response in RA patients.[14] However, the previous study only assesses the serum DUSP22 level but not its synovium level, and the correlation of synovium DUSP22 with serum DUSP22 is obscure; furthermore, previous study lacks the set of disease controls.

Therefore, the current study collected synovium tissues and serum samples from RA patients with knee involvement underwent arthroscopy and knee trauma patients, as well as serum samples from healthy controls, then detected DUSP22 expression in both synovium and serum samples, aimed to investigate the interaction between synovium DUSP22 and serum DUSP22 levels, and to explore their correlation with RA risk, inflammation, and disease activity.

2 | METHODS

2.1 | Subjects

Forty-two RA patients with knee involvement underwent arthroscopy between February 2017 and June 2020 were consecutively enrolled in this study. The inclusion criteria were as follows: (1) meeting the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for RA[15]; (2) age over 18 years old; (3) poorly controlled symptomatic knee synovitis after adequate medical treatment; (4) about to undergo arthroscopic synovectomy; (5) agreed with collection of synovium and blood sample for study use. The exclusion criteria were as follows: (1) knee synovitis due to acute trauma or chronic strain of the knee joint; (2) knee osteoarthritis (KOA), rheumatism, or other inflammatory diseases; (3) active infections; (4) history of knee surgery; (5) pregnant or breast-feeding women. In addition to RA patients, during same period, another 20 subjects about to undergo knee surgery due to trauma were included in the study as trauma controls according to a previous study,[16] and they were screened based on the following criteria: (1) trauma of knee requiring surgical treatment; (2) age ≥18 years old; (3) had no history of RA, KOA, rheumatism, inflammatory diseases, or other knee diseases; (4) agreed with collection of synovium and blood sample for study use; (5) not in pregnant or breast-feeding. Besides, 40 healthy subjects were also recruited as healthy controls during health examination, and they were confirmed to be healthy status without history of RA, KOA, rheumatism, inflammatory diseases, or other knee diseases. All subjects singed the informed consents, and the approval was acquired from the Ethics Committee of Wuxi 9th People's Hospital, Wuxi 9th Affiliated Hospital of Soochow University.

2.2 | Data recording

Clinical features of RA patients were recorded after recruitment, including age, gender, body mass index (BMI), disease duration, rheumatoid factor (RF) status, anti-citrullinated protein antibody (ACPA) status, tender joint count (TJC), swollen joint count (SJC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), disease activity score in 28 joints based on ESR ($DAS28_{ESR}$), Lysholm score, and history of treatments (biologics, disease-modifying antirheumatic drugs (DMARDs). Lysholm score is a common score evaluating knee function, which consists of eight items that measure: pain (25 points), instability (25 points), locking (15 points), swelling (10 points), limp (5 points), stair climbing (10 points), squatting (5 points), and need for support (5 points).[17] Every question response has been assigned an arbitrary score on an increasing scale. The total score is the sum of each response to the eight questions and may range from 0 to 100. Higher scores indicate a better outcome with fewer symptoms or disability. In addition, in aspect of trauma controls, their demographics were also collected at enrollment.

2.3 | Sample collection

For RA patients, synovium sample was obtained during arthroscopic synovectomy, and whole blood sample was, respectively, collected before surgery and at 1 month (M1) after surgery when patients came to the hospital for reexamination. In RA patients after surgery recovery, DMARDs treatment is applied to control the general disease of RA apart from knee involvement if appropriate. For trauma controls, the synovium sample was separated and validated from surgically remove trauma tissue according to the method in a previous study,[16] and the whole blood sample was also collected. For healthy controls, the whole sample was collected at the time of health examination. The collected synovium sample of RA patients and trauma controls was processed for determination of DUSP22 level by reverse transcription quantitative polymerase chain reaction (RT-qPCR) assay. The whole blood sample was centrifugalized to isolate serum for determination of DUSP22 level by enzyme-linked immunosorbent assay (ELISA).

