The change of Th17/Treg cells and IL-10/IL-17 in Chinese children with Henoch-Schonlein purpura
A PRISMA-compliant meta-analysis
Bowen Li, MSa, Qian Ren, MDb, Jizu Ling, MSa, Zhongbin Tao, BSa, Xuemei Yang, MSa, Yuning Li, BSa,*

Abstract
Background: To date, the relationship of Th17 and Treg cells to Henoch-Schonlein purpura (HSP) in children remains controversial. Therefore, a systematic review and meta-analysis was conducted to reveal the potential role of the Th17 and Treg cells in children in acute stage of HSP.

Methods: PubMed, Embase, Web of Science and China National Knowledge Internet (CNKI) were systematically searched for eligible studies up to November 03, 2017. Quality assessment was carried out according to the modification of the Newcastle-Ottawa Scale (NOS). The data were analyzed by Stata SE12.0 (StataCorp, College Station, TX). Standard mean difference (SMD) with 95% confidence intervals (CI) was calculated to test the hypothesis.

Results: A total of 25 eligible studies were identified after a thorough literature search. The pooled results of the meta-analysis showed that values of Th17 frequency (SMD = 2.60; 95% CI: 1.98 to 3.23; P < .0001; I² = 90.3%, P < .0001) and IL-17 level (SMD = 3.53; 95% CI: 2.71 to 4.35; P < .0001; I² = 95.6%, P < .0001) were significantly higher in children with HSP as compared to healthy children. In contrast, our analysis showed significant lower values of Treg frequency (SMD = -2.86; 95% CI: -3.53 to -2.19; P < .001; I² = 92.4%, P < .001). However, no significance of IL-10 level was observed between children with HSP and healthy children (SMD = -1.22; 95% CI: -2.78 to 0.33; P < .01; I² = 95.9%, P < .001).

Conclusion: In conclusion, our meta-analysis indicated that increased frequency of Th17 cells and level of IL-17, but lower frequency of Treg cells are associated with HSP in childhood. Considering the limitations of this meta-analysis, large-scaled studies need to be conducted to validate the current results.

Abbreviations: CI = confidence intervals, CNKI = China national knowledge internet, HSP = Henoch-Schonlein purpura, SMD = standard mean difference, Th17 = CD4+ T helper 17 cells, Treg = CD4+CD25+ regulatory T cells.

Keywords: Henoch-Schonlein purpura (HSP), meta-analysis, Th17, Treg

1. Introduction

Henoch-Schonlein purpura (HSP) is a disease of the skin, gastrointestinal tract, joints and kidneys that most commonly affects children. More than 90% of patients are under 10 years of age, with a mean age of 6 years.[1] Recent studies suggest that HSP is related to inflammation and disordered immune response.[2,3] Several proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-8 may be involved in the pathogenesis of HSP.[3-5] However, the etiology and pathogenesis of HSP have not been completely understood.

CD4+ T helper 17 cells (Th17) are a new subset of pro-inflammatory T helper cells defined by their production of interleukin 17 (IL-17).[6] Th17 cells play a critical role in the pathogenesis of serious autoimmune diseases, such as psoriasis, rheumatoid arthritis, multiple sclerosis and inflammatory bowel diseases.[7-10] The CD4+ CD25+ regulatory T cells (Treg) are a subpopulation of T cells and subset distinct from Th1 and Th2 cells, which modulate the immune system, maintain tolerance to self-antigens, and prevent autoimmune disease. Treg cells release anti-inflammatory cytokines, IL-10 and transforming growth factor (TGF)-β1, to exert their anti-inflammatory properties.[11] Previous studies suggested that the imbalance between Th17 cells and Treg cells is important in the development of inflammatory and autoimmune diseases.[12] It has recently been shown that the proportions of Th17 cells were increased significantly in HSP children than in healthy controls.[13,14] In addition, the Th17/Treg imbalance may be involved in the pathogenesis of HSP.[14,15] Additionally, although many studies have indicated that the Th17/Treg imbalance was closely related to the pathogenesis of HSP, the small sample sizes and the single-center setting of those studies restrict the generalizability of the findings. Therefore, it is very imperative to perform a meta-analysis to systematically evaluate the relationship between the Th17/Treg imbalance and the children with HSP.
2. Materials and methods
This study is a systematic review, and does not involve individual data. Thus, it does not need approval of ethics committee.

