
Contribution of Th2-like Treg cells to the pathogenesis of Takayasu's arteritis

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Received on June 6, 2019; accepted in
revised form on September 2, 2019.

Clin Exp Rheumatol 2020; 38 (Suppl. 124):
S48-S54.

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EXPERIMENTAL RHEUMATOLOGY 2020.

Key words: Takayasu's arteritis,
Th2-like Treg cells

ABSTRACT

Objectives. Takayasu's arteritis (TAK) involves inflammatory vasculitis of large vessels and mainly affects the aorta and its major branches. Abnormal immunity may play a vital role in TAK pathogenesis. Regulatory T cells (Treg cells) are important for peripheral tolerance, but under certain conditions Treg cells can differentiate into Th-like cells that have lost immune suppressive function and promote the development of autoimmune diseases. The role of Th-like Treg cells in TAK is unclear and this study aims to investigate the function of Th-like Treg cell subsets and associated cytokines in TAK.

Methods. A total of 51 patients with TAK and 32 healthy controls were enrolled. The percentage of Th1, Th2, Th17, Tregs and Th-like Treg cells in blood samples was analysed by flow cytometry. Serum cytokine levels were detected using a cytometric bead array for cytokines.

Results. TAK patients had decreased numbers of Th2-like Treg cells in the peripheral blood ($p=0.002$) relative to healthy controls. The percentage of Treg cells in samples from TAK patients also decreased ($p=0.002$), but the Th2 cell percentage ($p=0.04$) increased compared to healthy controls. TAK patients had higher serum levels of IL-4 ($p<0.001$) and IL-13 ($p<0.001$) than healthy controls, and levels of both cytokines correlated to IL-6 levels.

Conclusions. We studied changes in T helper-like Treg cell subsets in TAK for the first time and discovered that the number of Th2-like Treg cells in peripheral blood decreased. Results of this study suggested that Th2-like Treg cells could contribute to TAK pathogenesis.

Introduction

Takayasu's arteritis (TAK) is a rare, systemic inflammatory vasculitis of large vessels and particularly affects

the aorta and its branches as well as pulmonary arteries. Arterial inflammation in TAK results in vascular wall thickening and remodelling followed by artery stenosis, occlusion, aneurysm or dissection. Clinical manifestations of TAK include tissue and organ ischaemia and haemorrhagic shock caused by vascular rupture. In severe cases, TAK can be life-threatening (1). The mortality of patients with TAK is 2.73-fold higher than that of healthy controls (2). Although the pathogenesis of TAK remains unclear, abnormal immune function may play a vital role. There is evidence that in TAK, macrophages and a variety of lymphoid cells including CD4⁺ and CD8⁺ T cells, $\gamma\delta$ T cells, NK cells and B cells infiltrate the arterial wall, and circulating levels of pro-inflammatory cytokines such as interleukin 6 (IL-6), IL-8 (CXCL8), CCL2 and CCL5 are elevated (1).

Regulatory T cells (Treg cells) are a subset of CD4⁺T cells that express high levels of IL-2 receptor α -chain (CD25) in addition to the transcription factor Foxp3. Treg cells are important for peripheral tolerance that is necessary to inhibit the development of autoimmune diseases. T cells of this lineage function via cell contact mechanisms or secretion of inhibitory cytokines such as IL-10, TGF- β and IL-35 (3). Defects in either the number or function of Treg cells may be involved in many autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis and giant cell arteritis (4-5). However, there is limited information concerning the role of Treg in TAK (6-8). Emerging evidence indicates that Treg cells can differentiate into Th1, Th2 or Th17-like cells and in turn lose their immune suppressive function under certain conditions. Treg cell plasticity can contribute to autoimmune disease pathogenesis. In this study, we focused on these T helper-like Tregs and related cytokines

Funding: This research was supported by the National Natural Science Foundation of China (91739111).

Competing interests: none declared.

in the peripheral blood of TAK patients, and also investigated how their number and function correlate with TAK disease activity (3).

Materials and methods

Study subjects

A total of 51 consecutive Chinese patients with TAK who were referred between March 2018 and November 2018 to Anzhen Hospital, affiliated with Capital Medical University in China, fulfilled the criteria for classification of TAK developed by American College of Rheumatology (ACR) in 1990. Activity of TAK was defined by an Indian Takayasu Activity (ITAS-A) integral score ≥ 5 determined using an integral method (9). Of the 51 TAK patients, 16 (31.4%) and 35 (68.6%) were in an active and inactive disease state, respectively. The pattern of angiographic involvement in TAK patients was described according to the classification of Numano *et al.* (10). As controls, 32 age and sex-matched healthy volunteers were enrolled. The study protocol was approved by the Medical Ethics Committee of Anzhen Hospital.