2.4 | RT-qPCR assay

TRIzol™ Reagent (Invitrogen) was applied for separation of total RNA from synovium sample; then, the total RNA was reversely transcribed into complementary DNA using QuantiNova Reverse Transcription Kit (Qiagen). Afterward, fluorescent quantitative PCR was performed using QuantiNova SYBR Green PCR Kit (Qiagen), where the thermocycling conditions were set as follows: pre-denaturation at 95°C for 3 min, followed by 40 cycles of denaturation at 95°C for 15 s and annealing/elongation at 61°C for 20 s. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was severed as an internal reference. The DUSP22 level was computed by $2^{-\Delta\Delta Ct}$ method. The primers used in PCR were as follows: DUSP22 forward (5′->3′): GCAAGAACAAGGTGACACATATTC, reverse (5′->3′): GAGATGGTGAATCCGCTGCT; GAPDH forward (5′->3′): TGACCACAGTCCATGCCATCAC, reverse (5′->3′): GCCTGCTTCACCACCTTCTTGA.

2.5 | ELISA

Human DUSP22 ELISA Kit (Shanghai Enzyme-linked Biotechnology Co., Ltd) was applied to determine DUSP22 concentration in serum sample. All reagents and samples were prepared as described in the product instructions, and all experimental procedures were carried out strictly following the experimental protocol recommended by the manufacturer of the kit. Standard curve was run in each assay, which was obtained by curve-fitting, and the concentration of DUSP22 was calculated based on the standard curve.

2.6 | Statistical analysis

Comparison of DUSP22 level among different subjects was analyzed by Kruskal–Wallis H rank sum test and Wilcoxon rank sum test. Multiple comparisons were corrected by Bonferroni method. Comparison of DUSP22 level change from baseline to M1 was analyzed by Wilcoxon signed-rank test. The distinguishing performance of DUSP22 level for different subjects was evaluated by receiver operating characteristic (ROC) curve analysis. Correlation of DUSP22 level with clinical features of RA patients was estimated by Spearman's rank correlation test. SPSS 24.0 (IBM Corp.) and GraphPad Prism 6.01 (GraphPad Software Inc.) were applied for data analysis and graphing. *P* value less than 0.05 was considered statistical significance.

3 | RESULTS

3.1 | Patients' characteristics

The enrolled RA patients included 32 (76.2%) females and 10 (23.8%) males, with a mean age of 58.2 ± 10.8 years. Besides, the disease activity score $DAS28_{ESR}$ was 5.0 ± 0.8, and knee function score Lysholm score was 42.4 ± 8.6. The detailed characteristics of RA patients were exhibited in Table 1. In addition, the age of trauma controls was 29.5 ± 7.2 years, with 30.0% females and 70.0% males, while the age of healthy controls was 56.5 ± 6.5 years, with 77.5% females and 22.5% males.

TABLE 1 Clinical features

Items	RA patients (*N* = 42)
Age (years), mean ± SD	58.2 ± 10.8
Gender, *N* (%)	
Female	10 (23.8)
Male	32 (76.2)
BMI (kg/m^2), mean ± SD	22.9 ± 2.6
Disease duration (years), median (IQR)	7.8 (6.3–9.8)
RF Positive, *N* (%)	
No	10 (23.8)
Yes	32 (76.2)
ACPA Positive, *N* (%)	
No	14 (33.3)
Yes	28 (66.7)
TJC, median (IQR)	6.0 (4.0–9.0)
SJC, median (IQR)	6.0 (3.0–9.0)
ESR (mm/h), median (IQR)	29.1 (21.4–49.6)
CRP (mg/L), median (IQR)	20.1 (9.5–37.0)
$DAS28_{ESR}$ score, mean ± SD	5.0 ± 0.8
Lysholm score, mean ± SD	42.4 ± 8.6
History of DMARDs, *N* (%)	
No	0 (0.0)
Yes	42 (100.0)
History of biologics, *N* (%)	
No	32 (76.2)
Yes	10 (23.8)

Abbreviations: ACPA, anti-cyclic citrullinated peptide antibody; BMI, body mass index; CRP, C-reactive protein; $DAS28_{ESR}$, Disease Activity Score 28-joint ESR; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; IQR, interquartile range; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; SJC, swollen joint count; TJC, tender joint count.

