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BRIEF REPORT

Elevated serum levels of interleukin-10 in adult-onset Still's disease are associated with disease activity

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Abstract

To evaluate the serum levels of the anti-inflammatory cytokine interleukin-10 (IL-10) in patients with adult-onset Still's disease (AOSD), a rare, systemic, and multigenic inflammatory disease. The serum levels of IL-10, IL-1β, IL-6, IL-18, and TNF-α were examined by electrochemiluminescence assay. The serum levels of IL-10 were higher in AOSD patients than in healthy controls and positively correlated with systemic score, erythrocyte sedimentation rate (ESR), C-reactive protein level (CRP), ferritin, and inflammatory cytokine (IL-1β, IL-6, IL-18, and TNF-α) levels. Moreover, the levels of IL-10 were significantly higher in AOSD patients who had fever, sore throat, rash, lymphadenopathy, splenomegaly, pneumonia, and arthralgia than in patients who did not. IL-10 was increased in AOSD patients and correlated with disease activity.

Key Points

- *In this manuscript, we confirmed the elevated serum levels of the anti-inflammatory cytokine IL-10 in AOSD patients, which was previously poorly defined.*
- *We revealed for the first time that the levels of IL-10 were correlated with disease activity and inflammatory cytokine levels in AOSD.*

Keywords Adult-onset Still's disease · Disease activity · IL-10 · Inflammation

Introduction

Adult-onset Still's disease (AOSD) is a rare, systemic, and multigenic inflammatory disease with typical manifestations of temporal fever, scattered rash, and arthritis [1, 2]. Although the etiology of the disease is poorly known, the hyperactivation of innate immune cells (including macrophages and neutrophils) and the release of inflammatory cytokines contribute to the development of AOSD [2, 3]. The activation of the inflammasome and subsequent increased production of IL-1β and IL-18 are one of the major steps of AOSD pathogenesis [4]. Meanwhile, high levels of pro-inflammatory cytokines (such as TNF-α, IL-6, and IL-8) have been found in AOSD patients [5]. Thus, activation of the inflammatory cascade and disorder of inflammatory cytokine production are well defined in the pathogenesis of AOSD [1–3].

IL-10 is a typical anti-inflammatory cytokine that mainly exhibits regulatory effects during infection and protects against tissue damage [6, 7]. IL-10 potently inhibited pro-inflammatory IL-1β, IL-6, and TNF-α expression in activated macrophages and suppressed inflammasome activation [8, 9], which might be involved in the pathogenesis of inflammatory diseases. Elevated levels of IL-10 have been found in chronic inflammatory diseases such as systemic lupus erythematosus (SLE) [10], rheumatoid arthritis (RA) [11], and systemic sclerosis (SSc) [12]. The serum levels of IL-10 in AOSD patients were increased in a small sample size study and case report [13, 14]. However, researchers still speculated that the

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production of IL-10 was insufficient, resulting in the failure to control the cytokine storm in AOSD [1]. As the levels of IL-10 in patients with AOSD and its correlation with disease activity are inconclusive, we aimed to examine the levels of IL-10 by a hypersensitive electrochemiluminescence assay and evaluate the correlation between the levels of IL-10 and the clinical characteristics of AOSD patients.

Materials and methods

Patients

A total of 58 patients diagnosed with AOSD according to the criteria of Yamaguchi et al. [15] were enrolled in this study from the Department of Rheumatology and Immunology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. Participants with infections, malignancies, and other autoimmune diseases were excluded from the study. Forty-two age- and sex-matched volunteers were recruited as healthy controls (HCs).

Medical histories and clinical and laboratory characteristics were collected from all subjects. Serum samples were collected from patients with active AOSD before steroid or synthetic disease-modifying anti-rheumatic drug treatment. Follow-up samples were collected from ten patients with active AOSD after the resolution of disease activity. AOSD disease activity was assessed according to the systemic disease score method [13], which comprised 12 disease manifestations as follows: fever, evanescent rash, sore throat, arthritis, myalgia, pleuritis, pericarditis, pneumonitis, lymphadenopathy, hepatomegaly or abnormal liver function tests, elevated leukocyte count > 15,000/μl, and serum ferritin > 3000 μg/l. Patients with AOSD were considered to have clinically active disease if they had fever and/or inflammatory arthralgia/arthritis and/or any suggestive cutaneous lesions and/or sore throat. Their AOSD was otherwise considered inactive [16].

