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Prognostic Significance of Serum Interleukins and Soluble ST2 in Traditional Chinese Medicine (TCM) Syndrome-Differentiated Rheumatoid Arthritis

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Data Interpretation D
Manuscript Preparation E
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Backgrounds: The aim of this study was to explore the possible correlations of serum interleukins and soluble ST2 (sST2) protein with clinical features and inflammatory cytokines in rheumatoid arthritis (RA) patients, as well as to assess ability of TCM (Traditional Chinese Medicine) syndromes to differentiate RA patients and evaluate prognosis.

Material/Methods: Thirty RA patients and 25 healthy individuals were enrolled. Syndrome activity was evaluated, and lab tests were performed. Serum levels of IL-10, IL-17, IL-33, and sST2 were assessed by ELISA.

Results: Serum levels of sST2, IL-33, and pro-inflammation cytokine IL-17 were all up-regulated, while the immunosuppressive cytokine IL-10 was decreased in RA patients. Serum IL-33 level was positively associated with ESR, CRP, and RF, as well as with HAQ score, VAS score, and DAS28 scores ($P<0.05$). Serum sST2 level was correlated with the morning stiffness time and ESR, as well as scores of HAQ and DAS28 ($P<0.05$). In addition, IL-33 level was positively corelated with IL-17 ($r=0.83$, $P<0.01$) and the relative ratio of IL-10/IL-17 ($r=0.904$, $P<0.01$), and was negatively related with IL-10 ($r=-0.632$, $P<0.01$). TCM syndrome differentiation was conducted for RA patients, including the hot syndromes and cold syndromes groups. Hot syndromes RA patients had significantly more severe inflammation compared with cold syndromes patients.

Conclusions: IL-33 is a possible index for monitoring disease activity and inflammation condition in RA. IL-33 contributes to RA pathogenesis through unbalancing IL-10 and IL-17. In terms of TCM, hot syndromes RA presented more serious inflammation and more active disease activity, indicating a poorer prognosis.

MeSH Keywords: Arthritis, Juvenile • Inflammation • Interleukin-23 Subunit p19

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Background

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by uncontrolled proliferation of synovial tissue and a wide array of multisystem comorbidities [1]. RA typically causes pain, swelling, and progressive damage to synovial joints [2]. Despite progress in elucidating the pathogenesis of RA, its causes remain unknown, which limits development of RA treatments. Currently, RA patients are generally treated by synthetic and biological disease-modifying anti-rheumatic drugs (DMARDs) [3]. Nevertheless, many RA patients do not respond well to DMARDs [4]. More efforts are needed to identify novel targets for disease treatment. Recently, it has been suggested that cytokines participate in regulating the pathogenesis of RA.

IL-33 was first found in 2005 as a new member of the IL-1 family [5]. It was reported that IL-33 exerts its biological effects via IL-1 receptor ST2, activate NF-κB (nuclear factor κB), and MAP (mitogen-activated protein) kinases, and drives production of Th2-associated cytokines [6]. Accumulating evidence has indicated that IL-33 plays key roles in RA progression [7,8], although the specific mechanism remains unknown. The soluble form of ST2 – sST2 – which is considered a decoy receptor that blocks the effect of IL-33, is reported to reduce symptoms in collagen-induced arthritis (CIA) [9]. Inhibition of the IL-33 signaling pathway through blocking sST2 can also attenuate the severity of CIA [10]. The effect of sST2 on RA has become a novel direction in the developing treatments for RA. However, there has been little clinical research on the sST2 and IL-33 levels of different syndromes (ZHENG in Mandarin) of RA.

In Traditional Chinese Medicine (TCM) theory, RA is considered as an impediment disease ("Bi" syndrome in Mandarin) and is caused by the invasion of wind, dampness, or heat pathogens into the human body [11]. Clinically, RA patients are classified into cold and hot syndromes: the cold syndrome is characterized by severe arthralgia which can be relieved by warming but aggravated by cooling, loose stools, an absence of thirst, clear profuse urine, and a thin white tongue coating combined with a fast pulse. In contrast, hot syndrome patients suffer from severe arthralgia with red swelling of the skin and high skin temperature which can be relieved by cooling but is aggravated by warming, constipation, thirst, dark-colored urine, a red tongue with a yellow coating, and rapid pulse [12]. Because RA patients with different syndromes showed distinct medical manifestations, interventions, and molecular mechanisms, it would be of great interest to study the serum levels of sST2 and IL-33 in RA patients with different syndromes.