Flow cytometry

Cell phenotype was analysed by flow cytometry. A 400 μ L aliquot of heparinised blood samples was stimulated with 20 ng/mL phorbol-12-myristate-13-acetate (PMA) and 1,000 ng/mL ionomycin in the presence of Golgi-Stop (BD Biosciences) for 5 hours, and then incubated with anti-human mouse antibodies against CD3-FITC-A, CD4-BV510-A (BD Pharmingen) and CD25-BV711-A (BD Pharmingen). After fixation and permeabilisation, samples were incubated with antibodies against FoxP3-Alexa Fluor 647-A (BD Pharmingen), IL-4-PE-Cy7-A (BD Pharmingen), and IL-17-BV650-A (BD Pharmingen). In all experiments, a control antibody for the respective IgG isotype was included. Flow assays were conducted using a FACS Calibur flow cytometer (BD, USA) and analysed with FlowJo v.7.6.4 software (Tree Star).

Cytokine assay

Serum samples for 46/51 TAK patients and 24/32 healthy controls were col-

lected and cytokine levels were detected using the Bio-Plex Pro™ Human Cytokine 27-plex Assay (Bio-Rad) according to the manufacturer's instructions. Levels of serum cytokines IL-4, IL-13, IL-5, IL-6, IFN- γ , TNF- α and IL-17 were measured.

Statistical analysis

Statistical descriptions and inferences were performed with the SPSS v. 24.0 statistics package (Chicago, IL, USA). According to the normality, variables were described as mean \pm SE or as median (PM25, PM75); Student's t-test or Wilcoxon rank test were used to compare differences between two groups. The Pearson correlation test was used to evaluate correlations between parameters. *p*-values < 0.05 were considered to be statistically significant.

Results

Clinical characteristics

of TAK patients

Among the TAK patients in this sample, the percentage of females was 11.75 times that of males and on average disease onset occurred during the third decade of life. The median ITAS-A level was < 5 points. Most patients were taking several concomitant medications (Table I). Type V was the most common angiographic classification pattern (Table II).

Decreased numbers of peripheral

Treg cells and increased numbers

of Th2 cells in patients with TAK

In this study, CD3⁺CD4⁺IFN- γ ⁺T cells, CD3⁺CD4⁺IL-4⁺ T cells, CD3⁺CD4⁺IL-17⁺ T cells and CD3⁺CD4⁺CD25⁺Foxp3⁺ T cells were defined as Th1, Th2, Th17 and Treg cells, respectively. We found that TAK patients had a significantly lower proportion of Treg cells compared to healthy controls [Fig. 1A; 1.58 (1.05, 3.1)% vs. 2.66 (1.93, 3.61) %, *p*=0.002;]. The number of Th2 cells was significantly higher in patients with TAK relative to the control group [0.92 (0.35, 1.69)% vs. 0.42 (0.02, 1.32) %, *p*=0.04]. Meanwhile, the percentages of Th1 and Th17 cells in peripheral blood from TAK patients and controls were not significantly different: 5.61 (2.75,

Table I. Demographic data, disease activity and medications of TAK patients.

Gender, n (%)	
Male	4 (7.8%)
Female	47 (92.2%)
Age (years, mean \pm SE)	39.50 \pm 1.70
Age of onset (years, mean \pm SE)	32.04 \pm 1.57
ESR [mm/h, median (P25, P75)]	9 (5, 15)
CRP [mg/L, median (P25, P75)]	1.91 (0.44, 6.18)
NIH [median (P25, P75)]	2 (0, 2)
ITAS-A [median (P25, P75)]	2 (0, 6)
ITAS-2010 [median (P25, P75)]	1 (0, 5)
Medications, n (%)	
Steroids	32 (62.7)
Tocilizumab	12 (23.5)
Cyclophosphamide	11 (21.6)
Mycophenolate mofetil	17 (33.3)
Tacrolimus	2 (3.9)
Methotrexate	21 (41.2)
Leftunomide	1 (2)
Azathioprine	2 (3.9)
Antimalarials	3 (5.9)
Tripterygium	3 (5.9)

Table II. Angiographic classification of TAK patients.

Angiographic classification, n (%)	
Type I	8 (15.7)
Type IIa	0 (0)
Type IIb	11 (21.6)
Type III	3 (5.9)
Type IV	2 (3.9)
Type V	27 (52.9)

11)% vs. 7.34 (4.95, 10.92)%, *p*=0.210 and 1.24 (0.89, 1.81)% vs. 1.47 (0.92, 1.84)%, *p*=0.522, respectively (Fig. 1B).