2.1. Literature search
This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16,17] PubMed, Embase, Web of Science and China National Knowledge Internet (CNKI) were comprehensively searched for eligible studies to November 03, 2017. No restrictions on publication date, type or language were applied to identify publications. The Search strategy was determined by the combination terms including “Th17 cells”, “IL-17”, “Treg cells”, or “IL-10”, and “Henoch–Schonlein purpura”. The reference lists of retrieved articles were manually screened to determine whether they should be included.

2.2. Study selection
The studies included in the present meta-analysis had to follow the criteria:

(1) compared the outcomes of frequency of Th17 cells and Treg cells investigated in HSP children;
(2) written in English or Chinese.

In contrast, the exclusion criteria included the following aspects:

(1) duplicate of a previous publication;
(2) studies were published as Editorials, case reports, conference abstracts;
(3) animal experiment.

2.3. Data extraction and quality assessment
Data from the included studies were extracted by 2 independent investigators. Any inconsistency between the investigators was resolved by the third reviewer. Study and patient baseline characteristics including name of first authors, year of publication, study design, simple size, age range of patients, sex of patients, frequency of Th17 cells, levels of IL-17, frequency of Treg cells, and levels of IL-10.

The modified 9-star Newcastle–Ottawa scale (NOS) was applied to evaluate the quality of studies, in which patient selection, comparability exposure, and assessment of outcome were scored respectively and then these scores were added up to get a total score.[17] The maximum total score obtained by this scoring system was 9, and studies with scores ≥ 7 were defined as high quality.

2.4. Statistical methods
In the present meta-analysis, all data were pooled using stata SE12.0 (StataCorp, College Station, TX). Standard mean difference (SMD) with a 95% CI was used to analyze continuous variables. Heterogeneity across the included studies was estimated based on I², with I² >50% regarded as significant heterogeneity. If outcomes were associated with significant heterogeneity, a random-effects model was used to minimize bias.

To assess the sources of heterogeneity or to confirm the stability of pooled estimation of outcomes, a sensitivity analysis was performed. The results were considered statistically significant at 2-sided P values < .05. Publication bias was assessed by funnel plots and Begg and Egger test.[18,19] Duval nonparametric trim-and-fill method was used to evaluate the potential effect of publication bias,[20] if significant publication bias exists.

3. Results

3.1. Study selection and study characteristics
The study screening and selection processes were shown in the flowchart reported in Figure 1. We identified 108 publications, with 21 from PubMed, 32 from Embase, 26 from Web of science, and 39 from China National Knowledge Internet (CNKI). After 7 duplicates were removed, 101 studies were checked by screening title and abstract by 2 investigators. Then a total of 63 full texts remained after excluding the studies on irrelevant topics (n = 58), review article and comments (n = 5). Then we further reviewed the full texts of those remained publications. Subsequently, 4 conference abstracts and 16 studies with no data of interest were excluded, at last, with 25 articles included in the present meta-analysis.[2,13,14,21–43] Among all the included studies, 24 were retrospective studies and 1 were case-control analysis. The main baseline characteristics of the included publications are at length provided in Table 1 and Table 2.

3.2. Quality judgments of studies
The scores obtained according to the modification of the Newcastle–Ottawa scale ranged from 5 to 7 (Table 1). All of the included studies were awarded at least 6 points except that one study obtained 5 points, which were judged as moderate quality. In particular, 5 studies were awarded 7 points, and judged as high-quality.

3.3. The results of meta-analysis

3.3.1. Values of Th17 frequency and IL-17 level in children with HSP.
The pooled random-effects SMD estimate showed significant higher values of Th17 frequency (SMD = 2.60; 95% CI: 1.92 to 3.23; P < .0001; I² = 93.0%, P < .0001) in children with HSP as compared to healthy children (Fig. 2). The result also showed significant higher values of IL-17 level (SMD = 3.53; 95% CI: 2.71 to 4.35; P < .0001; I² = 95.6%, P < .0001) in children with HSP as compared to healthy children (Fig. 3).

