Increased interleukin-11 associated with disease activity and development of interstitial lung disease in patients with rheumatoid arthritis

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Abstract

Objective

To investigate the association of serum interleukin-11 (IL-11) with disease activity and occurrence of interstitial lung disease (ILD) in patients with rheumatoid arthritis (RA).

Methods

One hundred and six RA patients were included, including 31 with ILD. All patients were divided into two groups according to the 28-joint Disease Activity Score (DAS28), active-disease group (DAS28>3.2) and target-achieved group (DAS28≤3.2). Serum IL-11 was detected by ELISA. Serum autoantibodies [anticitrullinated protein antibody (ACPA) and rheumatoid factor (RF)], inflammatory markers [C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)], and complete blood count were measured with routine methods.

Results

Serum IL-11 was upregulated in RA patients compared with healthy controls (HC), and increased more significantly in patients with ILD (RA-ILD) than patients without ILD (RA-nonILD). In both RA-ILD and RA-nonILD patients, serum level of IL-11 was higher in the active-disease group than that in the target-achieved group. Pearson correlation analysis confirmed that IL-11 was positively correlated with DAS28. No significant correlation was found between serum level of IL-11 and ACPA or RF. IL-11 was positively correlated with ESR and CRP levels and PLT count in RA patients.

Conclusion

IL-11 was found to be involved in the development of arthritis and ILD in RA patients, and might constitute a potential target for the treatment of RA-ILD.

Key words

interleukin-11, interstitial lung disease, rheumatoid arthritis, anticitrullinated protein antibody, platelet

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Received on November 6, 2020; accepted in revised form on February 1, 2021.

Competing interests: none declared.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease, characterised by synovial inflammation of the joint and clinical presentation of joint swelling and pain and morning stiffness. Uncontrolled persistent inflammation will ultimately lead to joint damage and deformities, and seriously affect the patients' life quality (1). In addition to joints, RA can affect many other body systems, including the respiratory system, blood system, and nervous system, etc. Among the extra-articular manifestations, interstitial lung disease (ILD) is the most frequent and can be detected in 10–50% of RA patients depending on the definition (*i.e.* clinical or preclinical ILD, detected by high-resolution chest computed tomography (HRCT)) (2). The pathogenesis of RA-ILD has not been fully elucidated, and the pivotal factors precipitating RA-ILD warrant further clarification, so as to search for the potentially promising target for the treatment of RA-ILD.

Transforming growth factor–β (TGFβ) family proteins are considered the principal cytokines that promote fibrosis and may play a role in lung fibrosis (3). A recent study showed that upregulation of interleukin-11 (IL-11) is the dominant transcriptional response to TGFβ1 exposure and required for its pro-fibrotic effect (4). IL-11 is a member of the IL-6 family of cytokines, which include IL-6 and IL-27 and contain a common receptor subunit gp130 (5). The main source of IL-11 is stromal fibroblasts, which produce IL-11 under the influence of other cytokines including TGFβ, IL-1β and IL-22. The IL-11 receptor subunit α-1, IL-11RA1, is mainly expressed in T cells, macrophages, megakaryocytes, osteoblasts and epithelial cells. After binding to its receptor, IL-11 exerts its effect through activation of JAK-STAT3, ERK and PI3K/AKT/mTORC1 pathway (5, 6).

Studies have shown that IL-11 is closely related to pulmonary fibrosis. The expression of IL-11 gene was upregulated in lung tissue of idiopathic pulmonary fibrosis (IPF) patients (7), and was positively correlated with the severity of pulmonary fibrosis while negatively correlated with pulmonary function (8). In a mouse model of bleomycin-induced pulmonary fibrosis, lung fibroblasts from IL-11RA1 gene deficient mice did not respond to profibrotic stimulation, and the mice were protected from fibrosis. Neutralising antibody against IL-11 could diminish lung inflammation and reverse pulmonary fibrosis while inhibiting the activation of ERK and SMAD (8). In addition, the expression of IL-11 was increased in skin fibroblasts of patients with systemic sclerosis (SSc) and lung fibroblasts of SSc-related ILD patients (9, 10).