Cytokine assessment

Serum levels of IL-10, IL-1β, IL-6, TNF-α, and IL-18 were measured using an electrochemiluminescence assay (Meso Scale Discovery, MSD, Rockville, MD, USA) according to the manufacturer's instructions. Briefly, a precoated plate (human pro-inflammatory panel or human IL-18) was washed three times with 150 μl of wash buffer per well and incubated with 50 μl of serum or standard calibrators for two h at room temperature. After three washes, 25 μl of detection antibody was added to each well and incubated for another two h at room temperature. After washing, 150 μl of read buffer was added, and the plate was quickly read on an MSD instrument. The sensitivities of the assays were 0.01–233 pg/ml for IL-10, 0.01–375 pg/ml for IL-1β, 0.01–488 pg/ml for IL-6, 0.01–248 pg/ml for IL-10, and 0.86–100,000 pg/ml for IL-18, according to the manufacturer's instructions.

Statistical analysis

The results are expressed as median with interquartile range (IQR) for nonparametric data or mean ± SD for parametric data and were analyzed by Prism version 7.00 software (GraphPad Software Inc., San Diego, USA). The associations between the levels of IL-10 and different variables were analyzed by Kendall's correlation test using IBM SPSS Statistics V25 software (IBM Corp., Chicago, USA). The nonparametric Mann-Whitney *U* test was used to compare differences between each group. The Wilcoxon matched-pairs signed rank test was used to compare serum IL-10 levels from individual patients before and after treatment. The analyses were carried out under the two-sided principle. The differences were considered significant when $P < 0.05$.

Results

Increased serum levels of IL-10 in AOSD patients

To examine the serum levels of IL-10, 58 AOSD patients and 42 HCs were enrolled in the current study. The clinical and laboratory information is listed in Table 1. The levels of IL-10 in the serum were examined by electrochemiluminescence assay, and the serum levels of IL-10 in patients with AOSD (2.092 ± 3.475 pg/ml) were dramatically higher than those in the HC group (0.146 ± 0.165 pg/ml, $p < 0.0001$), as shown in Fig. 1a. Next, we investigated differences in the levels of IL-10 between patients with active AOSD and inactive AOSD and found that the serum IL-10 levels were significantly higher in active AOSD patients than in inactive AOSD patients (Fig. 1b). Moreover, ten patients with a high level of disease activity were followed up, as shown in Fig. 1c, and IL-10 production was dramatically decreased in the remission phase of AOSD ($p < 0.05$).

The levels of IL-10 were positively correlated with disease activity

To further explore the correlation between serum IL-10 levels and disease activity, we analyzed the relationship between the levels of IL-10, the systemic score, and the results from the laboratory examination. The levels of IL-10 were positively correlated with the systemic score ($r = 0.292$; $p = 0.008$) (Fig. 1d), and the levels of IL-10 were significantly higher in patients with a systemic score ≥ 7 than in other patients (Fig. 1e), which suggest a high risk of mortality and complications [17]. Meanwhile, we

Table 1 Clinical characteristics of patients at the time of enrollment

	AOSD ($n = 58$)		HC ($n = 42$)
	Active($n = 44$)	Inactive($n = 14$)	
Age (year)	38.6 ± 15.1	36.0 ± 14.5	37.6 ± 10.0
Gender(F/M)	33/11	11/3	32/10
Duration (month)	2.5 ± 1.9	15.1 ± 12.2	
Clinical features			
Fever	37 (84.1)	0	
Sore throat	29 (65.9)	0	
Skin rash	36 (81.8)	0	
Lymphadenopathy	31 (70.5)	1 (7.1)	
Splenomegaly	15 (34.1)	0	
Hepatomegaly	1 (2.3)	0	
Pericarditis	8 (18.2)	0	
Pleuritis	10 (22.7)	0	
Pneumonia	18 (40.9)	0	
Myalgia	15 (34.1)	0	
Arthralgia	38 (86.4)	0	
Arthritis	14 (31.8)	0	
Systemic score	6.3 ± 1.6	0.1 ± 0.4	
Laboratory markers			
Hemoglobin (g/l)	110.9 ± 24.9	129.4 ± 19.9	
Leukocyte ($\times 10^9$/l)	16.1 ± 6.0	10.0 ± 6.4	
Platelet ($\times 10^9$/l)	281.2 ± 110.6	236.8 ± 72.5	
ESR (mm/h)	68.7 ± 28.7	22.5 ± 23.5	
CRP (mg/l)	91.8 ± 61.5	36.2 ± 27.9	
ALT (U/l)	59.7 ± 59.6	30.0 ± 20.6	
AST (U/l)	47.0 ± 25.5	28.2 ± 22.3	
Ferritin (ng/ml)	2798.0 ± 4275.0	187.9 ± 138.2	
ANA positivity	6 (13.6)	1 (7.1)	
RF positivity	3 (6.8)	0	
Treatments			
Steroids and sDMARDs naïve	44 (100.0)	0	
Low dosage of steroid monotherapy	0	0	
High dosage of steroid monotherapy	0	0	
sDMARD(s)	0	6 (42.9)	
Combination therapy, steroids + sDMARD(s)	0	8 (57.1)	