3.2 | DUSP22 level in RA patients, trauma controls, and healthy controls

Synovium DUSP22 level was greatly decreased in RA patients compared to trauma controls ($p < 0.001$) (Figure 1A). Besides, serum DUSP22 level was lowest in RA patients, followed by trauma controls, then highest in healthy controls ($p < 0.001$) (Figure 1B). Subsequent ROC curve analyses discovered that synovium DUSP22 level well distinguished RA patients from trauma controls with AUC of 0.899 (95%CI: 0.820–0.978) (Figure 2A). Furthermore, ROC curve analyses also uncovered that

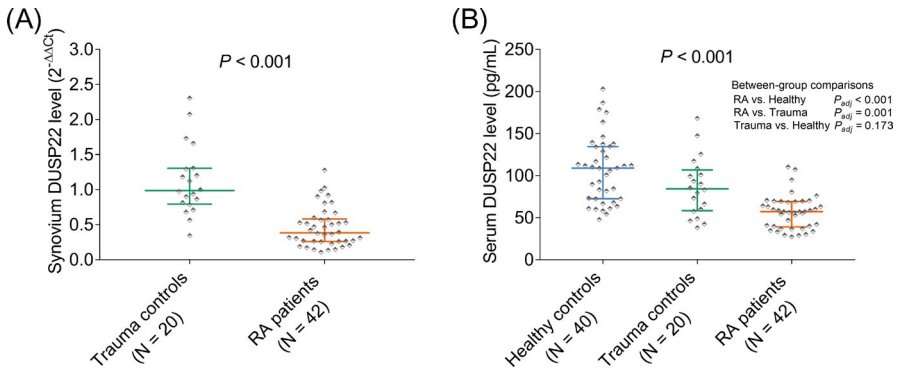

FIGURE 1 DUSP22 expression. Synovium DUSP22 level in RA patients and trauma controls (A). Serum DUSP22 level in RA patients, trauma controls, and healthy controls (B)

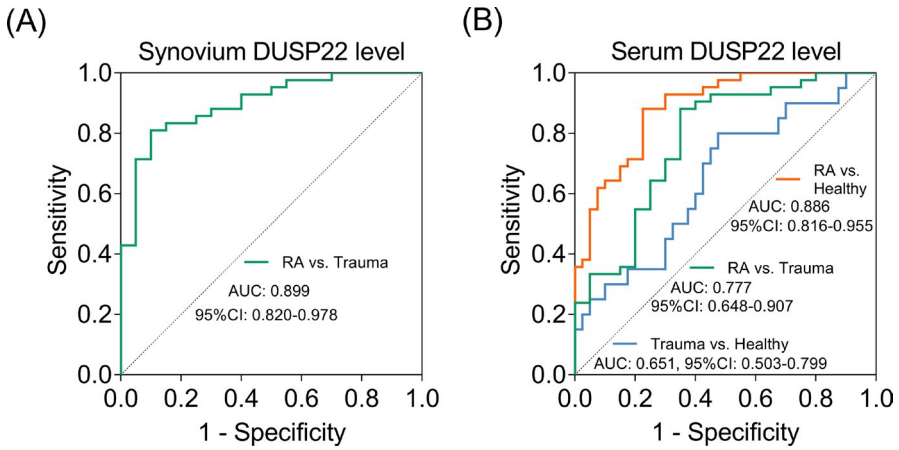

FIGURE 2 ROC curve analyses. ROC curve analyses of synovium DUSP22 level in distinguishing RA patients from trauma controls (A). ROC curve analyses of serum DUSP22 level in distinguishing RA patients, trauma controls, and healthy controls from each other (B)

serum DUSP22 level well differentiated RA patients from healthy controls with AUC of 0.886 (95%CI: 0.816–0.955) and from trauma controls with AUC of 0.777 (95%CI: 0.648–0.907) (Figure 2B).

3.3 | Consistence of DUSP22 level between synovium and serum in RA patients

Whether synovium DUSP22 and serum DUSP22 were intercorrelated was an interesting topic, which was then investigated. It was observed that synovium DUSP22 level positively related to serum DUSP22 level in RA patients ($r = 0.394$, $p = 0.010$) (Figure 3A); however, they were not correlated with each other in trauma controls (Figure 3B).