For patients with active and inactive TAK, no significant difference was seen in the percentage of either Treg cells [1.87 (1.35, 3.23)% vs. 1.42 (0.92, 3.04)%, *p*=0.253] or Th2 cell percentage [0.70 (0.31, 1.40)% vs. 0.95 (0.37, 1.80)%, *p*=0.261].

We also investigated the ratio of effector T cells to Treg cells, and discovered that the ratios of Th2 to Treg cells and Th17 to Treg cells were significantly higher in TAK patients compared to controls [0.37 (0.19, 1.31) vs. 0.19 (0.09, 0.32), *p*=0.001 and 0.84 (0.38, 1.42) vs. 0.48 (0.30, 0.98), *p*=0.031, respectively]. However, there was no significant difference in the ratio of Th1 to Treg cells in TAK patients and controls (3.20 (1.88, 7.93) vs. 2.46 (1.46, 5.60), *p*=0.213; Fig. 2).

The Th2/Treg ratio [0.77 (0.25, 1.48)

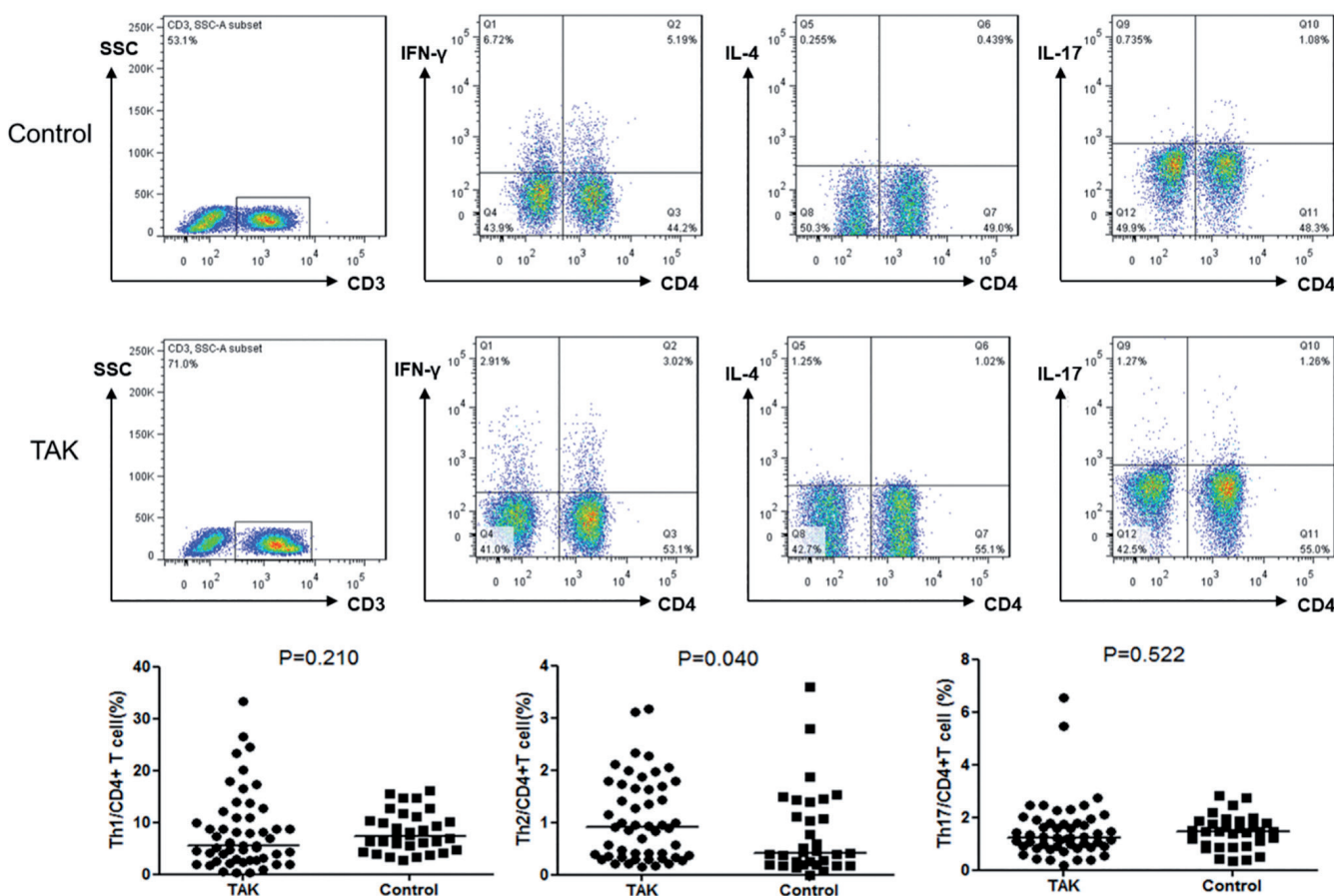
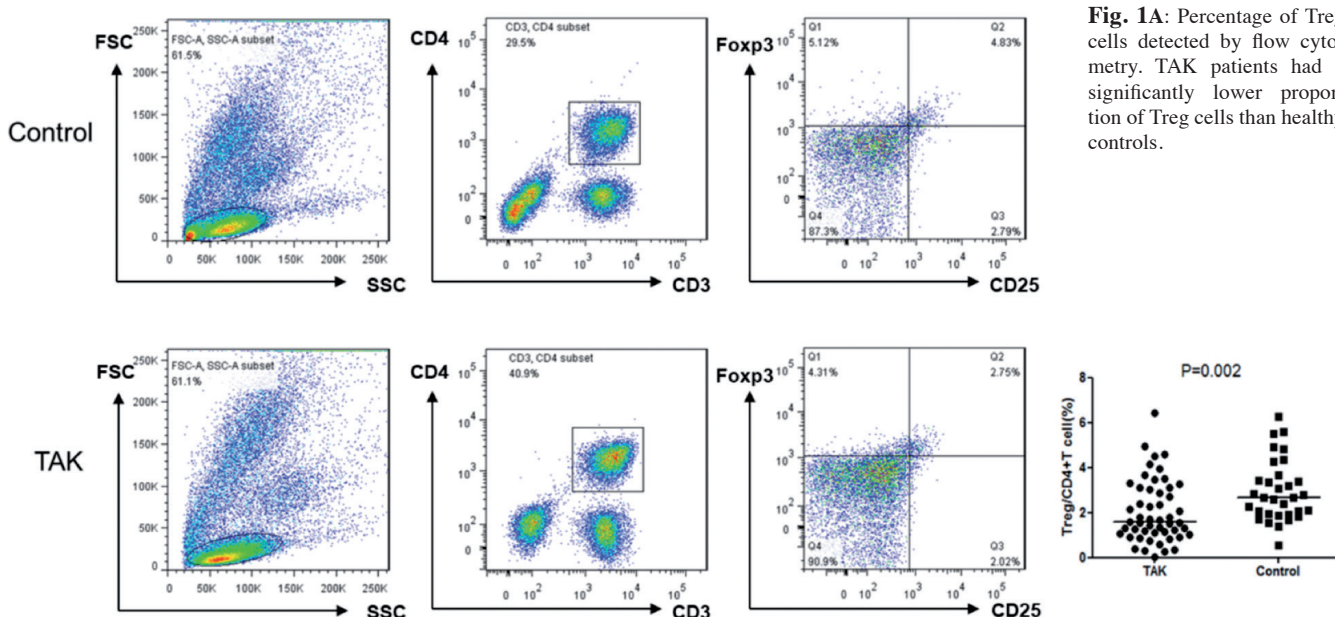