All values are presented as n (percent) or mean ± SD

AOSD adult-onset Still's disease, *HC* healthy control, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *AST* aspartate transaminase, *ALT* alanine transaminase, *ANA* anti-nuclear antibody

found that the levels of IL-10 were positively correlated with the erythrocyte sedimentation rate (ESR, $r = 0.305$; $p = 0.005$), C-reactive protein level (CRP, $r = 0.309$; $p = 0.007$), and ferritin level ($r = 0.411$; $p = 0.011$) (Fig. 1f–h) and inversely correlated with the levels of hemoglobin ($r = -0.233$; $p = 0.029$) (data not shown) but were not significantly correlated with the number of leukocytes, the percentage of neutrophils, or the levels of alanine transaminase and aspartate transaminase (AST).

The levels of IL-10 were positively correlated with inflammatory cytokines in AOSD patients

As the increased levels of the pro-inflammatory cytokines IL-1β, IL-6, IL-18, and TNF-α are the hallmark of AOSD, we also detected the production of these cytokines by electrochemiluminescence assay and analyzed the correlation between IL-10 and the levels of these cytokines. The IL-10 level exhibited a strong correlation with the levels of

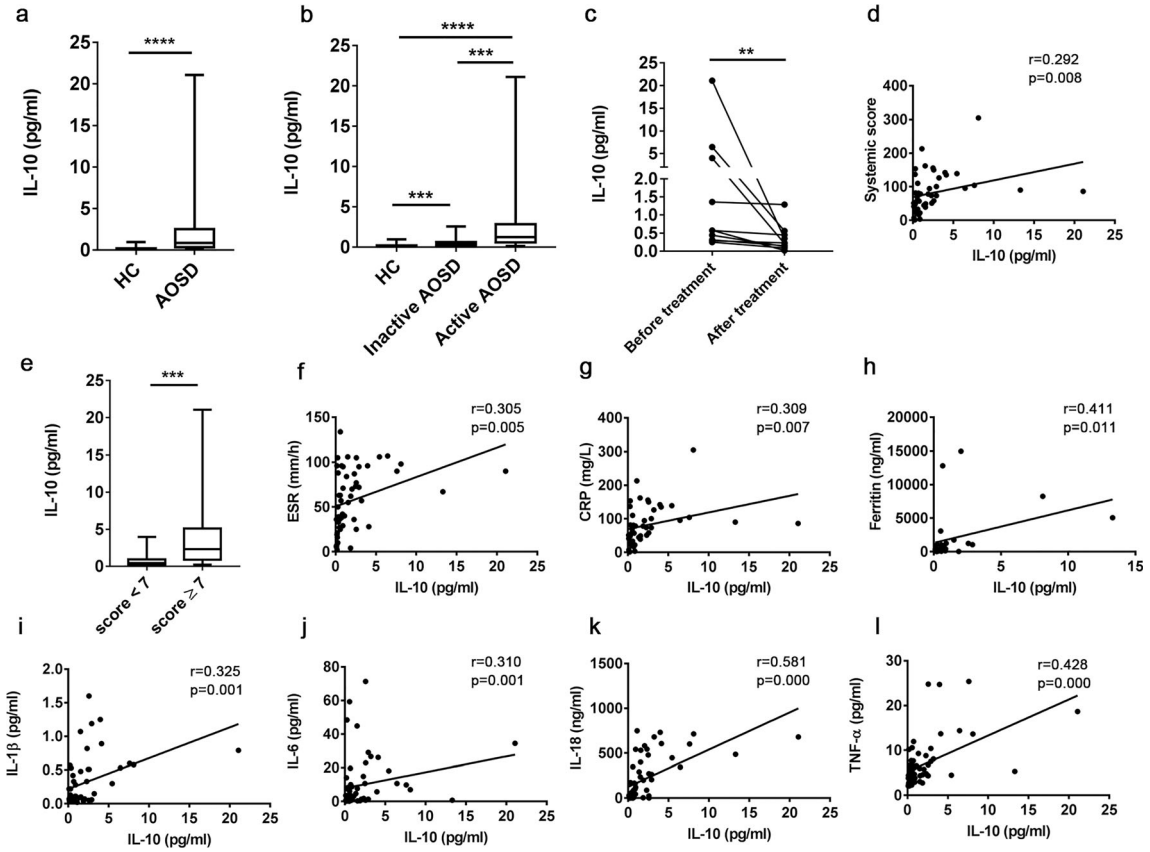

Fig. 1 The serum levels of IL-10 were increased in AOSD patients compared to those in HCs. IL-10 production was examined by electrochemiluminescence assay in from the sera of 58 AOSD patients and 42 healthy controls (HCs). **a** IL-10 production in HCs and AOSD patients. **b** IL-10 production in HCs and patients with unactivated AOSD and activated AOSD. **c** Serum IL-10 production before and after clinical treatment. **e** Differences between the levels of IL-10 in patients with a systemic score < 7 and those with a systemic score ≥ 7. The correlations between the levels of IL-10 and systemic score (**d**), ESR (**f**), CRP level (**g**), ferritin level (**h**), IL-1β level (**i**), IL-6 level (**j**), IL-18 level (**k**), and TNF-α level (**l**) were determined by Kendall's correlation test. ESR erythrocyte sedimentation rate, CRP C-reactive protein, AST aspartate transaminase. $^{**}p < 0.01$, $^{***}p < 0.001$ and $^{****}p < 0.0001$

