

Circulating JNK pathway-associated phosphatase level correlates with decreased risk, activity, inflammation level and reduced clinical response to tumor necrosis factor- α inhibitor in Crohn disease patients

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Abstract

Objective: This study aimed to investigate the correlation of serum Jun-amino-terminal kinase (JNK) pathway-associated phosphatase (JKAP) level with disease risk, severity, inflammation, and treatment response to tumor necrosis factor (TNF)- α inhibitor in Crohn disease (CD) patients.

Method: Ninety-six active CD patients and 90 healthy controls (HCs) were consecutively enrolled. Serum JKAP level of participants was determined via enzyme-linked immunosorbent assay (ELISA). In CD patients, C-reactive protein (CRP), erythrocyte sedimentation rate, Crohn disease activity index (CDAI), and inflammatory cytokine levels (determined by ELISA) were recorded. All CD patients underwent infliximab (IFX) treatment for 12 weeks, then treatment response (defined as decrement of CDAI ≥ 70) was assessed at week 12 (W12).

Results: Serum JKAP level in CD patients was lower compared to HCs, and it disclosed a good predictive value for decreased CD risk; meanwhile, it was negatively correlated with CRP level, CDAI score, TNF- α , interleukin (IL)-6, and IL-17 levels in CD patients. Sixty-eight (70.8%) patients achieved treatment response to IFX at W12, and JKAP level was increased at W12 compared to baseline. Interestingly, baseline JKAP level in response patients was decreased compared to nonresponse patients, and it exhibited a good predictive value for decreased treatment response to IFX, multivariate logistic regression revealed that JKAP was an independent factor for predicting reduced IFX response.

Conclusion: Circulating JKAP expression correlates with decreased disease risk, activity, and inflammation level, and it could be served as a novel biomarker for predicting reduced clinical response to TNF- α inhibitor in CD patients.

Abbreviations: AUC = area under curve; CD = Crohn disease; CDAI = Crohn disease activity index; CI = confidence interval; CRP = C-reactive protein; DUSPs = dual-specificity phosphatases; EAE = experimental autoimmune encephalomyelitis; ELISA = enzyme-linked immunosorbent assay; ESR = erythrocyte sedimentation rate; HCs = health controls; IBD = inflammatory bowel disease; IFN = increased serum interferon; IFX = infliximab; IL = interleukin; JKAP = JNK pathway-associated phosphatase; JNK = Jun-amino-terminal kinase; MAPK/ERK = mitogen-activated protein kinase / extracellular signal-regulated kinase; ROC = receiver operating characteristic; SAPK = stress-activated protein kinase; SLE = systemic lupus erythematosus; SLEDAI = systemic lupus erythematosus disease activity index; STAT3 = signal transducer and activator of transcription 3; TNF = tumor necrosis factor; W12 = 12 weeks.

Keywords: Crohn disease, JNK pathway-associated phosphatase, serum, treatment response, tumor necrosis factor- α

1. Introduction

Crohn disease (CD), a chronic inflammatory disease which mainly affects the gastrointestinal tract, is becoming more and

more popular around the world. According to a previous study, the annual overall incidence of CD in China is highest among Asia countries, with more than 1 per 100,000 individuals, and the

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number is still increasing.^[1,2] Owing to the elevated morbidity and the high recurrence rate, the CD has grown into one of the most burdensome chronic diseases worldwide.^[2,3] Among various therapeutic agents, tumor necrosis factor (TNF)- α inhibitors are commonly applied for inducing and maintaining therapies in severe CD patients, especially for patients who lose response or become intolerant to conventional treatment drugs such as mercaptopurine and methotrexate.^[4] Despite of the superb efficacy of TNF- α inhibitors in treating CD, the high cost and the potential nonresponse bother both families and doctors, thus, exploring novel markers that could predict treatment response to TNF- α inhibitors in CD patients is pivotal.^[5,6]

Dual-specificity phosphatases (DUSPs) that dephosphorylate both tyrosine and serine/threonine residues are involved in numerous biological activities.^[7,8] As a member of the DUSPs family, Jun-amino-terminal kinase (JNK) pathway-associated phosphatase (JKAP, also named DUSP 22) is a 184-residue protein tyrosine phosphatase that is widely expressed in diverse human tissues.^[9,10] A few studies discover that JKAP is involved in T-cell-mediated signaling pathways, and the decreased JKAP expression in peripheral blood T cells positively correlates with disease risk, activity, and inflammation level of systemic lupus erythematosus (SLE).^[11,12] Meanwhile, JKAP expression in intestinal mucosa is reported to be associated with higher disease risk, activity, and inflammation level of inflammatory bowel disease (IBD). However, JKAP level in intestinal mucosa is not feasible to obtain and the sample size is small, while the correlation of circulating JKAP level with disease risk, activity, and inflammation level of CD as well as clinical response to TNF- α inhibitors is still unknown.^[13] Therefore, the present study aimed to investigate the association of serum JKAP expression with disease risk, activity, and inflammation cytokine levels of CD, and more importantly, to explore whether JKAP level could be served as a novel biomarker for predicting treatment response to TNF- α inhibitor in CD patients.