3.4 | Correlation of DUSP22 level with clinical features in RA patients

Synovium DUSP22 level negatively correlated with TJC ($r = -0.318$, $p = 0.040$), CRP ($r = -0.330$, $p = 0.033$), and Lysholm score ($r = -0.423$, $p = 0.005$), but did not relate to disease duration, SJC, ESR, or $DAS28_{ESR}$ score in RA patients (Figure 4A–G). As to serum DUSP22 level, it was negatively associated with TJC ($r = -0.438$, $p = 0.004$), SJC ($r = -0.372$, $p = 0.015$), CRP ($r = -0.391$, $p = 0.011$), and $DAS28_{ESR}$ score ($r = -0.406$, $p = 0.008$), but did not link with disease duration, ESR, or Lysholm score in RA patients (Figure 5A–G).

3.5 | Variation of serum DUSP22 level after treatment in RA patients

At 1 month postknee arthroscopy surgery, serum DUSP22 level was increased compared to that at baseline ($p = 0.001$) (Figure 6).

4 | DISCUSSION

Dual specificity phosphatase (DUSP) family has attracted great attention in terms of their regulation of immunology, inflammation, or related bioprocess of autoimmune disease including RA.[18–21] For instance, DUSP1 deficiency promotes inflammation and bone destruction in collagen-induced arthritis[18]; besides, DUSP5 represses autoimmune arthritis by regulating Th17/Treg balance and inactivating osteoclastogenesis in mice.[19] In aspect of DUSP22, although no experimental study been reported, two clinical studies revealed that circulating DUSP22 is closely involved in RA risk and progression.[20,21] In our present study, we observed that synovium DUSP22 level was decreased in RA patients compared knee trauma patients; furthermore, serum DUSP22 level was also reduced in RA patients compared to knee trauma patients and healthy controls. The possible explanations were as follows: DUSP22 level reflected the immune aberrance and less inflammatory situation; therefore, it was less expressed in RA patients compared to knee trauma patients and healthy controls.[8–11,22,23] In addition, we also observed

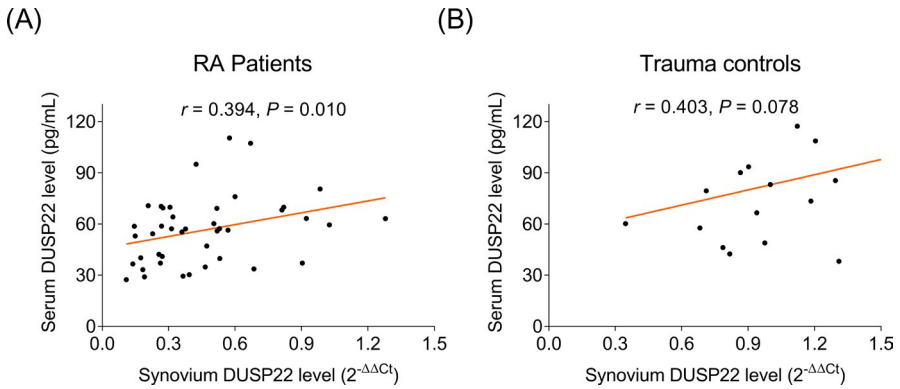

FIGURE 3 Correlation between synovium and serum DUSP22. Correlation between synovium and serum DUSP22 levels in RA patients (A) and trauma controls (B)