In the present research, the serum levels of IL-10, IL-17, IL-33, and sST2 in RA patients were confirmed and their intra-correlations and the correlations with RA clinical features were further analyzed. IL-33 was found to be a possible index for monitoring disease activity and inflammation condition. Notably, our study also classified RA patients into cold syndrome and hot syndrome groups according to TCM syndromes. Hot syndromes RA presented more serious inflammation and more active disease activity, indicating a poorer prognosis.

Material and Methods

Patients

All the samples were collected from RA patients in an outpatient clinic of the Department of Integrated Chinese and Western Medicine, Tongji Hospital, from April 2013 to July 2013. The healthy subjects were from the Physical Examination Center, Tongji Hospital. All RA patients were grouped according to the American College of Rheumatology/European League Against Rheumatism classification criteria for RA (Table 1) [13]. RA patients were classified to cold or hot syndrome according to the TCM criteria [12].

Cohort selection

Participants were recruited according to the following criteria: (i) satisfied the RA classification criteria and the TCM cold/hot syndrome criteria; (ii) joint x-ray showed stage I to III; (iii) age 18–70 years; and (iv) signed the informed consent. Patients with the following major diseases or conditions were exclude: (i) end-stage rheumatoid arthritis; (ii) Sjogren syndrome or systemic lupus erythematosus; (iii) cardiovascular, pulmonary, hepatic, renal, or hematological diseases; (iv) severe extra-articular manifestations such as fever, interstitial pneumonia, renal

Table 1. Correlations between the serum levels of IL-33, sST2, and clinical feature.

	Disease duration	Morning stiff time	ESR	CRP	RF	CCP	HAQ	VAS	DAS28
IL-33	0.38	0.32	0.75*	0.73*	0.48*	0.47*	0.83*	0.69*	0.81*
sST2	0.33	0.41*	0.36*	0.30	0.17	0.08	0.37*	0.30	0.41*

* P<0.05. VAS – visual analog scale; HAQ – health assessment questionnaire; DAS28 – 28-joint count disease activity score; ESR – erythrocyte sedimentation rate; CRP – C-reactive protein; RF – rheumatoid factor; CCP – citrullinated peptide.

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amyloidosis, constrictive pericarditis, or angiitis of the central nervous system that required use of corticosteroids; (v) aged below 18 or above 70 years; (vi) pregnant and lactating women; and (vii) psychiatric diseases.

Clinical data

Clinical data were recorded, including the following information: morning stiffness time, visual analogue scales (VAS) score, modified health assessment questionnaire score, 28-joint count Disease Activity Score (DAS28), swollen joint counts (SJC), and tender joint counts (TJC).

Quantitative analysis for IL-10, IL-17, IL-33, and sST2

A volume of 5 mL blood was collected from participants. Blood samples were subjected to 3000 g centrifugation for 15 min to obtain plasma, and stored at –80°C until analysis. The plasma levels of IL-10, IL-17, IL-33, and sST2 were tested using the corresponding enzyme-linked immunosorbent assay (ELISA) kit.

Laboratory tests

Complete blood count (CBC), erythrocyte sedimentation rate (ESR), serum levels of C-reactive protein (CRP), rheumatoid factor (RF), and anti-citrullinated peptide (anti-CCP) antibody were checked by the Clinical Laboratory Department.

Statistical analysis

Results are presented as mean ±SEM. By using SPSS 19.0, comparisons between groups were assessed using the *t* test. Multiple linear regression and linear correlation analyses were used to assess correlations between 2 parameters. P<0.05 was considered as statistically significant.

Results

Patient characteristics

The basic characteristics of the 55 patients were summarized. The RA group consisted 22 females and 8 males, aged 44.8±12.7 years (range, 22–66 years), with disease duration of 5.5±4.0 years (range, 0.5–20 years); while the healthy group consisted 18 females and 7 males, aged 43.6±12.1 years (range, 21–68 years). There was no significant difference between the 2 groups in age or sex distribution (P>0.05).