2. Materials and methods

2.1. Participants

Ninety-six active CD patients underwent infliximab (IFX) treatment, at Tongji Hospital between January 2014 and September 2017 were consecutively enrolled in this study. Patients with the following conditions were included: diagnosed as CD according to clinical characteristics, radiological findings, endoscopic examination, and histological confirmation^[14]; age above 18 years; active disease condition which was defined as Crohn disease activity index (CDAI) equal or above 150; and about to undergo IFX treatment. While patients with the following conditions were excluded: complicated with other severe intestinal tract diseases; moderate to severe renal, hepatic, or heart diseases; history of intestinal surgery, solid tumor, or hematological malignancies; underwent biologics treatment within 6 months or underwent glucocorticoid treatment within 1 month; unable to be followed up for 12 weeks after the treatment; pregnancies; or lactation. In addition, 90 healthy controls (HCs) with age and gender matching to CD patients were also recruited to investigate the value of JKAP expression for predicting CD risk. This study was approved by the Ethics Committee of Tongji Hospital and conducted in according to the declaration of Helsinki; besides, each participant signed informed consent.

2.2. Baseline data collection

Age, gender, disease duration, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) of CD patients were recorded, and CDAI was evaluated.

2.3. Sample collection

Peripheral blood was obtained from CD patients before treatment and at week 12 (W12) after treatment, and from HCs after enrollment. The blood sample was then centrifuged at 4000 revolutions per minute for 6 minutes, and the serum sample was subsequently collected.

2.4. Enzyme-linked immunosorbent assay

Serum JKAP, tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , IL-6, IL-10, IL-17 and IL-23 expressions were determined by enzyme-linked immunosorbent assay (ELISA) with the application of commercial ELISA kits (Shanghai Enzyme-linked Biotechnology Co, Ltd, China).

2.5. Treatment response assessment

Treatment response to IFX was assessed at W12, which was defined as a decrease of CDAI score equal or above 70 after IFX treatment, and according to whether treatment response was achieved at W12, CD patients were divided into response group and nonresponse group.

2.6. Statistics

Statistical analyses were performed using SPSS 19.0 Software (IBM, New York), and graphs were drawn using GraphPad Prism 6.01 Software (GraphPad, California). Data were displayed as mean $\pm$ standard deviation, median (25th–75th quantiles) or count (with or without percentage). Comparison between 2 groups was determined by Wilcoxon rank sum test, comparison between each visit in the same group was determined by Wilcoxon signed-rank sum test. Correlation of JKAP level with continuous data was determined by Spearman test. Receiver operating characteristic curves were made to assess the predictive value of JKAP expression for CD risk and IFX treatment response. In addition, logistic regression analysis was performed to detect the factors affecting IFX treatment response. $P < .05$ was considered as significant.

3. Results

3.1. Study flow

One hundred sixty-five CD patients were invited in the present study, among whom 29 patients missed the invitation, while 12 patients declined to attend prescreening procedure (Fig. 1). Thus, a total of 124 CD patients were screened for eligibility; during this process, 21 patients were ineligible, 7 patients disagreed to sign informed consents. Subsequently, the remaining 96 CD patients were enrolled and no patient quit during the study. Therefore, all the 96 CD patients completed our study and were included in analysis.

3.2. Baseline characteristics of CD patients and HCs

In CD patients, mean age was 34.5 ± 10.4 years, the numbers of females and males were 59 and 37, respectively. Meanwhile,

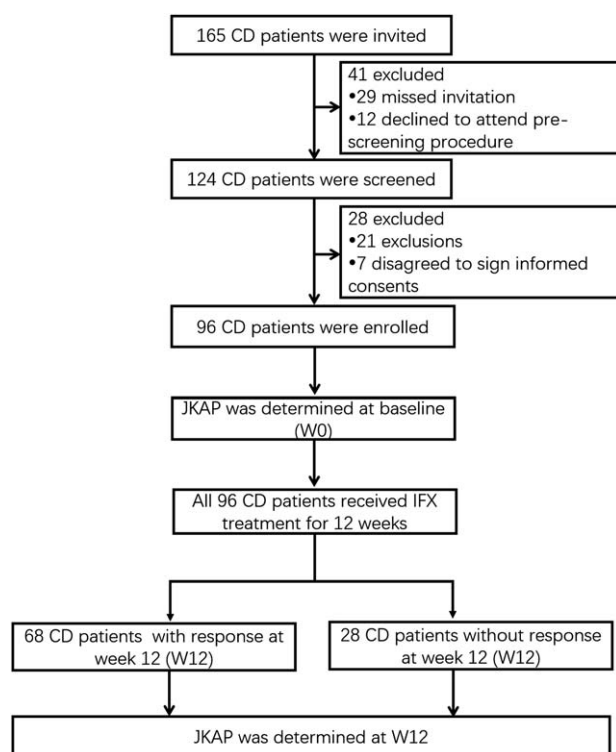


Figure 1. Study flow. CD=Crohn disease, IFX=infliximab, JKAP=JNK pathway-associated phosphatase, W12=12 weeks.