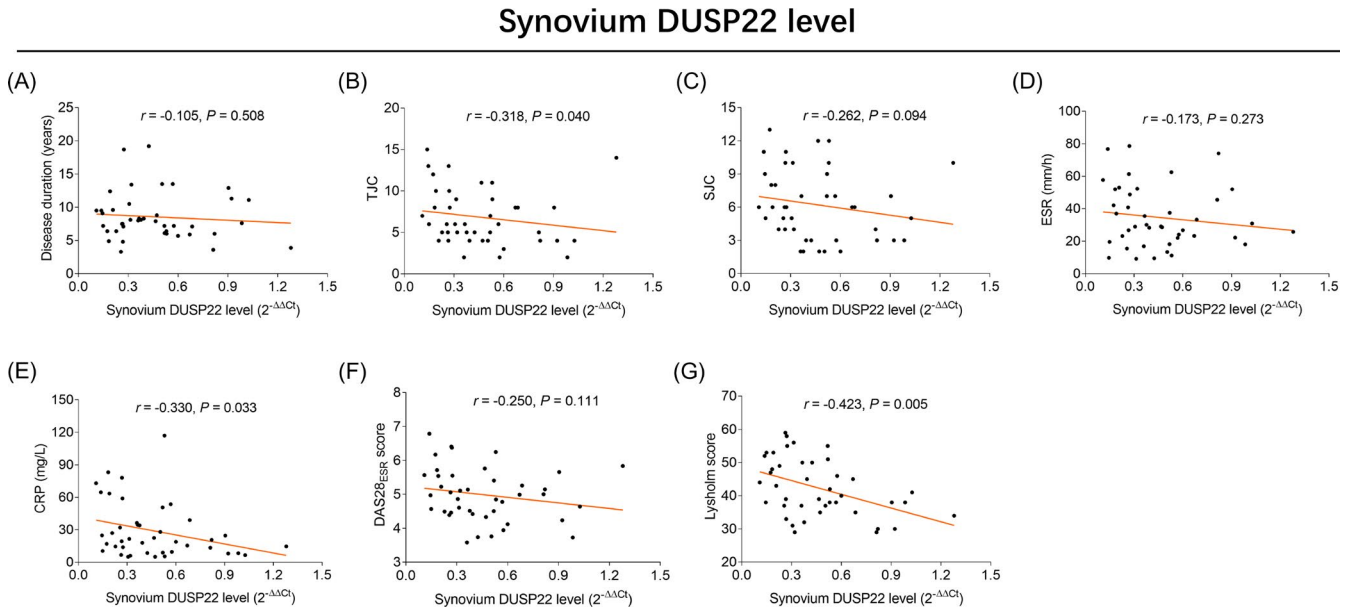

FIGURE 4 Correlation of synovium DUSP22 level with RA disease features. Correlation of synovium DUSP22 level with disease duration (A), TJC (B), SJC (C), ESR (D), CRP (E), $DAS28_{ESR}$ (F), and Lysholm score (G) in RA patients

that serum DUSP22 level was positively related to synovium DUSP22 level, which might result from that DUSP22 was translated from blood T cells into synovium, while this hypothesis needed further validation by experiments. Generally, according to our opinion and related articles, we thought serum DUSP22 mainly originated from blood lymphocytes, then blood DUSP22 infiltrated into synovium via cell-to-cell cross. That was to say, we speculated serum DUSP22 affected synovium DUSP22.

Since DUSP22 is a regulator of T-cell activation and differentiation, the correlation of blood DUSP22 dysregulation with inflammation is identified in several diseases featured by dysregulated immune or inflammation.[12,20,21,24–27] For instance, serum DUSP22 relates to decreased CRP, number of joints with active arthritis, physician's global assessment of disease activity in juvenile idiopathic arthritis patients.[25] In addition, serum DUSP22 correlates with less sever inflammation and disease activity in Crohn disease patients.[27] Furthermore, a previous study also observes that serum DUSP22 level reflects decreased ESR, CRP, and DAS28 score in RA patients[14]; then, another study also reports its hypomethylation relates to disease activity of RA.[28] In our present study, we also observed that serum DUSP22 level negatively correlated with TJC, SJC, CRP, and $DAS28_{ESR}$, which were in line with previous studies. The possible explanation was that (1) DUSP22 suppressed TCR pathway and related autoimmunity via Lck and MAPKs pathways to inhibit RA development and progression, therefore correlated with less disease activity[8,22]; (2) DUSP22 attenuated systemic inflammation via multiple ways (such as TCR pathway, Th17 differentiation, and TNF-α), which then contributed to less synovial hyperplasia and inflammatory infiltration, so correlated with less TJC, SJC, and CRP.

DUSP22 is also reported to suppress cell proliferation via multiple ways such as epidermal growth factor receptor (EGFR) pathway and MAPK pathway.[29,30] Considering RA is featured by both inflammation and synovial hyperplasia, and the involvement of DUSP22 in regulating immunity, inflammation, and proliferation, we hypothesized that synovium DUSP22 also related to the disease properties. Therefore, we then analyzed the correlation of knee synovium DUSP22 level with inflammation, disease activity, and knee function in the enrolled RA patients, then observed that synovium