Fig. 1B: Percentage of Th1, Th2, Th17 cells detected by flow cytometry. TAK patients had a significantly higher proportion of Th2 cells than healthy controls.

vs. 0.46 (0.21, 1.53), $p=0.170$] and Th17/Treg ratio [0.91 (0.32, 1.34) vs. 0.84 (0.38, 1.57), $p=0.792$] were also not statistically different between active and inactive TAK groups.

Numbers of peripheral Th2-like Treg cells were decreased in patients with TAK
Treg cells could acquire characteristics of Th1, Th2 or Th17-like cells in the

presence of some stimulator agents and the plasticity of Treg cells contributes to autoimmune disease pathogenesis. We defined CD3⁺CD4⁺Foxp3⁺IFN- γ ⁺ T cells, CD3⁺CD4⁺Foxp3⁺IL-4⁺ T cells,

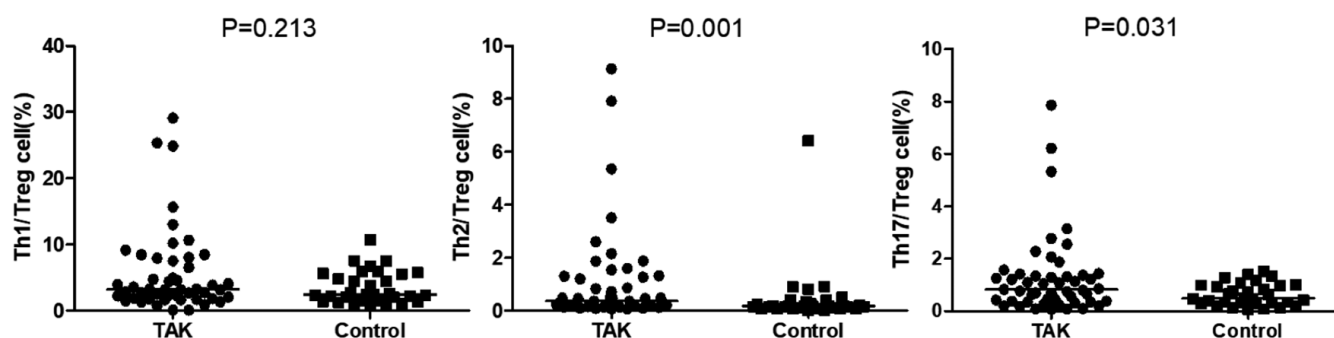


Fig. 2. Ratios of helper T cells to Treg cells in TAK patients and controls. The ratios of Th2 to Treg cells and Th17 to Treg cells were significantly higher in TAK patients than controls.