The immunomodulatory role of IL-11 in RA has also been investigated. It has been reported that the expression of IL-11 was elevated in synovial membranes, synovial fluids, and blood sera of RA patients (11, 12). The serum IL-11 level of RA patients in remission decreased, which was related to the improvement of DAS28 (13). In *ex vivo* assays using synovial tissue from RA patients, IL-11 gene expression was the highest in the whole genome in fibroblasts activated by macrophages (14). Besides, IL-11 and IL-11Rα were co-expressed in RA synovial tissue fibroblasts and endothelial cells. Activated fibroblasts could also secrete angiogenic factors such as vascular endothelial growth factor (VEGF), which, together with IL-11, promoted neovascularisation and formation of RA pannus (12). All these studies confirmed that IL-11 plays an important role in the development of RA synovitis. However, whether IL-11 contributes to RA-ILD has not been reported. In this study, we explored the correlation between serum IL-11 and ILD in RA patients, and analysed the relationship between IL-11 and disease activity, autoantibodies [rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPAs)], and platelet count as well. We found that IL-11 was related to RA-ILD, disease activity and platelet elevation, suggesting that IL-11 may be a crucial factor in the development of synovitis and ILD in RA patients, which makes it a potential target for the treatment of RA as well as RA-ILD.

Table I. Demographic and clinical characteristics of RA patients and healthy controls.

	RA with ILD		RA without ILD		HC
Groups	active disease	target-achieved	active disease	target-achieved	
number	19	12	40	35	50
Age (years)	59.84 ± 7.10	60.50 ± 6.71	58.83 ± 8.76	56.49 ± 11.33	57.14 ± 6.92
Sex (male/female)	6:13	3:9	5:35	6:29	10:40
DAS28	5.01 ± 0.59	2.83 ± 0.25	4.95 ± 0.48	2.39 ± 0.56	
Remission (DAS28≤2.6) (n)	-	4	-	19	-
LDA (2.6<DAS28≤3.2) (n)	-	8	-	16	-
MDA (3.2<DAS28≤5.1) (n)	10	-	26	-	-
HDA (DAS28>5.1) (n)	9	-	14	-	-
ACPA (RU/ml)	588.2 (253.0, 3200.0)	368.8 (267.3, 2832.4)	302.5 (152.9, 856.2)	473.0 (178.0, 917.1)	-
RF (IU/ml)	61.6 (28.1, 322.0)	101.5 (29.4, 410.5)	96.2 (20.0, 338.5)	67.0 (25.9, 249.0)	-
ESR (mm/h)	94.4 ± 27.4	33.3 ± 12.6	74.2 ± 29.2	22.8 ± 12.5	-
CRP (mg/L)	49.3 ± 36.1	9.8 ± 0.4	27.1 ± 20.6	5.0 ± 4.0	-
PLT ($\times 10^9$/L)	331.0 ± 65.5	255.6 ± 109.6	233.9 ± 77.2	206.4 ± 57.3	217.4 ± 49.1
ILD disease duration (year)	2.8 ± 1.7	3.1 ± 1.6			
HRCT pattern					
NSIP (n)	12	10	-	-	-
UIP (n)	7	2	-	-	-
Warrick score	7.0 ± 3.8	8.4 ± 3.7	-	-	-

RA: rheumatoid arthritis; HC: healthy control; ILD: interstitial lung disease; DAS28: the 28-joint Disease Activity Score; LDA: low disease activity; MDA: moderate disease activity; HAD: high disease activity; ACPA: anticitrullinated protein antibody; rheumatoid factor: RF; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood cell; Hb: haemoglobin; PLT: platelet. HRCT: high resolution computed tomography; NSIP: non-specific interstitial pneumonia; UIP: usual interstitial pneumonia.

Materials and methods

Patients and controls

This was a retrospective study performed in Nanjing First Hospital, a tertiary referral centre. We included 106 patients with complete clinical data who attended our Rheumatology clinic or was admitted into hospital from January 2019 to December 2019. All the patients met either the 1987 American College of Rheumatology (ACR) criteria for definite RA (15) or 2010 ACR/European League Against Rheumatism (EULAR) classification criteria for RA (16). Patients with infection, malignancy or another connective tissue disease were excluded. At inclusion, demographic, clinical and laboratory details were obtained from hospital databases (Table I). Among the patients, 31 were diagnosed ILD by HRCT. ILD HRCT-pattern and Warrick score were determined by a radiologist. The Warrick score was calculated based on the radiological appearance and extent as described before (17). The total score can vary between 0 and 30 where the higher score indicates a higher degree of radiological change. According to DAS28-ESR, patients were classified as in remission (DAS28≤2.6), low disease activity (2.6<DAS28≤3.2), moderate disease activity (3.2<DAS28≤5.1), or high disease activity (DAS28>5.1). To simplify statistical analysis, we divided the patients into two groups: active-disease group which included patients with DAS28>3.2, and target-achieved group which included patients with DAS28≤3.2 who had achieved treatment target of remission or low disease activity (18). Fifty age- and gender-matched healthy controls were selected from Physical Examination Center in Nanjing First Hospital during the same period. The serum of patients and controls was obtained from the discarded serum after laboratory test in our hospital, processed with standard procedure and then frozen at -80°C until analysis. This study was carried out in accordance with the Declaration of Helsinki and was approved by the ethics committee of Nanjing First Hospital.