3.3.2. Values of Treg frequency and IL-10 level in children with HSP.
The pooled SMD indicated lower values of Treg frequency (SMD = -2.86; 95% CI: -3.53 to -2.19; P < .01; I² = 92.4%, P < .0001) in children with HSP as compared to healthy children (Fig. 4). However, the pooled SMD suggested no statistically different values of IL-10 level (SMD = -1.22; 95% CI: -2.78 to 0.33; P = .09; I² = 95.9%, P < .0001) in children with HSP as compared to healthy children (Fig. 5).

3.3.3. Sensitivity analysis.
Sensitivity analysis was conducted by removal of single study in each step. As Figures 6–8 showed, respectively, the pooled analysis of Th17, IL-17 and Treg did not alter significantly when any study was omitted, which indicated that our pooled results were robust. The Sensitivity analysis for the pooled result of IL-10 was not performed due to the limitation of the number of eligible studies.

3.4. Publication bias
The publication bias for the pooled results of Th17, IL-17 and Treg values using the Begg funnel plot and Egger tests, but the
Figure 1. Flow diagram of study selection.

Table 1

The main characteristic of the included studies.

| Author  | Year | Study design | Simple size | Age, year | Sex | NOS |
|---------|------|--------------|-------------|-----------|-----|-----|
| Chang   | 2016 | R            | 42 Healthy, 30 HSP | 6.5 Healthy, 6.7 HSP | 25/17 Male, 20/10 Female | 6 |
| Chen    | 2013 | R            | 18 Healthy, 23 HSP | 6.8 Healthy, 6.2 HSP | 10/8 Male, 14/9 Female | 6 |
| Fan     | 2010 | R            | 30 Healthy, 40 HSP | 9.8 Healthy, 10.7 HSP | 18/12 Male, 24/16 Female | 7 |
| Gao     | 2014 | R            | 15 Healthy, 42 HSP | 7.0 Healthy, 7.5 HSP | 8/7 Male, 22/20 Female | 5 |
| Huang   | 2014 | R            | 25 Healthy, 25 HSP | NR Healthy, 8.7 HSP | NR Male, 13/12 Female | 7 |
| Jen     | 2011 | R            | 30 Healthy, 30 HSP | NR Healthy, 7.3 HSP | NR Male, 15/15 Female | 7 |
| Li      | 2014a| R            | 30 Healthy, 30 HSP | 6.21 Healthy, 5.93 HSP | 15/15 Male, 17/13 Female | 6 |
| Li      | 2014b| R            | 20 Healthy, 30 HSP | 7.6±2.54 Healthy, 8.5±2.86 HSP | 11/9 Male, 16/14 Female | 5 |
| Liang   | 2015 | R            | 30 Healthy, 30 HSP | NR Healthy, NR HSP | 16/14 Male, 24/17 Female | 7 |
| Liu     | 2015 | R            | 30 Healthy, 30 HSP | 8.93±3.1 Healthy, 8.9±2.8 HSP | 17/13 Male, 16/14 Female | 6 |
| Liu     | 2014 | R            | 30 Healthy, 78 HSP | 28.6±4.4 Healthy, 28.4±4.5 HSP | 17/13 Male, 44/34 Female | 7 |
| Liu     | 2012 | R            | 30 Healthy, 54 HSP | 7.2 Healthy, 7.5 HSP | 18/12 Male, 34/20 Female | 6 |
| Ma      | 2010 | R            | 38 Healthy, 59 HSP | 10.13±3.31 Healthy, 10.42±3.60 HSP | 19/19 Male, 28/30 Female | 7 |
| Meng    | 2011 | R            | 20 Healthy, 60 HSP | 7.58±1.56 Healthy, 7.79±2.31 HSP | 10/10 Male, 34/26 Female | 6 |
| Miao    | 2014 | R            | 30 Healthy, 30 HSP | NR Healthy, NR HSP | 15/15 Male, 17/13 Female | 6 |
| Tan     | 2017 | R            | 16 Healthy, 15 HSP | 7.6±2.8 Healthy, NR HSP | 9/7 Male, NR Female | 6 |
| Wang    | 2015a| R            | 40 Healthy, 40 HSP | 4.5 Healthy, 5.0 HSP | 24/16 Male, 27/13 Female | 6 |
| Wang    | 2015b| R            | 30 Healthy, 35 HSP | NR Healthy, NR HSP | 16/14 Male, 20/15 Female | 7 |
| Xiao    | 2014a| R            | 22 Healthy, 39 HSP | 8.2 Healthy, 7.4 HSP | 12/10 Male, 23/16 Female | 7 |
| Xiao    | 2014b| R            | 40 Healthy, 42 HSP | 10.5±4.8 Healthy, 10.6±4.8 HSP | 20/20 Male, 22/20 Female | 6 |
| Xing    | 2017 | R            | 35 Healthy, 68 HSP | 5 Healthy, 4 HSP | 20/15 Male, 40/28 Female | 6 |
| Yang    | 2000 | R            | 20 Healthy, 20 HSP | NR Healthy, NR HSP | 10/10 Male, 12/8 Female | 6 |
| Zhang   | 2015 | R            | 30 Healthy, 52 HSP | 7.61±3.8 Healthy, 7.28±4.0 HSP | 16/14 Male, 30/22 Female | 6 |
| Zhang   | 2016 | R            | 30 Healthy, 35 HSP | 8.56 Healthy, 8.31 HSP | 17/13 Male, 22/13 Female | 7 |
| Zi      | 2014 | R            | 30 Healthy, 42 HSP | 6.5 Healthy, 6.7 HSP | 20/10 Male, 25/17 Female | 6 |