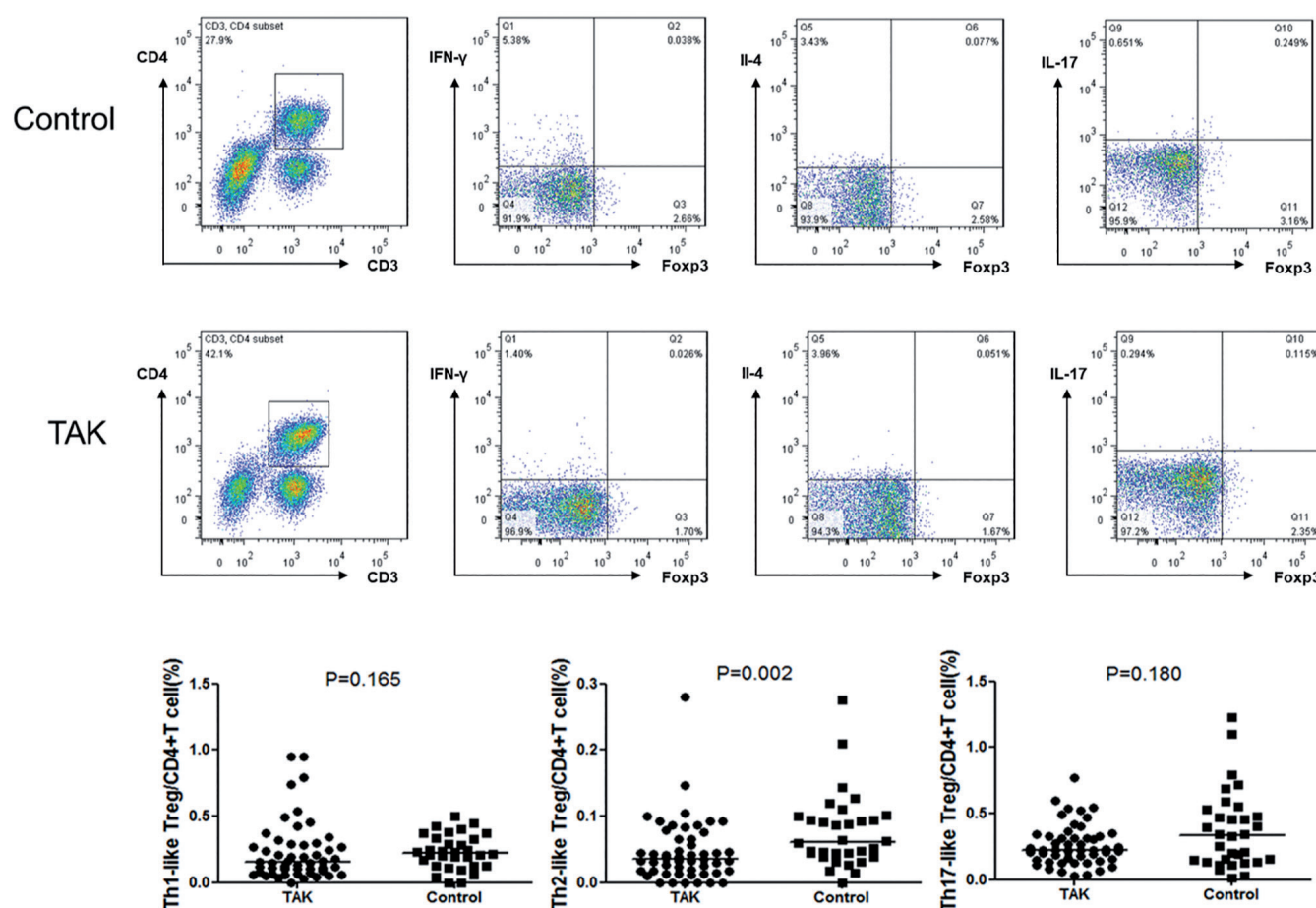


Fig. 3. Percentage of Th-like Treg cells detected by flow cytometry. TAK patients had a significantly lower proportion of Th2-like Treg cells than healthy controls.