IL-1β ($r = 0.325$, $p = 0.001$, IL-6 ($r = 0.310$, $p = 0.001$), IL-18 ($r = 0.581$, $p = 0.000$), and TNF-α ($r = 0.428$, $p = 0.000$) (Fig. 1i–l).

The association between the levels of IL-10 and the clinical manifestations of AOSD

Moreover, we analyzed the correlation between IL-10 and the clinical symptoms of AOSD. As shown in Table 2, the levels of IL-10 were significantly higher in AOSD patients who had fever, sore throat, rash, lymphadenopathy, splenomegaly, pneumonia, and arthralgia than in AOSD patients who did not ($p < 0.05$).

Discussion

The expression of IL-10, which exhibits anti-inflammatory effects on the immune system, is altered in many autoimmune diseases. Although the levels of IL-10 are increased in inflammatory diseases such as SLE, RA and SSc [10–12], the levels of IL-10 in AOSD patients are still controversial. Rau M. et al. mentioned that the levels of IL-10 were increased in AOSD patients ($n = 18$) compared with those in HCs ($n = 7$), but this study had the disadvantage of a small number of samples [13]. However, Feist et al. speculated that the production of IL-10 in AOSD was insufficient [1]. Thus, to address this issue, we examined the serum levels of IL-10 in a larger number of AOSD samples with a highly sensitive electrochemiluminescence assay. We confirmed the increased serum levels of IL-10 in AOSD patients. In addition, we found that IL-10 levels were significantly correlated with systemic score, clinical and laboratory manifestations, and the levels of inflammatory cytokines in AOSD patients.

IL-10, a typical anti-inflammatory cytokine, inhibits pro-inflammatory cytokine expression and acts as important regulatory factor in both innate and adaptive immune responses [6]. For instance, IL-10 impaired inflammasome activation and IL-1β production in macrophages by regulating metabolic reprogramming [9]. IL-10 also suppressed neutrophil

Table 2 Comparison of the serum levels of IL-10 according to the disease manifestations in AOSD patients