HSP = Henoch-Schonlein Purpura, NR = not reported, R = Retrospective design.
Table 2

| First author | Healthy Th17 frequencies (%) | HSP Th17 frequencies (%) | Healthy Treg frequencies (%) | HSP Treg frequencies (%) | Levels of IL-17 (ng/L) | Levels of IL-10 (ng/L) |
|--------------|------------------------------|--------------------------|------------------------------|----------------------------|-----------------------|-----------------------|
| Chang 2016   | NR                           | NR                       | NR                           | NR                         | NR                    | NR                    |
| Chen 2013    | 0.7                          | 0.1                      | 1.7                          | 0.3                        | 3.8                   | 0.2                   |
| Fan 2010     | 1.19                         | 1.31                     | 2.97                         | 1.57                       | NR                    | NR                    |
| Gao 2014     | NR                           | NR                       | NR                           | NR                         | NR                    | NR                    |
| Huang 2014   | 0.49                         | 0.08                     | 0.76                         | 0.16                       | 8.73                  | 0.60                  |
| Jen 2011     | 0.71                         | 0.15                     | 1.67                         | 0.36                       | NR                    | NR                    |
| Li 2014a     | 1.20                         | 0.23                     | 2.30                         | 0.55                       | 12.20                 | 3.95                  |
| Li 2014b     | 0.84                         | 0.41                     | 2.14                         | 0.90                       | NR                    | NR                    |
| Liang 2015   | 0.27                         | 0.10                     | 0.41                         | 0.16                       | 9.79                  | 0.99                  |
| Liu 2015     | 0.52                         | 0.07                     | 0.71                         | 0.14                       | 8.81                  | 0.59                  |
| Liu 2012     | NR                           | NR                       | NR                           | NR                         | NR                    | NR                    |
| Ma 2010      | 0.39                         | 0.15                     | 1.87                         | 0.56                       | NR                    | NR                    |
| Meng 2011    | NR                           | NR                       | NR                           | NR                         | NR                    | NR                    |
| Xiao 2014a   | 0.59                         | 0.27                     | 1.73                         | 0.68                       | NR                    | NR                    |
| Tan 2017     | 0.77                         | 0.05                     | 1.23                         | 0.11                       | 3.64                  | 0.16                  |
| Wang 2015a   | NR                           | NR                       | NR                           | NR                         | NR                    | NR                    |
| Wang 2015b   | 0.25                         | 0.12                     | 0.37                         | 0.28                       | 10.91                 | 1.11                  |
| Xiao 2014b   | 1.62                         | 0.44                     | 6.45                         | 1.62                       | NR                    | NR                    |
| Xing 2017    | 0.59                         | 0.18                     | 2.98                         | 0.51                       | 5.45                  | 2.61                  |
| Yang 2006    | NR                           | NR                       | NR                           | NR                         | NR                    | NR                    |
| Zhang 2015a  | 0.54                         | 0.28                     | 1.20                         | 0.41                       | 5.95                  | 0.45                  |
| Zhang 2016   | 0.66                         | 0.26                     | 1.35                         | 0.46                       | 3.15                  | 0.67                  |
| Zi 2014      | NR                           | NR                       | NR                           | NR                         | NR                    | NR                    |