median disease duration was 1.0 (0.0–5.0) year, median CRP, median ESR, and mean CDAI score were 36.2 (23.8–49.3) mg/L, 42.7 (32.6–53.1) mm/H, and 210.4±43.9, respectively. For disease type, the numbers of CD patients with inflammatory type, structuring type, and penetrating type were 67 (69.8%), 16 (16.7%), and 13 (13.5%), respectively. Other baseline characteristics of CD patients were depicted in Table 1. As to HCs, their mean age was 33.4±8.1 years, the numbers of females and males were 47 and 43, respectively. Both age ($P=.419$) and gender ($P=.204$) between CD patients and HCs were matched.

3.3. Predictive value of serum JKAP level for CD risk

Serum JKAP expression in CD patients was decreased compared to HCs ($P<.001$, Fig. 2A) and it disclosed a good predictive value

Table 1

Baseline characteristics of Crohn disease patients.

Characteristics	CD patients (N=96)
Age (years)	34.5±10.4
Gender (female/male)	59/37
Disease duration (years)	1.0 (0.0–5.0)
Disease type	
Inflammatory	67 (69.8)
Structuring	16 (16.7)
Penetrating	13 (13.5)
CRP (mg/L)	36.2 (23.8–49.3)
ESR (mm/H)	42.7 (32.6–53.1)
CDAI	210.4±43.9
TNF-α (pg/mL)	105.4 (55.0–172.4)
IL-1β (pg/mL)	11.0 (7.1–21.3)
IL-6 (pg/mL)	62.8 (37.5–103.6)
IL-10 (pg/mL)	35.4 (17.5–56.4)
IL-17 (pg/mL)	81.8 (44.9–171.6)
IL-23 (pg/mL)	205.7 (148.8–245.5)

Data were presented as mean value ± standard deviation, count, count (percentage) or median (25th–75th quantiles).

CD = Crohn disease, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, CDAI = Crohn disease activity index, TNF-α = tumor necrosis factor-α, IL-1β = interleukin-1β, IL-6 = interleukin-6, IL-10 = interleukin-10, IL-17 = interleukin-17, IL-23 = interleukin-23.

for CD risk with an area under curve (AUC) of 0.931 (95% confidence interval [CI]: 0.896–0.966). Meanwhile, the sensitivity and specificity were 87.5% and 88.9% at best cut-off point, at which the value of sensitivity plus specificity was largest (Fig. 2B).

3.4. Association of serum JKAP expression with characteristics of CD patients

JKAP level in serum was negatively associated with CRP ($P=.005$, Fig. 3A) level and CDAI score ($P=.002$, Fig. 3B), while no correlation of JKAP level with disease duration ($P=.569$, Fig. 3C), age ($P=.107$, Fig. 3D), ESR level ($P=.582$, Fig. 3E), or gender ($P=.967$, Fig. 3F) was discovered.

3.5. Association of serum JKAP expression with inflammatory cytokine levels in CD patients

Serum JKAP expression was negatively associated with TNF-α ($P=.006$, Fig. 4A), IL-17 ($P=.036$, Fig. 4B), and IL-6 ($P=.013$,

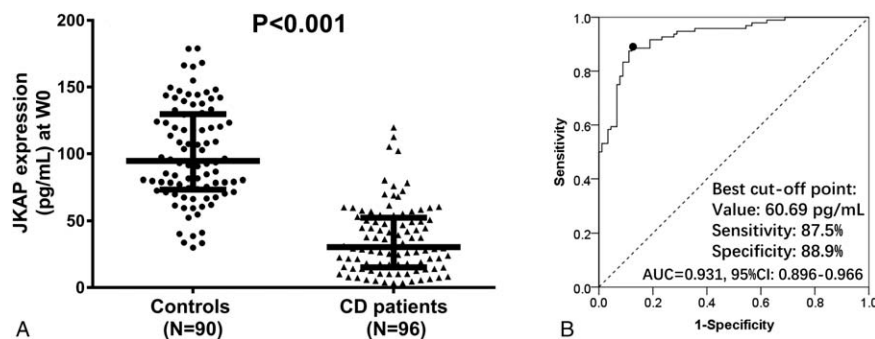


Figure 2. Serum JKAP level between CD patients and HCs (A) as well as its predictive value for CD risk (B). Comparison between two groups was determined by Wilcoxon rank sum test, ROC curve was drawn to assess the predictive value of JKAP expression for CD risk. $P<0.05$ was considered significant. AUC=area under curve, CD=Crohn disease, HCs=health controls, JKAP=JNK pathway-associated phosphatase, ROC=receiver operating characteristic.