and CD3⁺CD4⁺Foxp3⁺IL-17⁺ T cells as Th1-like, Th2-like, and Th17-like Treg cells, respectively, in this study. The percentage of Th2-like Treg cells was significantly lower in patients with TAK than healthy controls [0.04 (0.02, 0.07)% vs. 0.06 (0.04, 0.10)%, $p=0.002$], whereas there were no differences in either the proportion of Th1-like or Th17-like Treg cells between TAK patients and control groups [0.16 (0.08, 0.29) vs. 0.22 (0.12, 0.34), $p=0.165$ and

0.22 (0.15, 0.33) vs. 0.34 (0.14, 0.52), $p=0.180$] (Fig. 3). No significant difference in the percentage of Th2-like Treg cells was seen between active and inactive TAK groups [0.04 (0.02, 0.05)% vs. 0.03 (0.02, 0.08)%, $p=0.747$].

Elevated serum levels of Th2-associated cytokines in patients with TAK and positive correlation with IL-6 levels

To determine whether there are abnor-

malities in Th2-associated cytokines involved in TAK, the serum levels of IL-4, IL-5, IL-13 were measured. IL-4 levels were significantly elevated in patients with TAK relative to healthy controls (6.70 ± 0.21 vs. 5.39 ± 0.20 pg/ml, $p<0.001$). Meanwhile, IL-5 was detected in only one TAK patient and no samples from healthy controls had detectable IL-5 levels. TAK patients had higher levels of IL-13 [6.10 (3.91, 10.82) vs. 1.98 (0, 4.79) pg/ml, $p<0.001$].

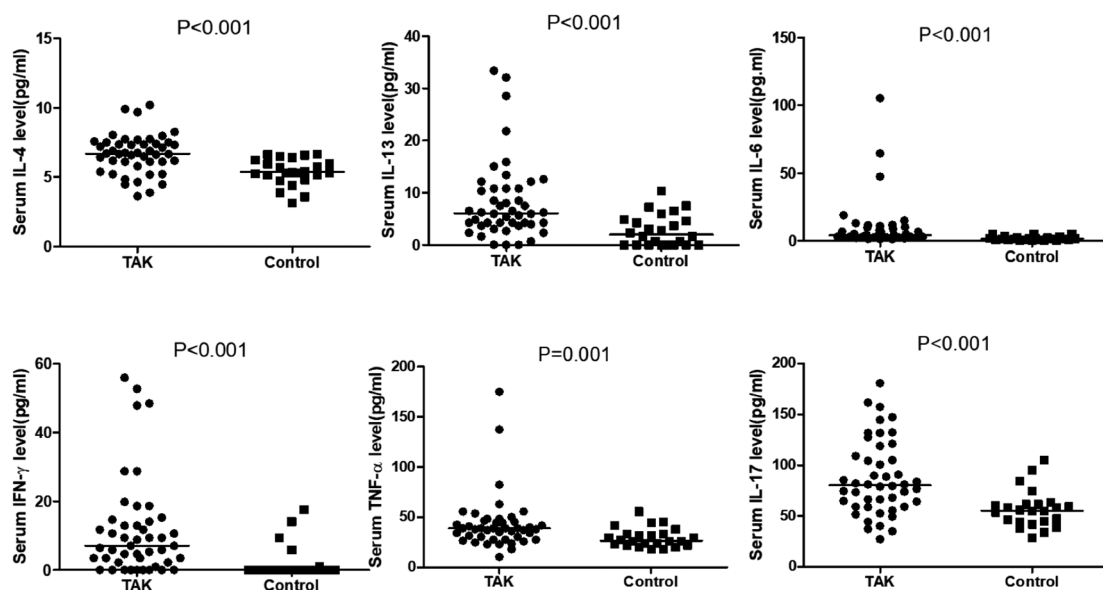


Fig. 4. Serum levels of cytokines detected by a cytometric bead array for cytokines. TAK patients had a significantly higher levels of cytokines including IL-4, IL-13, IL-6, IFN- γ , TNF- α and IL-17 than healthy controls.

As expected, levels of other serum cytokines including IL-6 [4.13 (2.95, 9.93) vs. 1.60 (0.81, 2.46) pg/ml, $p < 0.001$], IFN- γ [7.09 (2.20, 14.25) vs. 0 (0, 0) pg/ml, $p < 0.001$], TNF- α [39.05 (29.90, 48.36) vs. 26.83 (22.33, 33.43) pg/ml, $p = 0.001$] and IL-17 [80.41 (59.44, 111.73) vs. 55.62 (44.36, 61.63) pg/ml, $p < 0.001$] were markedly higher in TAK patients than in healthy controls (Fig. 4).