Laboratory tests

Both serum IL-11 and ACPA were measured by enzyme-linked immunosorbent assay (ELISA) according to the manufacturers' tutorial. IL-11 ELISA kit was purchased from CUSABIO technology LLC (Wuhan, China) while the ACPA ELISA kit was purchased from SVAR life science company (Malmö, Sweden). RF, complete blood count, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured with standard methods by the laboratory department of Nanjing First Hospital.

Statistical analysis

Data were analysed using GraphPad Prism, version 5 (GraphPad Software, San Diego, CA, USA). Descriptive statistics were used for presentation of patient characteristics.

Normality was checked using the Shapiro-Wilk test. Continuous variables in normal distribution were presented as mean ± standard deviation (SD) while continuous variables in non-normal distribution were presented as median (interquartile range (IQR)). The discrepancies between two groups were evaluated using two-sided Student's t-test or Mann Whitney U-test when non-normally distributed. Chi-square or Fisher's exact test was used to compare categoric variables. Correlation between two groups was examined using Pearson or Spearman correlation analysis, depending on data type and distribution. *p*-values <0.05 were regarded as statistically significant.

Results

Demographic and clinical characteristics of subjects

The demographic and clinical characteristics, including laboratory and imaging data, of the subjects are shown in Table I. Among the 31 patients with ILD, 19 had active disease while 12 reached treatment target of remission or low disease activity. Among the 75 patients without ILD, 40 had active disease while 35 reached treatment target. There was no significant difference in age and gender among RA groups and between RA patients and healthy controls. The ILD disease duration was 2.8±1.7 years and 3.1±1.6 years while the Warrick score was 7.0±3.8 and 8.4±3.7 in RA-ILD patients with active disease and target achievement, respectively, both showing no significant difference between the two groups. Among the 19 RA-ILD patients with active disease, 12 (63.2%) had HRCT pattern of NSIP and 7 (36.8%) had UIP, while among the 12 RA-ILD patients with target achievement, 10 (83.3%) had NSIP and 2 (16.7%) had UIP. Fisher's exact test showed no significant difference in HRCT-pattern composition between the two groups.

Serum IL-11 was upregulated in RA patients, even higher in RA-ILD patients and was correlated with disease activity.

The level of serum IL-11 in RA patients with or without ILD (marked as RA-ILD or RA-nonILD) was higher than that in healthy controls, and increased more significantly in RA-ILD patients (Fig. 1A). To assess whether the elevation of serum IL-11 was caused by active inflammation, we divided the patients into two subgroups, active-disease group and target-achieved group, based on DAS28 as described above. The analysis showed that in both RA-ILD and RA-nonILD patients, serum level of IL-11 was higher in the active-disease group than in the target-achieved group (Fig. 1B), suggesting that IL-11 is related to RA disease activity. Pearson correlation analysis confirmed that IL-11 was positively correlated with DAS28 score (Fig. 1C). To evaluate whether serum IL-11 was