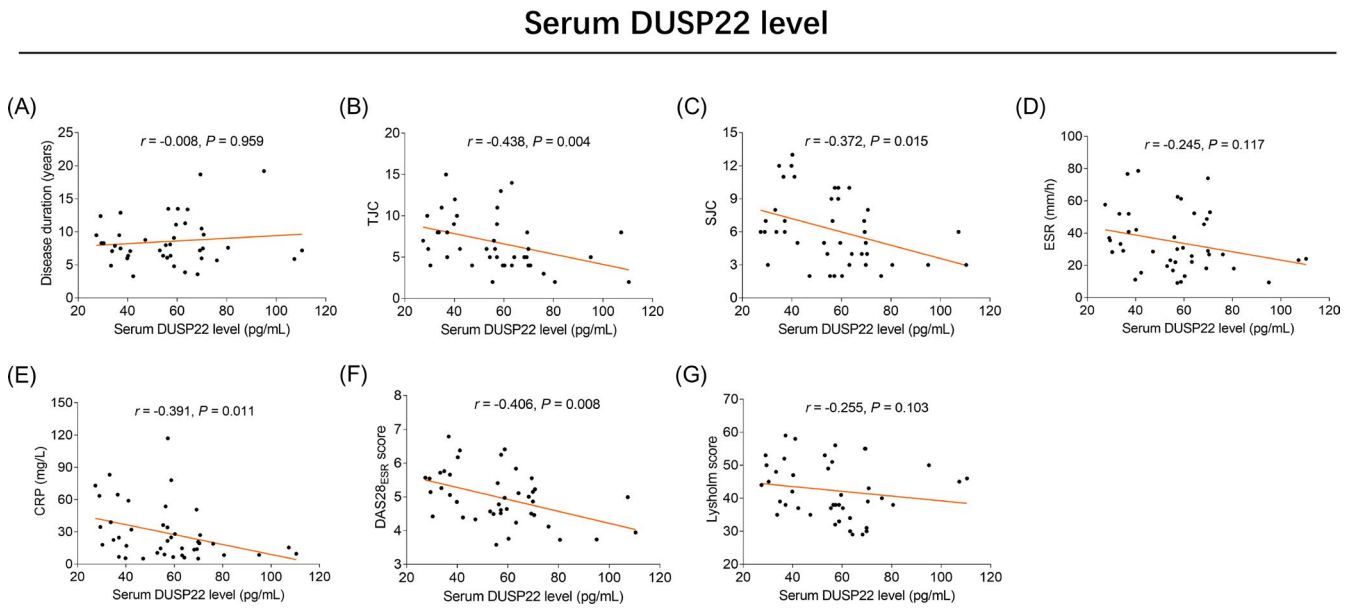

FIGURE 5 Correlation of serum DUSP22 level with RA disease features. Correlation of serum DUSP22 level with disease duration (A), TJC (B), SJC (C), ESR (D), CRP (E), $DAS28_{ESR}$ (F), and Lysholm score (G) in RA patients

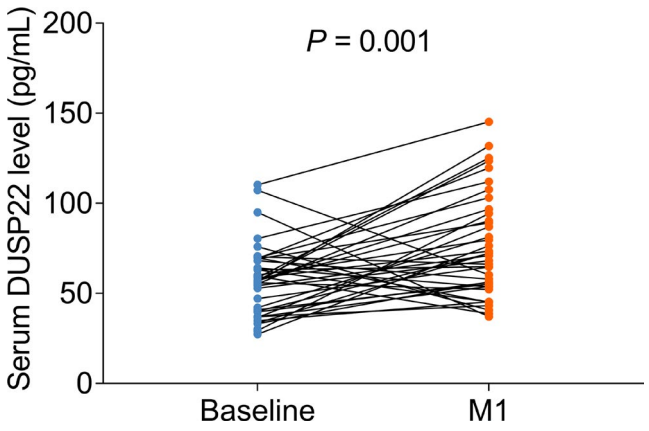

FIGURE 6 Change of serum DUSP22 after treatment

DUSP22 level negatively related to TJC, CRP, and Lysholm score, which might result from the regulation of DUSP22 on inflammation and proliferation.