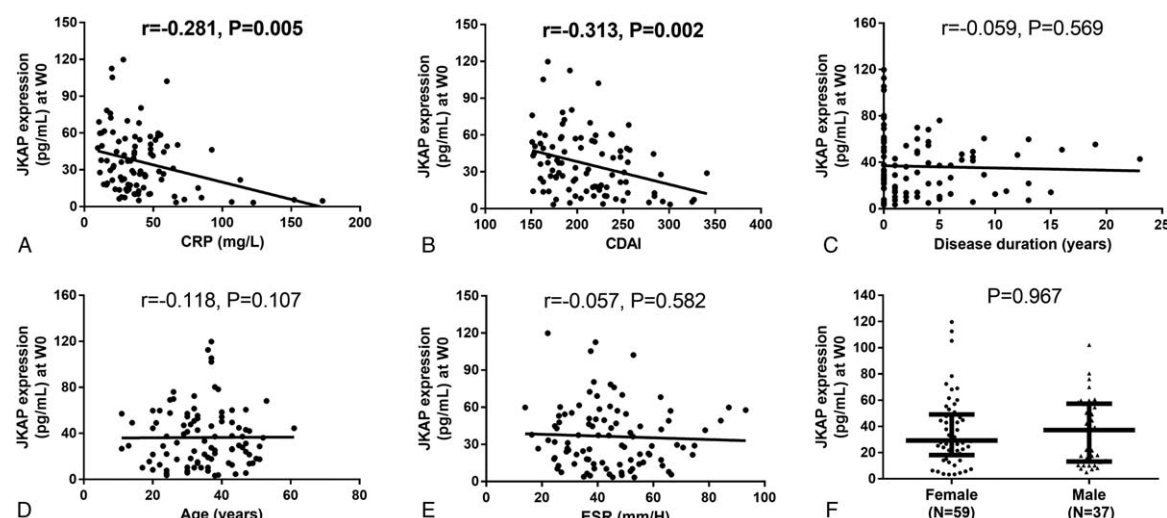


Figure 3. Correlation of serum JKAP level with CD patients' baseline characteristics. Serum JKAP expression negatively correlated with CRP level (A) and CDAI score (B), whereas no association of JKAP expression with disease duration (C), age (D), ESR level (E), or gender (F) was observed. Comparison between 2 groups was determined by Spearman test or Wilcoxon rank sum test. $P < .05$ was considered significant. CD = Crohn disease, CDAI = Crohn disease activity index, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, JKAP = JNK pathway-associated phosphatase.

Fig. 4C) levels, whereas no correlation was observed between JKAP expression and IL-10 ($P = .965$, Fig. 4D), IL-1 β ($P = .468$, Fig. 4E), or IL-23 ($P = .273$, Fig. 4F) level.

3.6. Treatment response rate and comparison of serum JKAP expression before and after IFX treatment in CD patients

A total of 68 (70.8%) CD patients achieved treatment response while the rest of 28 (29.2%) CD patients failed to achieve response after IFX treatment (W12) (Fig. 5A). After IFX treatment, serum JKAP expression in all CD patients was increased ($P < .001$, Fig. 5B), including response patients ($P < .001$, Fig. 5C) and nonresponse patients ($P < .001$,

Fig. 5D), and response patients seemed to present with higher change of JKAP expression after IFX treatment compared to nonresponse patients.

3.7. Predictive value of serum JKAP level at baseline for treatment response of IFX

As shown in Figure 6A, serum JKAP expression at baseline in response patients was lower than that in nonresponse patients ($P = .002$), baseline JKAP expression also exhibited a good predictive value for clinical response to IFX in CD patients with an AUC of 0.699 (95% CI: 0.590–0.808). The sensitivity and specificity were 67.6% and 71.4% at best cut-off point, respectively (Fig. 6B).