Serum levels of IL-10, IL-17, IL-33, and sST2 in RA patients

The serum levels of IL-10, IL-17, IL-33, and sST2 in RA patients were assessed and summarized in Figure 1. Compared to the healthy group, the serum levels of IL-33, sST2 and IL-17 were significantly increased in RA patients (P<0.01). In contrast, IL-10 was significantly decreased compared to the healthy control (P<0.01). We further determined the relative ratio of IL-17/IL-10 and found an increase in RA patients (P<0.01)

Correlations between IL-33, sST2, and clinical features

As shown in Table 1, we compared the correlations between IL-33, sST2, and clinicopathological features, including the symptom duration, morning stiffness time, ESR, CRP, RF, CCP, and scores of HAQ, VAS, and DAS28. The IL-33 level was positively associated with the ESR, CRP, RF, CCP, and scores of HAQ, VAS, and DAS28 (all P<0.05), but was not correlated with disease duration or morning stiffness time. However, the sST2 level was significantly associated with the morning stiffness time, ESR, and scores of HAQ and DAS28 (all P<0.05), and was not associated with the disease duration, CRP, RF, CCP, or VAS score.

Correlations between the serum levels of IL-33 with IL-10, IL-17, and IL-10/IL-17

We further determined the associations between the IL-33 with IL-10, IL-17, and IL-10/IL-17. The serum level of IL-33 was positively correlated with IL-17 and the relative ratio of IL-10/IL-17 (r=0.83, P<0.01; r=0.904, P<0.01), but the level of IL-33 was negatively correlated with IL-10 (r=–0.632, P<0.01).

Clinical characteristics of RA patients with hot/cold syndromes

According to the TCM criteria, the 30 RA patients were further classed into 2 groups: the hot syndromes group (n=11) and the cold syndromes group (n=19). The clinical features, including VAS score, HAQ score, TJC, SJC, and the DAS28 score, are compared in Table 2. All these characteristics of the hot syndromes RA patients were significantly higher than those of the cold syndromes group (all P<0.05).

Serum levels of IL-33, IL-10, and IL-17 in different syndromes of RA patients

By using TCM criteria, we further assessed the serum levels of IL-10, IL-17, IL-33, and sST2 in different syndromes of RA patients (Figure 2). Compared with those in the cold syndromes group, serum IL-33 and IL-17 levels were both up-regulated in RA patients with hot syndromes. For the serum IL-10, however, it showed a lower level in the hot syndromes group (P<0.01). Later, we found the ratio of IL-17/IL-10 was remarkably higher within the hot syndromes group compared to that of RA patients with cold syndromes.