Several limitations could be addressed in this study: Firstly, due to the limited RA patients underwent arthroscopy, the sample size of eligible RA patients was relatively low in our study leading to less reliability of our findings; therefore, further large sample-sized study and via multiple quantification methods of DUSP22 to validate the findings were future plans. Secondly, due to the cross-department requirement of synovium tissue of trauma patients, the samples obtained were less than RA patients. Thirdly, the age of enrolled RA patients was not limited in our study; therefore, the specific expression and clinical value of DUSP22 in elderly RA patients needed further exploration. Fourthly, the underlying mechanism of DUSP22 in RA pathogenesis needed further exploration.

In conclusion, synovium and serum DUSP22 are intercorrelated and insufficiently expressed in RA patients; meanwhile, their deficiency correlates with increased systemic inflammation, disease activity, and joint dysfunction in RA patients. These findings indicate that the measurement of DUSP22 (blood or synovium) may assist RA diagnosis and activity monitor, while further large sample-sized study is needed to further validate its value.

ACKNOWLEDGMENT

This study was supported by Innovation Project (PhD) of Wuxi 9th Affiliated Hospital of Soochow University (YB202101).

CONFLICT OF INTEREST

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

DATA AVAILABILITY STATEMENT

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

ORCID

Mingyu Xue https://orcid.org/0000-0002-8761-7382

REFERENCES

1. Chauhan K, Jandu JS, Goyal A, Bansal P, Al-Dhahir MA *Rheumatoid Arthritis*. StatPearls; 2021.
2. Cush JJ. Rheumatoid arthritis: early diagnosis and treatment. *Med Clin North Am*. 2021;105:355-365.
3. Wells AF, Curtis JR, Betts KA, Douglas K, Du EX, Ganguli A. Systematic literature review and meta-analysis of tumor necrosis factor-alpha experienced rheumatoid arthritis. *Clin Ther*. 2017;39(8):1680-1694.e2.
4. Ogata A, Kato Y, Higa S, Yoshizaki K. IL-6 inhibitor for the treatment of rheumatoid arthritis: a comprehensive review. *Mod Rheumatol*. 2019;29:258-267.