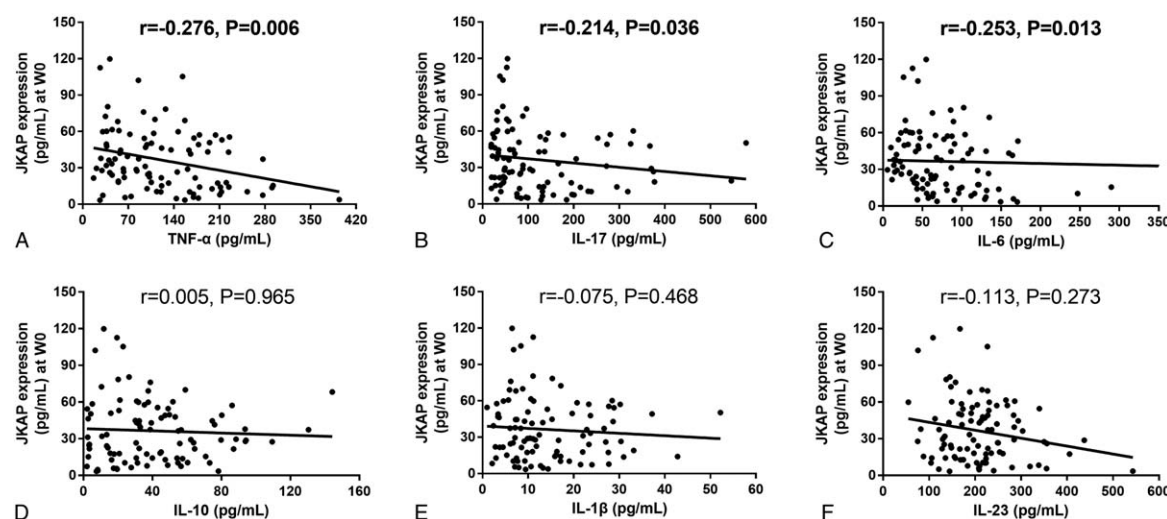


Figure 4. Correlation of serum JKAP level with CD patients' baseline inflammatory cytokine levels. JKAP expression in serum negatively correlated with TNF- α (A), IL-17 (B), and IL-6 (C) levels; however, no association of JKAP expression with IL-10 (D), IL-1 β (E), or IL-23 (F) levels was discovered. Comparison between 2 groups was determined by Spearman test. $P < .05$ was considered significant.

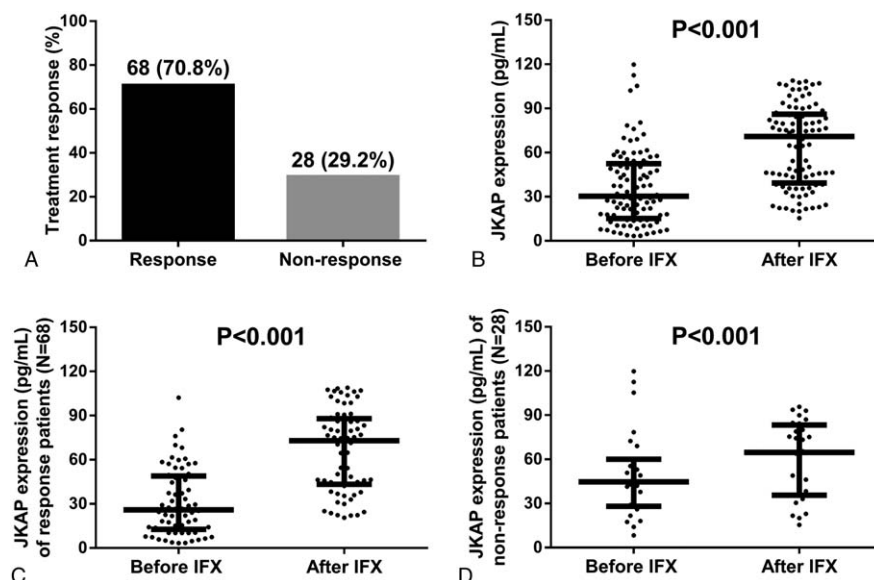


Figure 5. Clinical response rate to IFX and serum JKAP level before and after IFX treatment. Sixty-eight (70.8%) CD patients achieved clinical response while the other 28 (29.2%) CD patients failed to achieve response after IFX treatment (W12) (A). After IFX treatment, serum JKAP level in CD patients was increased (B), including response patients (C) and nonresponse patients (D). Comparison between 2 groups was determined by Wilcoxon signed-rank sum test. $P < .05$ was considered significant. CD=Crohn disease, IFX=infliximab, JKAP=JNK pathway-associated phosphatase, W12=12 weeks.

3.8. Logistic regression model analysis of factors affecting IFX treatment response

Univariate logistic regression was applied for analyzing factors affecting IFX treatment response in CD patients, which revealed that serum JKAP expression ($P=.003$) was correlated with worse IFX treatment response, while CRP ($P=.006$) and IL-17 levels ($P=.019$) were correlated with better IFX treatment response (Table 2). All factors were further analyzed via multivariate logistic regression, and the results elucidated that JKAP expression ($P=.008$) was an independent factor for predicting worse IFX treatment response, while CRP level ($P=.016$) was an independent factor for predicting better IFX treatment response.

4. Discussion

In the present study, we discovered that: serum JKAP level disclosed a great predictive value for decreased CD risk, and it was negatively associated with disease activity and inflammatory cytokines levels. All CD patients exhibited increased JKAP level after IFX treatment, and the decreased baseline JKAP level was an independent factor for predicting better IFX treatment response.