Manifestations	Serum IL-10 levels		95% CI	*p* value
Fever	(+), *n* = 37	1.56 (0.63–3.05)	0.000–0.000	0.000
	(−), *n* = 21	0.33 (0.18–0.65)		
Sore throat	(+), *n* = 29	1.36 (0.58–2.89)	0.012–0.017	0.015
	(−), *n* = 29	0.46 (0.21–1.70)		
Skin rash	(+), *n* = 36	1.43 (0.58–2.57)	0.001–0.002	0.002
	(−), *n* = 22	0.34 (0.17–1.16)		
Lymphadenopathy	(+), *n* = 31	1.56 (0.59–2.89)	0.001–0.003	0.002
	(−), *n* = 27	0.44 (0.20–0.93)		
Splenomegaly	(+), *n* = 15	2.33 (0.93–3.97)	0.000–0.002	0.001
	(−), *n* = 43	0.58 (0.25–1.54)		
Pericarditis	(+), *n* = 8	1.62 (0.95–2.99)	0.079–0.089	0.084
	(−), *n* = 50	0.69 (0.28–2.50)		
Pneumonia	(+), *n* = 18	2.18 (0.57–3.40)	0.018–0.024	0.021
	(−), *n* = 40	0.63 (0.27–1.78)		
Pleuritis	(+), *n* = 10	1.00 (0.57–2.11)	0.455–0.475	0.465
	(−), *n* = 48	0.74 (0.29–2.56)		
Myalgia	(+), *n* = 15	1.50 (0.57–3.97)	0.096–0.108	0.102
	(−), *n* = 43	0.72 (0.27–2.03)		
Arthritis	(+), *n* = 14	0.72 (0.33–3.40)	0.607–0.626	0.616
	(−), *n* = 44	0.88 (0.31–2.31)		
Arthralgia	(+), *n* = 38	1.52 (0.58–2.89)	0.000–0.001	0.000
	(−), *n* = 20	0.34 (0.19–0.85)		

Serum levels of IL-10 are shown as median (IQR); differences between two groups were performed with Mann–Whitney *U* test for nonparametric data

migration and inflammation in autoimmune disease [18] and promoted regulatory T cell (Treg) function while inhibiting Th1 helper cell development [7]. A recent study showed that macrophages are the main target cells of the inhibitory effects of IL-10 [9, 19]. IL-10 inhibited pro-inflammatory cytokine production (such as IL-1β, TNF-α, interferon-γ, and IL-6) in macrophages [8, 9]. Moreover, IL-10 stimulated macrophages (also referred to as "M2c" macrophages) during the resolution of inflammation. The level of CD163, the typical marker of M2 macrophage-mediated cellular anti-inflammatory functions, was specifically increased by IL-10 in CD14+ cells derived from PBMCs [20]. The upregulated levels of CD163 were found in monocytes from patients with systemic juvenile idiopathic arthritis, which shares clinical similarities with AOSD and macrophage activation syndrome (MAS) [20]. Additionally, CD163 was positively correlated with ferritin serum levels and disease activity in patients with AOSD [21]. Furthermore, miR-125a-5p was upregulated in monocytes and contributed to the polarization of M2 phenotypes [22]. Thus, we deduced that IL-10 induces M2 polarization and inhibits pro-inflammatory cytokine production in the pathogenesis of AOSD.

It is interesting that we also found increased levels of IL-37, another anti-inflammatory cytokine that inhibits the production of pro-inflammatory cytokines such as TNF-α and IL-1β, in the serum of AOSD patients [23]. The compensatory expression of anti-inflammatory cytokines might be a common phenomenon in the pathogenesis of AOSD. Moreover, anti-inflammatory cytokines such as IL-4, IL-10 or IL-37 [24] induce M2 polarization, and after M2 polarization, the level of IL-10 is increased, quelling the aberrant inflammation in active AOSD, which could partially explain the increased IL-10 levels. As a result, the uncontrollable inflammatory cascade involved in the pathogenesis of AOSD does not seem to be due to the insufficient expression of anti-inflammatory factors such as IL-10, as researchers expected [1].

It is important to emphasize the limitations of our study. First, this study was limited by a relatively small sample size and cross-sectional design. Second, further studies are still needed to test the correlation between IL-10 and indicators of disease outcome, such as clinical pattern, AOSD-related complications, and comorbidities. Finally, functional experiments are needed to explore the role of IL-10 in the pathogenesis of AOSD.

In conclusion, we found that the increased levels of IL-10 in AOSD patients were positively correlated with disease activity and inflammatory cytokine levels, which provide insight into the role of anti-inflammatory factors in the pathogenesis of AOSD.

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Compliance with ethical standards The study was performed in accordance with the Declaration of Helsinki and the principles of good clinical practice. Biological samples were obtained under a protocol approved by the Institutional Research Ethics Committee of Ruijin Hospital (identifier 2016-62), Shanghai, China. Informed consent was obtained from the recruited subjects.

Disclosures None.

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