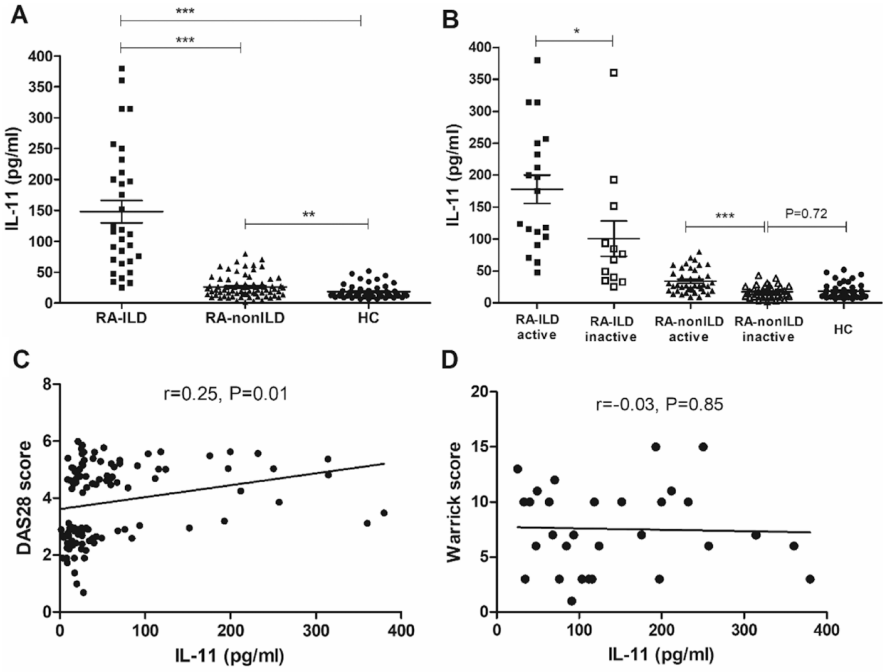

Fig. 1. Serum IL-11 was elevated in RA patients, especially in patients with ILD and active disease.
A: Comparison of serum IL-11 between RA-ILD patients, RA-nonILD patients and HC;
B: Comparison of serum IL-11 between RA-ILD or RA-nonILD patients subdivided by disease activity;
C: Correlation between serum IL-11 and DAS28;
D: Correlation between serum IL-11 and Warrick score of HRCT in RA-ILD patients. RA-ILD: RA patients with ILD; RA-nonILD: RA patients without ILD; HC: healthy controls; RA-ILD active: RA patients with ILD and active disease (DAS28 >3.2); RA-ILD inactive: RA patients with ILD but without active disease (DAS28 ≤3.2); RA-nonILD active: RA patients without ILD but with active disease; RA-nonILD inactive: RA patients without ILD or active disease.
*p<0.05, **p<0.01, ***p<0.001.

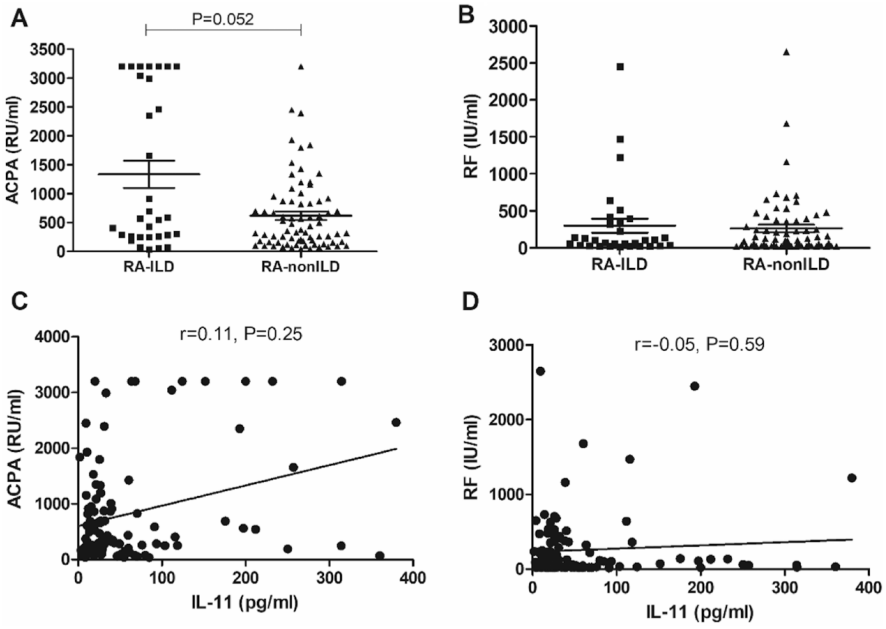

Fig. 2. Serum IL-11 was not correlated with ACPA and RF in RA patients.
A: Comparison of serum ACPA between RA-ILD and RA-nonILD patients;
B: Comparison of serum RF between RA-ILD and RA-nonILD patients;
C: Correlation between serum IL-11 and ACPA;
D: Correlation between serum IL-11 and RF.
RA-ILD: RA patients with ILD; RA-nonILD: RA patients without ILD; ACPA: anticitrullinated protein antibody; RF: rheumatoid factor.

associated with the severity of ILD, we performed correlation analysis between IL-11 and Warrick score in RA-ILD patients and no significant correlation was found (r= -0.03, p=0.85) (Fig. 1D).