5. Bertoldi I, Caporali R. Tofacitinib: real-world data and treatment persistence in rheumatoid arthritis. *Open Access Rheumatol*. 2021;13:221-237.
6. Salomon-Escoto K, Kay J. The "Treat to Target" approach to rheumatoid arthritis. *Rheum Dis Clin North Am*. 2019;45:487-504.
7. Shapiro SC. Biomarkers in rheumatoid arthritis. *Cureus*. 2021;13:e15063.
8. Li J-P, Yang C-Y, Chuang H-C, et al. The phosphatase JKAP/DUSP22 inhibits T-cell receptor signalling and autoimmunity by inactivating Lck. *Nat Commun*. 2014;5:3618.
9. Chuang HC, Tan TH. MAP4K family kinases and DUSP family phosphatases in T-cell signaling and systemic lupus erythematosus. *Cells*. 2019;8:1433.
10. Zhou R, Chang Y, Liu J, et al. JNK Pathway-associated phosphatase/DUSP22 suppresses CD4(+) T-cell activation and Th1/Th17-cell differentiation and negatively correlates with clinical activity in inflammatory bowel disease. *Front Immunol*. 2017;8:781.
11. Chuang H-C, Chen Y-M, Hung W-T, et al. Downregulation of the phosphatase JKAP/DUSP22 in T cells as a potential new biomarker of systemic lupus erythematosus nephritis. *Oncotarget*. 2016;7:57593-57605.
12. Yu D, Peng X, Li P. The correlation between Jun N-terminal kinase pathway-associated phosphatase and Th1 cell or Th17 cell in sepsis and their potential roles in clinical sepsis management. *Ir J Med Sci*. 2021;190:1173-1181.
13. Zhao M, Huang X. Downregulation of JKAP is correlated with elevated disease risk, advanced disease severity, higher inflammation, and poor survival in sepsis. *J Clin Lab Anal*. 2019;33:e22945.
14. Song D, Zhu X, Wang F, Sun J. Longitudinal monitor of Jun N-terminal kinase pathway associated phosphatase reflects clinical efficacy to triple conventional disease-modifying anti-rheumatic drugs treatment in rheumatoid arthritis patients. *Inflammopharmacology*. 2021;29:1131-1138.
15. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2010;62:2569-2581.
16. Sun L, Tu J, Liu C, Pan A, Xia X, Chen X. Analysis of lncRNA expression profiles by sequencing reveals that lnc-AL928768.3 and lnc-AC091493.1 are novel biomarkers for disease risk and activity of rheumatoid arthritis. *Inflammopharmacology*. 2020;28:437-450.
17. Kocher MS, Steadman JR, Briggs KK, Sterett WI, Hawkins RJ. Reliability, validity, and responsiveness of the Lysholm knee scale for various chondral disorders of the knee. *J Bone Joint Surg Am*. 2004;86:1139-1145.
18. Vattakuzhi Y, Abraham SM, Freidin A, Clark AR, Horwood NJ. Dual-specificity phosphatase 1-null mice exhibit spontaneous osteolytic disease and enhanced inflammatory osteolysis in experimental arthritis. *Arthritis Rheum*. 2012;64:2201-2210.
19. Moon S-J, Lim M-A, Park J-S, et al. Dual-specificity phosphatase 5 attenuates autoimmune arthritis in mice via reciprocal regulation of the Th17/Treg cell balance and inhibition of osteoclastogenesis. *Arthritis Rheumatol*. 2014;66:3083-3095.
20. Sun LI, Tu J, Chen X, et al. JNK pathway-associated phosphatase associates with rheumatoid arthritis risk, disease activity, and its longitudinal elevation relates to etanercept treatment response. *J Clin Lab Anal*. 2021;35:e23709.
21. Mou XY, Jin D, Zhang Q, Guan JT, Jin Y. JKAP correlates with lower disease risk and inflammation, and its increment during etanercept treatment associates with commendable treatment efficiency in rheumatoid arthritis patients. *Eur Rev Med Pharmacol Sci*. 2021;25:2654-2661.
22. Chen AJ, Zhou G, Juan T, et al. The dual specificity JKAP specifically activates the c-Jun N-terminal kinase pathway. *J Biol Chem*. 2002;277:36592-36601.
23. Li JP, Fu YN, Chen YR, Tan TH. JNK pathway-associated phosphatase dephosphorylates focal adhesion kinase and suppresses cell migration. *J Biol Chem*. 2010;285:5472-5478.
24. Yang Q, Zhuang J, Cai P, Li L, Wang R, Chen Z. JKAP relates to disease risk, severity, and Th1 and Th17 differentiation in Parkinson's disease. *Ann Clin Transl Neurol*. 2021;8:1786-1795.
25. Zhu S, Lv H, Luo Y, Huang Q, Shen J. JNK pathway-associated phosphatase as a serum marker for disease activity and treatment outcome of juvenile idiopathic arthritis. *Tohoku J Exp Med*. 2021;253:19-28.
26. Han H, Lu J, Chen C, Wang Y, Han Y. Reduced JKAP correlates with advanced disease features, inflammation, as well as increased exacerbation risk and severity in asthmatic children. *Ir J Med Sci*. 2021;190:1079-1085.
27. Shi X, Yang W, Wang N, Zhu J. Circulating JNK pathway-associated phosphatase level correlates with decreased risk, activity, inflammation level and reduced clinical response to tumor necrosis factor-alpha inhibitor in Crohn disease patients. *Medicine (Baltimore)*. 2019;98:e16622.
28. Mok A, Rhead B, Holingue C, et al. Hypomethylation of CYP2E1 and DUSP22 promoters associated with disease activity and erosive disease among rheumatoid arthritis patients. *Arthritis Rheumatol*. 2018;70:528-536.
29. Lin H-P, Ho H-M, Chang C-W, et al. DUSP22 suppresses prostate cancer proliferation by targeting the EGFR-AR axis. *FASEB J*. 2019;33:14653-14667.
30. Zhao XD, Huang C, Wang RX, Wang SA. DUSP22 promotes senescence of HS-1 skin cancer cells through triggering MAPK signaling pathway. *Eur Rev Med Pharmacol Sci*. 2018;22:7819-7825.

How to cite this article: Qian C, Chen J, Xu X, et al. Measurement of synovium and serum dual specificity phosphatase 22 level: Their inter-correlation and potency as biomarkers in rheumatoid arthritis. *J Clin Lab Anal*. 2022;36:e24111. https://doi.org/10.1002/jcla.24111