JKAP belongs to the low molecular weight atypical DUSPs family, which is involved in a variety of biological and pathological processes.^[15–19] Recently, several studies have reported the predictive value of JKAP for disease risk and its negative correlation with disease activity and inflammation level in several immune diseases.^[11–13] It is reported that JKAP-

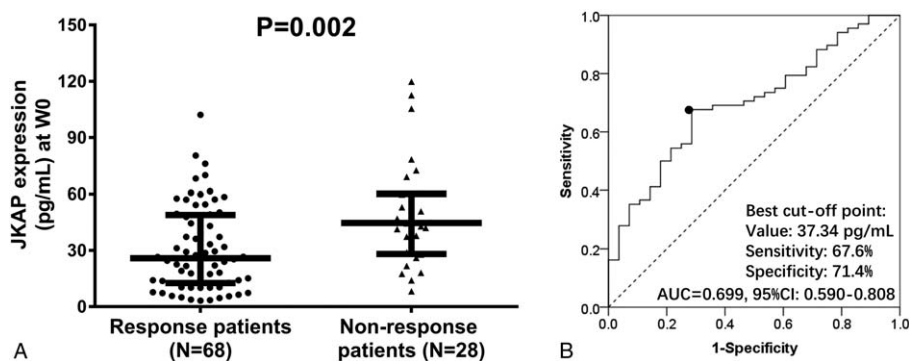


Figure 6. Serum JKAP level between response CD patients and nonresponse CD patients with IFX treatment (A) as well as its predictive value for clinical response to IFX (B). Comparison between two groups was determined by Wilcoxon rank sum test, ROC curve was drawn to assess the predictive value of JKAP expression for IFX treatment response. $P < 0.05$ was considered significant. AUC=area under curve, CI=confidence interval, IFX=infliximab, JKAP=JNK pathway-associated phosphatase, ROC=receiver operating characteristic.

Table 2**Factors affecting infliximab treatment response by logistic regression model analysis.**

Parameters	Univariate logistic regression				Multivariate logistic regression			
	P	OR	95% CI		P	OR	95% CI	
			Lower	Higher			Lower	Higher
JKAP expression (MO)	.003	0.971	0.953	0.990	.008	0.963	0.937	0.991
Age	.405	0.982	0.940	1.025	.569	0.981	0.920	1.047
Gender (female)	.715	0.844	0.339	2.102	.787	0.841	0.240	2.947
Disease duration	.258	0.950	0.869	1.038	.151	0.906	0.792	1.037
CRP	.006	1.044	1.013	1.077	.016	1.054	1.010	1.101
ESR	.315	1.015	0.986	1.044	.429	1.018	0.974	1.063
CDAI	.924	1.000	0.990	1.010	.798	1.184	0.324	4.322
TNF- α	.838	1.001	0.995	1.006	.154	0.994	0.985	1.002
IL-1 β	.398	1.021	0.973	1.071	.204	0.933	0.839	1.038
IL-6	.690	1.000	1.000	1.000	.749	1.000	1.000	1.001
IL-10	.833	0.998	0.984	1.013	.690	0.995	0.972	1.019
IL-17	.019	1.007	1.001	1.014	.286	1.004	0.996	1.012
IL-23	.545	1.002	0.996	1.007	.550	0.998	0.990	1.005

Data were presented as *P* value, OR, and 95% CI. Factors affecting IFX treatment response were determined by logistic regression model analysis. *P* < .05 was considered significant.

CDAI = Crohn disease activity index, CI = confidence interval, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, IFX = infliximab, IL-1 β = interleukin-1 β , IL-10 = interleukin-10, IL-17 = interleukin-17, IL-23 = interleukin-23, IL-6 = interleukin-6, JKAP = dual specificity protein phosphatase 22, OR = odds ratio, TNF = tumor necrosis factor.