We next calculated the correlation of levels of serum cytokines to TAK disease activity. Levels of serum IL-4 ($r = 0.313$, $p = 0.008$), IL-13 ($r = 0.347$, $p = 0.003$), IFN- γ ($r = 0.381$, $p = 0.001$), TNF- α ($r = 0.343$, $p = 0.004$) and IL-17 ($r = 0.336$, $p = 0.004$) were all positively correlated with IL-6 levels, a widely accepted marker of TAK disease activity, although ITAS-A results showed that levels of these cytokines were similar for the active and inactive TAK groups (IL-4: 6.58 ± 0.32 vs. 6.78 ± 0.28 pg/ml, $p = 0.638$; IL-13: 6.23 (4.28, 8.50) vs. 5.97 (3.68, 12.57) pg/ml, $p = 0.554$; IFN- γ : 9.45 (0, 14.10) vs. 7.09 (3.45, 14.68) pg/ml, $p = 0.762$; TNF- α : 36.25 (27.78, 48.36) vs. 39.05 (34.37, 48.36) pg/ml, $p = 0.191$; IL-17: 86.99 ± 9.44 vs. 87.71 ± 6.43 pg/ml, $p = 0.949$).

The number of circulating eosinophils in TAK patients was determined to be 0.07 ($0.05, 0.14$) $\times 10^9/L$ and the percentage of eosinophils among the total white blood cell count was 1.2 ($0.6, 2.175$)%. The eosinophil count was not correlated

with serum IL-4 ($r = -0.15$, $p = 0.32$) and IL-13 ($r = -0.03$, $p = 0.845$) levels.

The level of total IgE in TAK patients was 17.9 ($6.525, 46.417$) IU/ml but this value did not correlate with the serum levels of IL-4 ($r = -0.117$, $p = 0.44$) or IL-13 ($r = -0.163$, $p = 0.287$).

Discussion

In this study we investigated T helper-like Treg subsets in TAK and identified abnormal numbers of Th2-like Tregs in peripheral blood from TAK patients. Plasticity was recently found to be a characteristic of Treg cells that enables these cells to adapt to changing environmental signals. Under certain conditions, such as those seen in allergic animal models of autoimmune disease and food-allergic patients, as well as in and tumourigenic environments, Treg cells upregulate the expression of the transcription factors IRF4 and STAT3, and secrete the pro-inflammatory cytokines IL-4 and IL-13 to acquire Th2-like phenotypes. These Treg cells have diminished function, while maintaining Foxp3 expression (11). Reprogramming into Th2-like cells could elicit Treg cell dysfunction and induce autoimmune disease. In patients with systemic sclerosis, Treg cell plasticity can emerge in skin tissue and contribute to fibrosis. Treg cells in the affected skin of SSc patients appear to produce more of the Th2 cell-associated cytokines IL-4 and IL-13 than

healthy controls, indicating a role for tissue-specific differentiation of Treg cells into Th2-like cells in SSc fibrosis. These results suggest that Th2-like Treg cells may be involved in autoimmune disease pathogenesis, although Th2-like Treg cells in TAK have not been previously evaluated. Our findings characterised Th2-like Treg cells in TAK for the first time and show a potential role for Treg plasticity in vasculitis. Interestingly, we found that the proportion of Th2-like Treg cells decreased in peripheral blood of TAK patients relative to healthy controls, a result that suggests that Th2-like Treg cells may infiltrate and damage local tissues. Recent advances revealed that arteries are immune-privileged sites, but under certain stimulations, local immune responses can be activated and vessel injury may occur. Whether there is vessel-localised Th2-like Treg cells in the arteries of TAK patients requires further investigation.

As evidenced by recent studies, the mechanism by which Treg cells are reprogrammed into Th2-like cells is likely complex. Selective augmentation of IL-4R signalling may promote Th2-polarised Treg cells, whereas the absence of IL-4 and IL-13 could protect Treg-cell lineages from differentiating to Th2-like cells. Th2 cytokines also play an important role in induction of Th2-like Tregs (12). Interleukin-33 (IL-33) is a Th2 cell-inducing

cytokine that is principally expressed in endothelial cells upon induction by inflammation and acts as a major regulator of tissue Tregs as well as type-2 immune responses. Thus, IL-33 could modulate both homeostasis and inflammation (13). Expression of the IL-33 receptor ST2 colocalised with Foxp3 in skin tissue from SSc patients, supporting the notion that skin-localised Treg cells are poised to differentiate into Th2 cytokine-producing cells. Other mechanisms of Treg cell transdifferentiation to Th2-like cells showed the involvement of recombination signal-binding protein for the immunoglobulin kappa J region (Rbpj), a kind of transcriptional regulator that is commonly known to act as a co-factor during Notch signalling and that is critical for restraining Th2 responses. Meanwhile, Treg-specific Rbpj deletion could induce Th2-like differentiation potential of Treg cells in a mouse model (14). The hallmark transcription regulator of Treg, Foxp3, has a direct role in suppressing Th2-like Treg cells, so recapitulation of the Foxp3 variant could induce a Th2-mediated immune response that produces autoimmune symptoms due to type 2 cytokine production (15).