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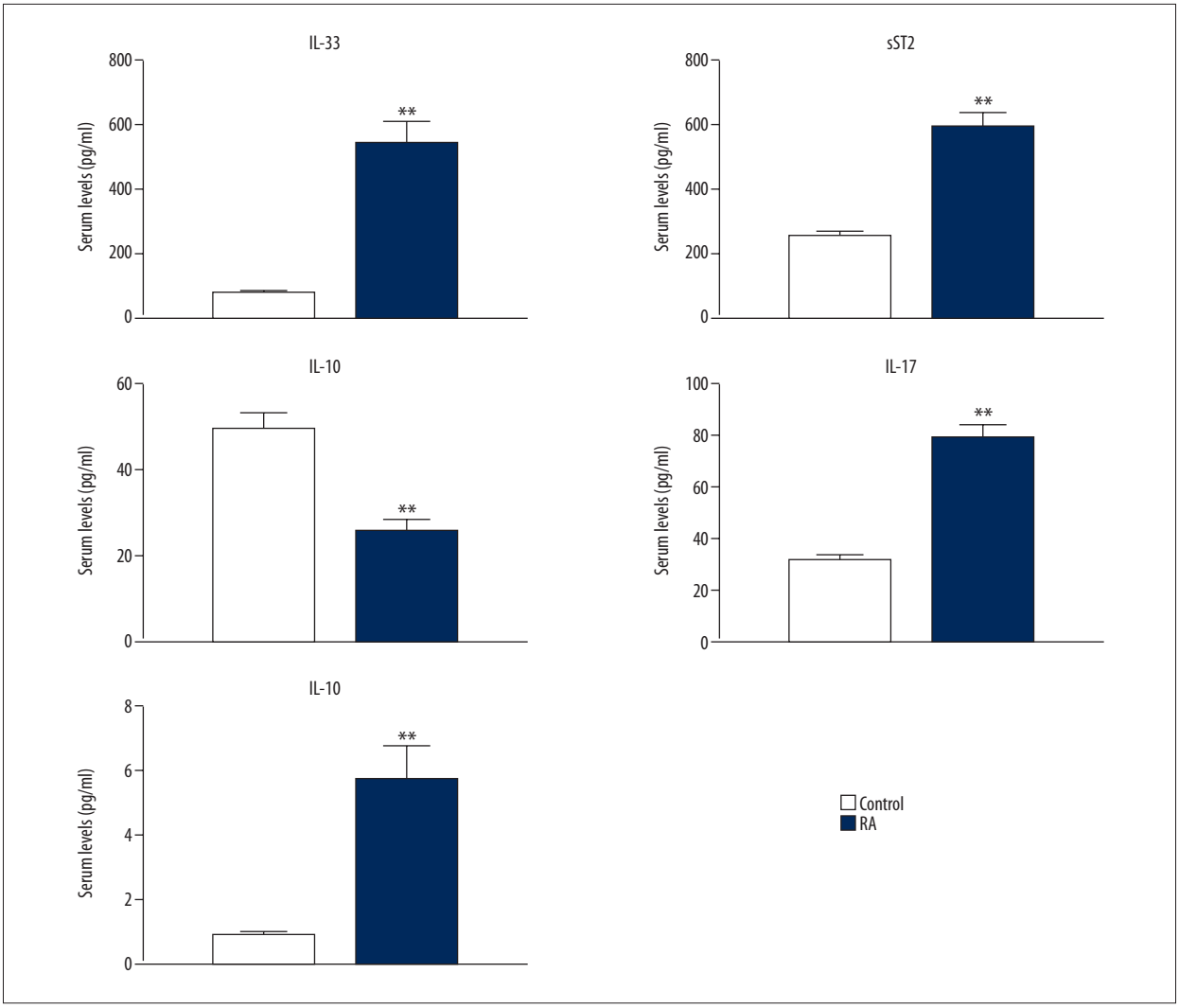

Figure 1. Serum levels of IL-33, sST2, IL-10, and IL-17 in RA patients. Values are presented as mean ±SEM. ** P<0.01 as compared to the RA group.

Table 2. Clinical features of RA patients with hot/cold syndromes.

Group	VAS Score	HAQ Score	DAS28 Score	SJC	TJC
Cold syndromes	2.21±1.23	2.28±3.10	3.52±0.83	3.11±2.98	2.26±2.31
Hot syndromes	4.72±3.00*	6.54±6.02**	4.62±1.44**	7.64±4.90*	7.27±5.71*

Values are expressed as mean ±SEM. * P<0.05 and ** P<0.01 as compared to the cold syndromes group. VAS – visual analog scale; HAQ ,– health assessment questionnaire; DAS28 – 28-joint count disease activity score; TJC – tender joint counts; SJC – swollen joint counts.

Discussion

In the current study, we confirmed that IL-33, sST2, and pro-inflammation cytokine IL-17 in patient serum were all up-regulated, while the immunosuppressive cytokine IL-10 was decreased in RA patients. Although we showed no correlation with disease duration or morning stiffness time, we demonstrated that serum IL-33 was positively correlated with ESR, CRP, RF, HAQ score, VAS score, and DAS28 scores (P<0.05). Of note, we systematically conducted TCM syndrome differentiation for RA patients, including the hot syndromes and cold syndromes groups. Hot syndromes RA patients had significantly more severe inflammation compared with cold syndromes RA patients.