Figure 2. The meta-analysis of values of Th17 frequency in children with HSP.
assessment of publication bias for the pooled result of IL-10 was not conducted due to the limitation of the number of eligible studies. From the results, significant publication biases were detected for the pooled results of Th17, IL-17 and Treg, which were reflected by Z value (Z = 3.69, 4.90 and 3.28) and P value (P < .001, P < .001 and P = .001) from Begg test, as well as t value (t [bias] = 5.12, 9.72 and -4.82) and P value (P < .001, P < .001 and P < .001) from Egger test. Furthermore, the asymmetry of the funnel plots for the pooled results of Th17, IL-17 and Treg also indicated the existence of significance publication biases, as in Figures 9–11 showed respectively. Then, the “trim and fill method” was applied to figure out whether the significant publications substantially influence the stability of our pooled results. From the results of “trim and fill method” analysis, we found that the adjusted pooled SMDs of Th17, IL-17, and Treg did not change significantly and the funnel plots also became relatively symmetric (Figs. 12–14), which indicated that the publication bias did not significantly impact the reliability of our pooled results of Th17, IL-17, and Treg values.

4. Discussion
To the best of our knowledge, this is the first meta-analysis to investigate the difference of Th17 frequency, IL-17 level, Treg frequency and IL-10 level between HSP children and healthy children. Our study found that the frequency of Th17 cells and the level of IL-17 were higher in HSP children than in healthy controls. In contrast, the frequency of Treg cell was lower in HSP children than in the healthy controls. These results indicate that a Th17/Treg cell imbalance exists in HSP children, and it appears to closely correlate with disease activity.

HSP is the most common type of connective tissue diseases and its pathogenesis remains unknown. Recently, many investigators have evaluated the balance of Th17/Treg and reported an imbalance in patients with various autoimmune and inflammatory diseases. Numerous studies in the past revealed that expression levels of proinflammatory cytokines, such as IL-6 and IL-8, were elevated in patients with HSP.[44,45] It has recently been shown that the increased frequency of Th17 cells and IL-17 level in childhood HSP may in part contribute to vascular inflammation.[2] Th17 cells mediate the pathology in the inflammation and autoimmune tissue injury through recruiting other inflammatory cell types and cytokines. Some studies have reported that several cytokines, such as TGF-β and IL-21, can induce Th17 cell differentiation, and these cytokines and Th17 cells appear to contribute to the clinical outcome of autoimmune diseases.[46,47] Th17 cells can induce inflammation and autoimmune tissue injury through expressing retinoic acid-related orphan receptor γt.[48] Previous studies suggested that Th17 cells involved in the development of autoimmunity through the production of IL-17 and IL-6.[49] Recent study has reported that IL-17 can stimulate monocytes/macrophages, smooth muscle
Figure 4. The meta-analysis of values of Treg frequency in children with HSP.

Figure 5. The meta-analysis of values of IL-10 level in children with HSP.
Figure 6. Sensitivity analysis of the pooled values of Th17 frequency in children with HSP.