Serum IL-11 was not correlated with ACPA and RF in RA patients

We compared the level of serum ACPA and RF between RA-ILD and RA-nonILD patients. The results showed that serum level of ACPA tended to be higher in RA-ILD than that in RA-nonILD patients, though not statistically significant (p=0.052) (Fig. 2A). Meanwhile, no significant difference was found in the level of serum RF between the two groups (Fig. 2B). Spearman correlation analysis showed that IL-11 had no significant correlation with ACPA or RF (Fig. 2C-D). Additional analysis also showed that serum ACPA and RF had no significant correlation with DAS28 either (data not shown).

Correlation between serum IL-11 and inflammatory markers

To investigate the correlation of IL-11 with inflammation, we performed correlation analysis between serum IL-11 and inflammatory markers, including ESR and CRP, as well as platelet (PLT) number which is also considered as an index for inflammation in RA (19). The results showed that serum IL-11 was positively correlated with both ESR (r=0.32, p<0.001) (Fig. 3A) and CRP (r=0.42, p<0.001) (Fig. 3B). Intriguingly, serum IL-11 was also positively correlated with PLT number in RA patients (r=0.57, p<0.001) (Fig. 3C), while no such correlation was found in healthy controls (Fig. 3D).

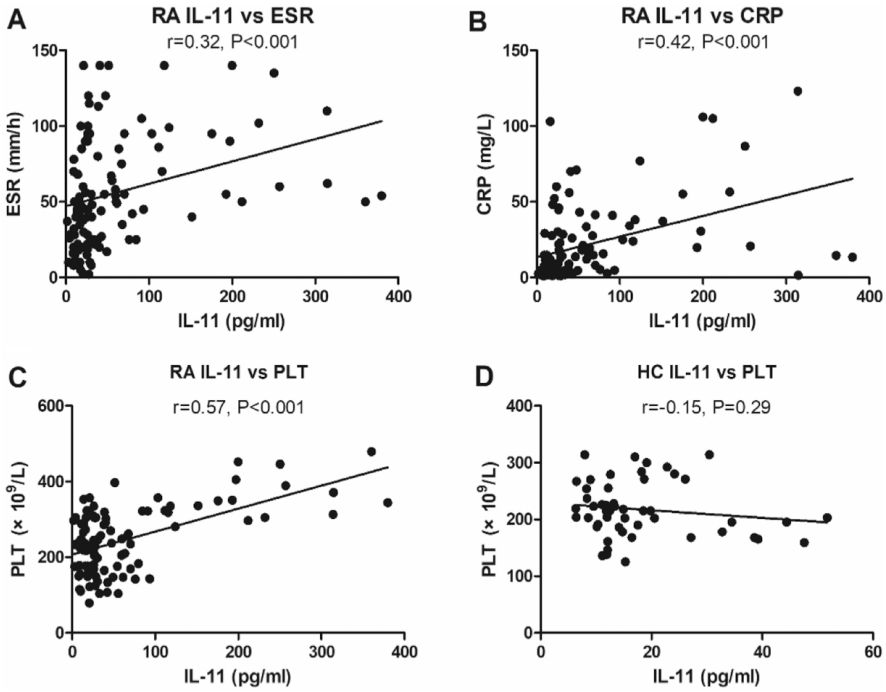

Fig. 3. Correlation between serum IL-11 and inflammatory markers.
A: Correlation between ESR and serum IL-11 in RA patients.
B: Correlation between CRP and serum IL-11 in RA patients.
C: Correlation between the number of PLT and serum IL-11 in RA patients.
D: Correlation between the number of PLT and serum IL-11 in healthy controls.
HC: healthy controls; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PLT: platelet.

Discussion

RA-ILD is a common complication of RA, but its pathogenesis has not been completely clarified. Therefore, current therapy is mainly conventional immunosuppressive agents and non-specific anti-fibrotic drugs whereas effective targeted therapy is not available. The results of this study showed that serum IL-11 was significantly increased in RA patients, which was related to the development of ILD and disease activity, suggesting that IL-11 might play a crucial role in the pathogenesis of RA and RA-ILD which makes it a promising therapeutic target. To our knowledge, this is the first report on the role of IL-11 in RA-ILD.