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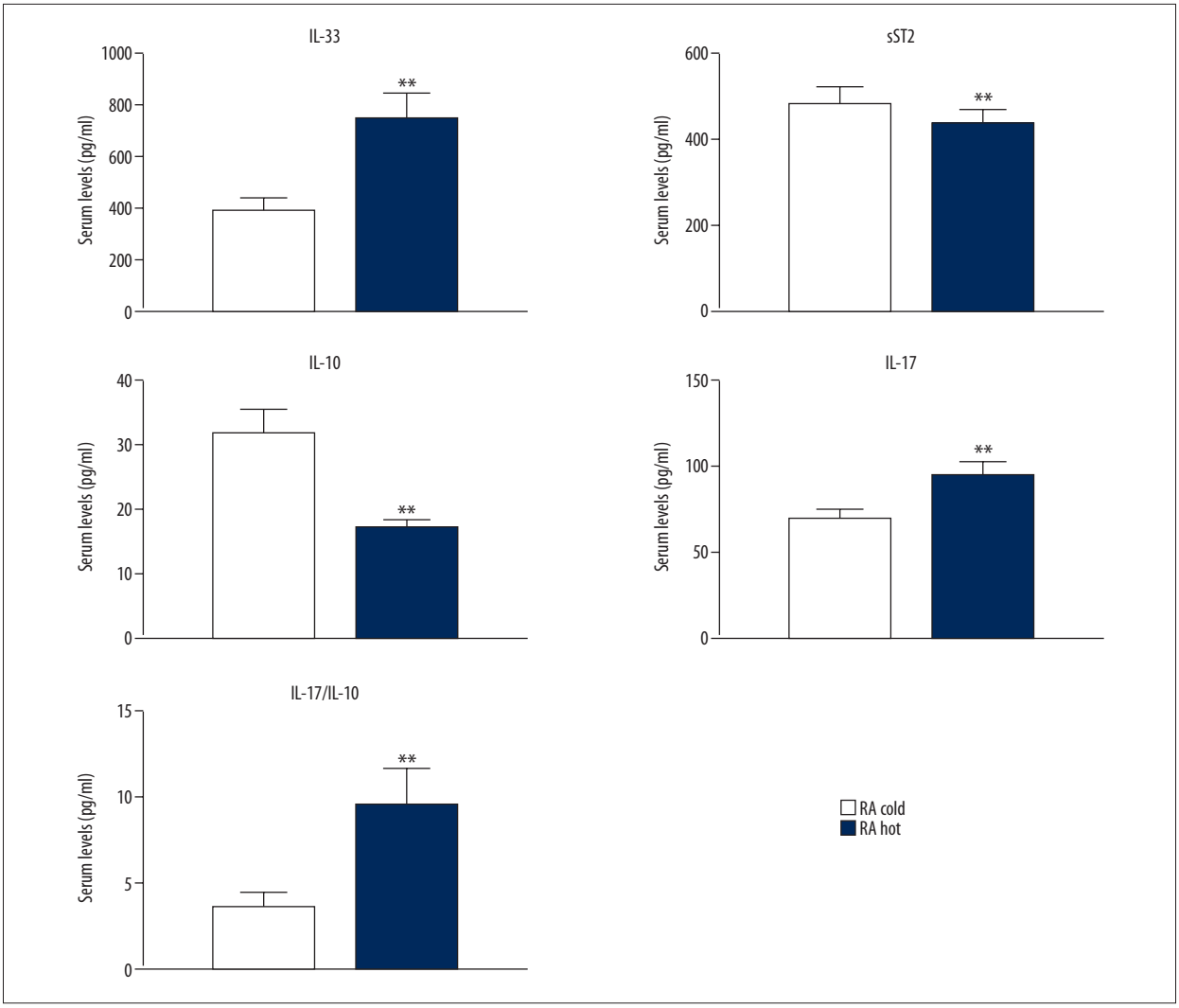

Figure 2. Serum levels of IL-33, sST2, IL-10, and IL-17 in different syndromes of RA patients. Values are presented as mean ± SEM. ** P<0.01 as compared to the RA group.