Figure 7. Sensitivity analysis of the pooled values of IL-17 level in children with HSP.
cells, epithelial cells and endothelial cells to enhance the expression of chemokines and inflammatory cytokines and promotes polymorphonuclear neutrophil recruitment to sites of inflammation.\(^{[50,51]}\)

Treg cells play a critical role in the maintenance of peripheral immunological tolerance by limiting the autoimmune process and inflammatory responses.\(^{[14]}\) Treg cells secrete some anti-inflammatory cytokines, such as IL-10 and TGF-\(\beta\), to exert their function. The number of Treg cells has been suggested decreased in several autoimmune diseases.\(^{[52,53]}\) Bettelli et al have reported that the Th17 and Treg cell populations are mutually regulated during differentiation.\(^{[54]}\) Several proinflammatory cytokines,
such as IL-6 and IL-21, can regulatory Treg cells and induced IL-17 production in a TGF-β-dependent manner. Through this way, the proinflammatory milieu could convert Treg cells to Th17 cells and shift the balance between the immune response and inflammation toward inflammation. Previous studies have suggested that the Th17/Treg imbalance is strongly associated with the pathogenesis of some immune inflammatory diseases. As a result, an appropriate balance between Treg cells and Th17 cells can ensure the avoidance of autoimmunity and inflammatory reactions.

HSP is the most common childhood vasculitis, affecting 10 to 20 children per 100,000 per year. Our meta-analysis suggests that increased Th17/IL-17 and decreased Treg frequency is associated with HSP. This finding may be important for the management of HSP patients in clinical practice. For instance, regulating the Th17/Treg cell ratio might play a beneficial role in the treatment
of HSP. Recently, metformin, a common medicine to treat type 2 diabetes, was shown to attenuate some autoimmune diseases, such inflammatory bowel disease and autoimmune arthritis, by regulating the between Treg/Th17 balance.[56–58] Given the involvement of the between Treg/Th17 imbalance in HSP, metformin may be suitable for treating HSP patients. Of course, this hypothesis needs to be confirmed in future studies. Nevertheless, as to the management of HSP in clinical practice, it should be stressed that in most cases HSP is self-limiting and very little intervention is necessary. Therefore, the application of metformin may be only considered in cases in which there is significant concern about long-term renal function.

Overall, this meta-analysis demonstrates that there is close relationship between the Th17/Treg imbalance and the children with HSP. However, there are several limitations in our present meta-analysis. Firstly, the sample size in our study was relatively small, which might have led to statistical bias. Secondly, the results should be interpreted with caution as a result of obvious limitations.
heterogeneity. Last but not least, the current meta-analysis did not investigate the relationship between Th17/Treg and other factors that influenced the development of HSP.

5. Conclusions

In conclusion, our meta-analysis indicated that increased frequency of Th17 cells and level of IL-17, but lower frequency of Treg cells are associated with HSP in childhood. Considering the limitations of this meta-analysis, large-scaled studies need to be conducted to validate the current results.

Author contributions

Data curation: Jizu Ling.
Funding acquisition: Yuning Li.
Investigation: Jizu Ling, Zhongbin Tao.
Methodology: Yuning Li.
Software: Zhongbin Tao, Xuemei Yang.
Supervision: Yuning Li.
Writing – original draft: Bowen Li, Qian Ren.
Writing – review & editing: Yuning Li.