The lung has a special role in human physiology, interfacing between the environment and the body to function as a physical and immunologic defensive barrier to a variety of pathogenic factors. Some researchers suggest that the lung may play a potential role in the initiation and propagation of RA-related autoantibodies (20). Environmental factors, such as smoking, air pollution and microbial infection, may elicit citrullination of lung proteins in genetically susceptible individuals, thus driving the production of ACPA and other RA related immune factors. The environmental factors can also activate the innate immune cells of the lung through the pathogen recognition molecules, thereby activating the inflammatory cytokine cascade and immune response, eventually leading to the development of ILD and other forms of lung diseases in RA (2). In this study, we found that the level of serum IL-11 in RA-ILD patients increased significantly compared with RA patients without ILD, implying that IL-11 was involved in the pathogenesis of ILD. We speculate that lung fibroblasts might be activated by environmental factors to produce IL-11, which contributes to the development of lung fibrosis and circulates into the joint synovium, promoting the occurrence of synovitis. However, we did not find any significant correlation between serum level of IL-11 and the severity of ILD as assessed by Warrick score, maybe due to the small number of ILD patients or the complicated mechanism underlying the development of RA-ILD.

The role of IL-11 in inflammation is complicated and controversial. It has been considered as an anti-inflammatory cytokine, which can directly affect macrophages and other effector cells in inflammatory sites by inhibiting the production of various cytokines, such as TNF-α, IL-1β, IL-12, IL-10, TGF-β and IL-6, and directly antagonise the TNF-α signalling pathway induced by monocytes/macrophages. Animal experiments showed that IL-11 can di-

rectly act on CD4+ T cells, thus stimulating the production of Th2 and inhibiting the production of Th1 (6). However, a few studies have shown that IL-11 has pro-inflammatory effect, such as inducing naïve CD4+T cells to differentiate into Th17 cells, and may play a role in the inflammatory response of MS (21). In collagen induced arthritis (CIA), systemic treatment with IL-11 reduced disease severity (22) while local injection of IL-11 exacerbated joint swelling (23). The results of this study showed that the serum level of IL-11 in RA patients was significantly increased and positively correlated with DAS28. This is consistent with the study by Chung *et al*. who reported that RA patients in remission had lower serum IL-11 levels that correlated with DAS28 improvement (13).

High disease activity is an independent risk factor for ILD in RA patients (24). Though the definite correlation between disease activity and ILD has not been elucidated, abnormal release of some inflammatory cytokines might be the culprit behind the scene. Studies have shown that RA-ILD is associated with the increase of various cytokines, including IL-33 and IL-18 (25, 26). In this study, we showed that the increase of serum IL-11 was related to both the disease activity of RA and RA-ILD, indicating that IL-11 might exert an upstream role in the development of arthritis and ILD in RA patients.

It has been reported that seropositivity of RF and ACPA is a risk factor for RA-ILD (27, 28). However, no significant difference of serum ACPA or RF titre was found between patients with or without ILD in this study, which might be due to the relatively small number of patients included, especially in the RA-ILD group. Meanwhile, correlation analysis showed no significant correlation between IL-11 and RF/ACPA, indicating that upregulation of IL-11 and autoantibodies occurs separately during the development of RA.

IL-11 was first discovered in bone-marrow-derived stromal cell lines and was found to support the growth of hematopoietic cells in the bone marrow niche. *In vivo* studies showed that IL-11 could increase the production of PLT, which led to the development of recombinant human IL-11 (rhIL-11) for the treatment of thrombocytopenia in chemotherapy patients (29). In this study, we found that the number of PLT was upregulated in RA patients alongside with increased level of serum IL-11, and further analysis confirmed a positive correlation between IL-11 and the PLT count. Besides, we also found that the PLT count was higher in patients with ILD and active-disease, in parallel with an increased level of serum IL-11 in these patients (data not shown). Taken together, IL-11 seems to be a crucial link among PLT elevation, ILD development and joint inflammation.

There are several limitations to this study. First, this is a single-centre, retrospective study, and the number of included patients, especially patients with ILD, is relatively small. A multicentre trial with larger sample size is necessitated to corroborate the findings. Second, we only detected the level of IL-11 in serum, but not in the lungs or synovium/synovial fluid, so we could not identify the origin of increased IL-11, and whether the expression of IL-11 was in parallel in these three different locations. In addition, we only analysed the correlation of IL-11 with ILD and disease activity, which could not ascertain the direct effect of IL-11 in pulmonary fibrosis and arthritis. Further experiments in animal models are needed to confirm the cause-effect relationship among IL-11, ILD, and arthritis.

In conclusion, the results of this study suggest that IL-11 might play an important role in RA-ILD, which makes it a potential target for the treatment of RA-ILD in the future.

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