RA is a chronic inflammatory autoimmune disease characterized by infiltration and activation of mast cells in the synovium [14]. Due to the complicated pathogenesis of RA, many patients are not satisfied with current treatments [4]. Over the past years, increasing studies revealed the involvement of IL-33/ST2 signaling in RA progression [10,14,15]. Recent reports observed the increased IL-33 levels in synovial tissue from RA patients [14,16]. Consistent with these previous reports, we confirmed that serum levels of IL-33 and sST2 were clearly increased in RA patients compared with healthy individuals. As the ligand of ST2 receptor, IL-33 can activate ST2L, which in turn activates NF-κB and MAPK in macrophages, resulting in the production of pro-inflammation cytokines and chemokines [17]. Administration of IL-10, an immunosuppressive cytokine, can suppress IL-33 and inhibit IL-33 activation in the NF-κB signaling pathway in RA [18]. In our study, we confirmed that IL-10 was decreased and pro-inflammation cytokine IL-17 increased in RA patients. Of note, sST2, another isoform of ST2, is also produced by human monocytes when stimulated with pro-inflammation cytokine [19]. Therefore, the observed up-regulation of sST2 indicates inflammation in RA patients. In addition, sST2 can compete with ST2L to bind with IL-33, thus inhibiting the IL-33/ST2 pathway, and may be a possible therapeutic direction for RA treatment.

To further explore the role of sST2 and IL-33 in RA remission and progression, and to explore the possible pathogenesis of RA, we studied the associations among the serum levels of sST2, IL-33, and clinicopathological features. The IL-33 level was positively correlated with the CRP, ESR, and score of HAQ, VAS, and DAS28, as well as CCP and RF (P<0.05), but not symptom duration or morning stiffness time. On one hand, IL-33 levels in RA patients were closely associated with disease activity but not with disease duration, indicating IL-33

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might serve as a monitoring index for disease activity as well as inflammation condition in RA. On the other hand, since anti-CCP antibody and RF are specific diagnostic indexes for RA and are of great significance in prognosis estimation [20,21], IL-33 could be an index for RA prognosis estimation because high IL-33 level indicates poor prognosis of RA. Although the serum sST2 level was only associated with morning stiffness time, ESR, and scores of HAQ and DAS28 ($P<0.05$), it indicates disease activity to some extent.

Although the RA pathogenesis is still elusive, many researchers suggest it is closely correlated with T cells, including both regulatory T cells (Tregs) and T helper cells. Th17, which was recognized to play significant roles in autoimmune and inflammatory diseases [22–24], can secrete the pro-inflammatory cytokine IL-17, while Tregs can maintain the immune homeostasis by secreting anti-inflammation cytokines like IL-10 [25,26]. It was reported that the Th17/Tregs ratio was positively correlated with the remission of disease activity in RA [27,28]. Notably, naive T cells can be induced to differentiate along a pathway favoring the development of Th17 or Tregs in a mutually exclusive manner [29,30]. Thus, the development of Th17 instead of Tregs under certain conditions may be responsible for the RA pathogenesis. Our results showed that serum IL-10 was significantly down-regulated in RA cases, while IL-17 and IL-17/IL-10 were all increased compared with healthy individuals, indicating an imbalance of Th17 and Tregs in RA. Additionally, serum IL-33 was shown to be positively correlated with IL-17/IL-10, indicating that IL-33 might contribute to RA pathogenesis through unbalancing Th17 and Tregs.

To the best of our knowledge, there are few traditional Chinese medical symptomatology studies of RA. A distinctive feature of TCM is treating diseases by means of differentiation of symptoms and signs [11]. In our study, we classified RA patients with hot syndromes and cold syndromes. In addition, we conducted a systematic analysis of the clinical features and levels of IL-33, sST2, IL-10, and IL-17 between RA patients with hot syndromes and those with cold syndromes. Clinical features of RA patients (Table 2) were significantly increased compared with cold syndromes groups. Meanwhile, up-regulation of IL-33, sST2, and IL-17, along with the decreased IL-10, were observed in RA patients with hot syndromes. Obviously, RA patients with hot syndromes presented more serious inflammation and more disease activity, indicating possible poorer prognosis. Further studies enrolling more hot syndromes RA patients will be necessary to validate our preliminary observations.

Conclusions

IL-33 contributes to RA pathogenesis through unbalancing IL-10 and IL-17, and thus is a potential biomarker in monitoring disease activity and inflammation condition.

Disclosure of conflict of interest

None.

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