Whether Th2-associated cytokines are involved in TAK pathogenesis remains a matter of debate. IL-4 is a typical Th2 cytokine that regulates T cell activation, differentiation, proliferation, and survival. IL-4 also controls immunomodulation of B cells and many other cell types. The function of IL-4 in inflammation is complex. On the one hand, IL-4 can inhibit production of proinflammatory cytokines such as TNF- α , IL-1, IL-6 and prostaglandin E2 (PGE2), while on the other hand, IL-4 signalling participates in proinflammatory mechanisms (16). IL-5 is essential for the induction and proliferation of eosinophils, as well as for B cells to induce antibody secretion. Th2 cells are a major producer of IL-5, which is mainly involved in allergic diseases, such as asthma, eosinophilic esophagitis and eosinophilic granulomatosis with polyangiitis (EGPA) (17). IL-13 is mainly produced by Th2 cells, but can originate from a range of sources, including Th1, Th17 and ILC2 cells.

IL-13 has prominent roles in immunity, inflammation, fibrosis, and allergic diseases. Previous studies indicated the involvement of IL-13 in the pathogenesis of autoimmune diseases, with abnormal expression levels in systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), ulcerative colitis (UC), type 1 diabetes (T1D) and Sjögren's syndrome (SS), which makes IL-13 a promising therapeutic target (18).

Changes in IL-5 and IL-13 levels in patients with TAK had not been previously examined, whereas the role of IL-4 in different autoimmune diseases, including TAK, is controversial, perhaps in part because of differences in disease activity and angiographic type (19). In this study, we found that serum IL-4 and IL-13 levels were elevated in TAK patients. Circulating IL-5 was detectable in only one TAK patient in this study. We propose that IL-4 and IL-13 may contribute to imbalances in autoimmune and inflammatory characteristics of TAK.

In terms of the correlation between Th2-like Tregs and TA disease activity, we saw no difference in the percentage of Th2-like Treg cells or Treg cells between groups with active and inactive TAK. Previous evidence showed that the frequency of CD4⁺Foxp3⁺CD25^{hi}CD127⁻Tregs was similar in peripheral blood from active and inactive TA groups. Specifically, the number of CD45RA⁻CD25⁺⁺⁺Foxp3⁺ activated memory Tregs (aTregs) or CD45RA⁺CD25⁺⁺Foxp3⁺ resting Tregs (rTregs) did not differ between the active TA group and the inactive TA group (20). Meanwhile, we saw no differences in IL-4 and IL-13 levels between active and inactive TA groups, although both IL-4 and IL-13 levels were positively correlated to IL-6 levels, a prime biomarker that reflects disease activity and is associated with ¹⁸F-FDG uptake in the arterial wall in TAK patients. To our knowledge, all assessments of TAK activity such as the National Institute of Health (NIH) score (21), the Indian Takayasu Activity score (ITAS) and disease-extent index (9), as well as Takayasu arteritis damage score (TADs) (22) have limitations and the incorpora-

tion of imaging data is needed to gain a more complete description of TAK disease activity. Whether serum IL-4 and IL-13 levels can reflect radiological changes in the arterial wall in TAK patients should be explored in a future study.

A previous study found a marked increase in Th1 and Th17 cells and associated cytokines in TAK patients (20). We discovered that the percentages of Th1 and Th17 cells in peripheral blood did not differ significantly between TAK patients and controls. The different results may be due to distinct angiographic types and/or medication status. However, in accordance with the results of the study by Saadoun *et al.*, we revealed the serum levels of Th1 cytokines IFN- γ and TNF- α , as well as Th17 cytokine IL-17 were significantly higher in TAK patients than in healthy controls, which suggested the secretion functions of Th1 and Th17 cells enhanced in TAK patients.

Here we found that the frequency of Th2-like Treg cells in peripheral blood decreased and serum levels of both IL-4 and IL-13 were increased in TAK patients. To our knowledge, this report is the first to show abnormalities in T helper-like Treg cell subsets in patients with TAK. The limitation of this study is a lack of functional research. Since TAK is a rare disease and surgeries on the aorta are infrequent, collection of arterial tissue specimens from patients with TAK was difficult. Further studies concerning Th2-like Treg cell functions in TAK pathogenesis are warranted and should focus on vessel-localised immune disturbances and explore the mechanism by which Th2-like Treg cells are involved in TAK pathogenesis.

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