knockout mice are more susceptible to experimental autoimmune encephalomyelitis (EAE) compared to wild-type mice. What is more, JKAP-knockout EAE mice exhibit increased serum interferon (IFN)- γ and IL-17 levels, they also present with greater numbers of infiltrating CD4⁺ T cells, IFN- γ ⁺ Th1 cells, and IL-17⁺ Th17 cells in their brain tissues compared to JKAP-knockout healthy mice or wild-type EAE mice, implying that the decreased JKAP level correlates with higher risk of immune disease and elevated inflammation level.^[13] Another study discovers that JKAP expression in T cells could be served as a diagnostic biomarker for SLE complicated with active lupus nephritis; and it is negatively associated with systemic lupus erythematosus disease activity index (SLEDAI) score, serum complement 3 (C3), and anti-dsDNA antibody levels in SLE nephritis patients, which suggest that JKAP expression also negatively correlates with disease risk, activity, and inflammation level in SLE nephritis patients.^[11] In addition, JKAP expression is observed to be decreased in inflamed intestinal mucosa of patients with active IBD, and it presents with good predictive value for active IBD risk, including CD and ulcerative colitis. More interestingly, JKAP expression in inflamed intestinal mucosa is also negatively associated with disease activity and inflammation level in IBD patients. However, JKAP expression in intestinal mucosa is less feasible to obtain compared to circulating JKAP expression, and the sample size in that previous is small, which leads to a low statistical power.^[12] In order to explore the role of circulating JKAP level in predicting disease risk, activity, and inflammation level of CD, the present study was conducted. It revealed that the serum JKAP expression in CD patients was lower than that in HCs, which also displayed predictive value for CD risk; meanwhile, the baseline JKAP expression was negatively correlated with disease activity and inflammation level in CD patients. The possible reason to our data might be that: JKAP might directly regulate the signal transducer and activator of transcription 3 (STAT3), which attenuated its activity through dephosphorylation of STAT3 at Tyr705 and Ser727, and subsequently regulated the differentiation of Th17 cells, thereby reduced the CD risk, activity, and inflammation.^[20,21] JKAP might also inhibit T-cell-mediated immune activity through other pathways such as

mitogen-activated protein kinase / extracellular signal-regulated kinase pathway and stress-activated protein kinase/JNK pathway, or through inactivating Lck (a src-family tyrosine kinase) by dephosphorylating Tyr394 during T-cell receptor signaling, thus the declined JKAP expression was correlated with increased disease risk, activity, and inflammation.^[9,13,22]

As previously described, a few studies that focus on the role of JKAP in immune disease diagnosis and monitoring have been reported, whereas only 1 study investigates the predictive value of JKAP level for treatment response to IFX in CD patients. In that previous study, both mRNA and protein levels of JKAP in intestinal mucosa are upregulated after IFX treatment compared to that before IFX treatment in response patients. Meanwhile, mRNA expression of JKAP is lower in patients who achieve response than that in patients who fail to achieve response.^[11,12,19] However, in that study, JKAP expression is assessed in intestinal mucosa where JKAP level is less feasible to be determined; besides, the sample size is too small, with only 25 patients included. Therefore, whether serum JKAP expression is capable of predicting treatment response to TNF- α in CD patients remains unknown. In the present study, we discovered that all CD patients exhibited increased JKAP level after IFX treatment, and baseline JKAP level was an independent factor for predicting lower possibility of IFX treatment response. The result might be due to that: as a TNF- α inhibitor, IFX was able to inhibit TNF- α -mediated inflammatory activity via repressing TNF- α level, and then reduced disease activity and inflammation level of CD; thus, JKAP expression was elevated after IFX treatment.^[23–26] Response patients presented with greater reduction of inflammation level after treatment compared to nonresponse patients, so the response patients exhibited higher elevation of JKAP level after IFX treatment compared to nonresponse patients. Firstly, treatment response to IFX was defined as a decrease of CDAI score equal or above 70 after IFX treatment, and patients with higher baseline JKAP level tended to present with decreased CDAI score and corresponding lower gap for CDAI decrement. Secondly, patients with higher JKAP level exhibited less disease activity and inflammation level, which might reduce the efficacy of anti-inflammation treatment (including IFX). Hence, patients with increased JKAP expression

at baseline were less likely to obtain clinical response to IFX treatment.

There were some limitations in the present study: the observation period of treatment response was only 12 weeks, thus the predictive value of serum JKAP expression for a long-term IFX treatment response in CD patients needed additional investigation in the future studies. We only investigated the value of JKAP in predicting response to IFX, while its predictive value for response to other TNF inhibitors (such as adalimumab and golimumab) was not explored. Considering that there is no relevant study investigating the value of JKAP for predicting response to other TNF inhibitors either, additional studies are required in the future. Most of the patients in the present study were from Middle China, which might lead to selection bias. The sample size in this study might not be sufficient enough, which might be due to the relatively low incidence of CD and the extremely high cost of IFX in China. Besides, a proportion of eligible CD patients were excluded from the study because they declined to sign the informed consents or other personal reasons. The association of serum JKAP level with fecal calprotectin level in CD patients also needed additional investigations.

In conclusion, circulating JKAP expression correlates with decreased disease risk, activity, and inflammation level, and it could be served as a novel biomarker for reduced clinical response to TNF- α inhibitor in CD patients.

Author contributions

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Methodology: Nian Wang.

Writing – original draft: Xue Shi.

Writing – review & editing: Junyi Zhu.

References

- [1] Ng SC, Tang W, Ching JY, et al. 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.e2–65.e2.
- [2] Baumgart DC, Sandborn WJ. Crohn's disease. *Lancet* 2012;380:1590–605.
- [3] Torres J, Mehandru S, Colombel JF, et al. Crohn's disease. *Lancet* 2017;389:1741–55.
- [4] Peyrin-Biroulet L, Desreumaux P, Sandborn WJ, et al. Crohn's disease: beyond antagonists of tumour necrosis factor. *Lancet* 2008;372:67–81.
- [5] Roblin X, Attar A, Lamure M, et al. Cost savings of anti-TNF therapy using a test-based strategy versus an empirical dose escalation in Crohn's disease patients who lose response to infliximab. *J Mark Access Health Policy* 2015;3: 29229.
- [6] Freeman K, Connock M, Auguste P, et al. Clinical effectiveness and cost-effectiveness of use of therapeutic monitoring of tumour necrosis factor alpha (TNF-alpha) inhibitors [LISA-TRACKER(R) enzyme-linked immunosorbent assay (ELISA) kits, TNF-alpha-Blocker ELISA kits and Promonitor(R) ELISA kits] versus standard care in patients with Crohn's disease: systematic reviews and economic modelling. *Health Technol Assess* 2016;20:1–288.
- [7] Liu R, Molkentin JD. Regulation of cardiac hypertrophy and remodeling through the dual-specificity MAPK phosphatases (DUSPs). *J Mol Cell Cardiol* 2016;101:44–9.
- [8] Bennett AM. DUSPs, twists and turns in the journey to vascular inflammation. *FEBS J* 2018;285:1589–92.
- [9] 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;277:36592–601.
- [10] Hamada N, Mizuno M, Tomita H, et al. Expression analyses of Dusp22 (Dual-specificity phosphatase 22) in mouse tissues. *Med Mol Morphol* 2018;51:111–7.
- [11] Chuang HC, Chen YM, Hung WT, et al. Downregulation of the phosphatase JKAP/DUSP22 in T cells as a potential new biomarker of systemic lupus erythematosus nephritis. *Oncotarget* 2016;7:57593–605.
- [12] Li JP, Yang CY, Chuang HC, et al. The phosphatase JKAP/DUSP22 inhibits T-cell receptor signalling and autoimmunity by inactivating Lck. *Nat Commun* 2014;5:3618.
- [13] 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.
- [14] Van Assche G, Dignass A, Panes J, et al. European Crohn's and Colitis Organisation (ECCO) The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. *J Crohns Colitis* 2010;4:7–27.
- [15] Li JP, Fu YN, Chen YR, et al. JNK pathway-associated phosphatase dephosphorylates focal adhesion kinase and suppresses cell migration. *J Biol Chem* 2010;285:5472–8.
- [16] Lountos GT, Cherry S, Tropea JE, et al. Structural analysis of human dual-specificity phosphatase 22 complexed with a phosphotyrosine-like substrate. *Acta Crystallogr F Struct Biol Commun* 2015;71(Pt 2):199–205.
- [17] Melard P, Idrissi Y, Andrique L, et al. Molecular alterations and tumor suppressive function of the DUSP22 (dual specificity phosphatase 22) gene in peripheral T-cell lymphoma subtypes. *Oncotarget* 2016;7: 68734–48.
- [18] Ouyang B, Baxter CS, Lam HM, et al. Hypomethylation of dual specificity phosphatase 22 promoter correlates with duration of service in firefighters and is inducible by low-dose benzo[a]pyrene. *J Occup Environ Med* 2012;54:774–80.
- [19] Yu D, Li Z, Gan M, et al. Decreased expression of dual specificity phosphatase 22 in colorectal cancer and its potential prognostic relevance for stage IV CRC patients. *Tumour Biol* 2015;36:8531–5.
- [20] Lu D, Liu L, Ji X, et al. The phosphatase DUSP2 controls the activity of the transcription activator STAT3 and regulates TH17 differentiation. *Nat Immunol* 2015;16:1263–73.
- [21] Onaindia A, de Villambrosia SG, Prieto-Torres L, et al. DUSP22-rearranged anaplastic lymphomas are characterized by specific morphological features and a lack of cytotoxic and JAK/STAT surrogate markers. *Haematologica* 2019;104:e158–62.
- [22] Luchtel RA, Dasari S, Oishi N, et al. Molecular profiling reveals immunogenic cues in anaplastic large cell lymphomas with DUSP22 rearrangements. *Blood* 2018;132:1386–98.
- [23] Choi J, Kang B, Kim MJ, et al. Early infliximab yields superior long-term effects on linear growth in pediatric Crohn's disease patients. *Gut Liver* 2018;12:255–62.
- [24] Doecke JD, Hartnell F, Bampton P, et al. Infliximab vs. adalimumab in Crohn's disease: results from 327 patients in an Australian and New Zealand observational cohort study. *Aliment Pharmacol Ther* 2017;45:542–52.
- [25] Fidler HH, Hommes DW. Anti-TNF and Crohn's disease: when should we start? *Curr Drug Targets* 2010;11:143–7.
- [26] Richter JA, Bickston SJ. Infliximab use in luminal Crohn's disease. *Gastroenterol Clin North Am* 2006;35:775–93.