References

[1] Chen O, Zhu XB, Ren P, et al. Henoch Schonlein Purpura in children: clinical analysis of 120 cases. Afr Health Sci 2013;13:94–9.
[2] Lee HY, Chuang YH, Lin SC, et al. Increased serum interleukin-17 and peripheral Th17 cells in children with acute Henoch-Schonlein purpura. Pediatr Allergy Immunol 2011;22:862–8.
[3] Yang YH, Chuang YH, Wang LC, et al. The immunobiology of Henoch-Schonlein purpura. Autoimmun Rev 2008;7:179–84.
[4] Lin CY, Yang YH, Lee CC, et al. Thrombopoietin and interleukin-6 levels in Henoch-Schonlein purpura. J Microbiol Immunol Infect 2006;39:476–82.
[5] Yang YH, Lai HJ, Huang CM, et al. Sera from children with active Henoch-Schonlein purpura can enhance the production of interleukin 8 by human umbilical venous endothelial cells. Ann Rheum Dis 2004;63:1511–3.
[6] Ouyang W, Kolls JK, Zheng Y. The biological functions of T helper 17 cell effector cytokines in inflammation. Immunity 2008;28:454–67.
[7] Bertelli E, Korn T, Okkaz M, et al. Induction and effector functions of T(H)17 cells. Nature 2008;453:1051–7.
[8] Harrington LE, Hatton RD, Mangan PR, et al. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. Nat Immunol 2005;6:1123–32.
[9] Mossec P, Korn T, Kuchroo VK. Interleukin-17 and type 17 helper T cells. N Engl J Med 2009;361:988–98.
[10] McGechy MJ, Cua DJ. Th17 cell differentiation: the long and winding road. Immunity 2008;28:445–53.
[11] Sakaguchi S, Oon M, Setoguchi R, et al. Foxp3+ CD25+ CD4+ natural regulatory T cells in dominant self-tolerance and autoimmune disease. Immunol Rev 2006;212:6–27.
[12] Littman DR, Rudensky AY. Th17 and regulatory T cells in mediating and restraining inflammation. Cell 2010;140:845–58.
[13] Li YY, Li CR, Wang GB, et al. Investigation of the change in CD4+ T cell subset in children with Henoch-Schonlein purpura. Rheumatol Int 2012;32:3785–92.
[14] Chen O, Zhu XB, Ren H, et al. The imbalance of Th17/Treg in Chinese children with Henoch-Schonlein purpura. Pediatr Blood Cancer 2013;63:457–63.
[15] Wang Q, Shi YY, Cao M, et al. Role of imbalance between Th17 Cells and Treg Cells in the Pathogenesis of Children with Henoch-Schonlein Purpura. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2015;23:1339–46.
[16] Higgins J, Green S. Cochrane handbook for systematic reviews of interventions 5 version 5.1.0. 2011;The Cochrane Collaboration, Available from: http://www.cochrane.org/handbook. Accessed December 25, 2017.
[17] Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.
[18] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical research ed) 1997;315:629–34.
[19] Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–63.
[20] Chang H, Cao Y, Lin YL, et al. Association between toll-like receptor 6 expression and auxiliary T cells in the peripheral blood of pediatric patients with allergic purpura. Exp Ther Med 2015;10:1536–40.
Li et al. Medicine (2019) 98:3

[22] Blom RL, Lagarde SM, Klinkenbijl JH, et al. A high body mass index in esophageal cancer patients does not influence postoperative outcome or long-term survival. Ann Surg Oncol 2012;19:766–71.

[23] Fan Q, Wang C, Sheng G. Role of Th17 cell and interleukin-17 in pathogenesis of Henoch-Schonlein purpura in children. J Chin Pract Diag Thor 2010;24:1089–90.

[24] Guo H, Tian L, Zhang H, et al. Expression of Toll-like receptor 2, Toll-like receptor 4 and Toll-like receptor 6 in peripheral blood mononuclear cells and their relationship with Treg immune response in children with Henoch-Schonlein purpura. Chin J Tissue Eng Res 2014;18:6222–7.

[25] Huang Y, Tang X, Zhang Y, et al. Effect of compound glycyrrhizin on Th17/Treg cells in peripheral blood with Henoch-Schonlein purpura. J Chongqing Med Univ 2014;39:990–4.

[26] Li Y, Wang Y, Zhu D, et al. Distribution of Th17 cells in peripheral blood of children with Henoch-Schonlein purpura and its clinical significance. J Clin Pediatr 2014;32:921–3.

[27] Liang Q, Wang Y, Zhang Y, et al. Alteration of gut mucosal Barrier function and Treg/Th17 imbalance in pathogenesis of Henoch-Schonlein purpura in children. Chin J Microecol 2015;27:1023–6.

[28] Huang W, Huang J, Liu Q, et al. Neutrophil-lymphocyte ratio is a reliable predictive marker for early-stage diabetic nephropathy. Clin Endocronol 2015;82:229–33.

[29] Feng R, Liu T, Wang N, et al. Correlation between neutrophil lymphocyte ratio, platelet/lymphocyte ratio and diabetic nephropathy. Chin J Clin Res 2016;29:1205–7.

[30] Liu P, Zhang Q. Function of Th17 cells and changes of CD4+CD25+ T regulatory cells in children with Henoch-Schonlein purpura in acute phase. Med J Qiu 2012;27:31–6.

[31] Ma L, Li X, Zhang Y, et al. Detection of Th17/Treg cell balance in peripheral blood of patients with Henoch-Schonlein purpura. Chin J Dermatol 2010;43:617–9.

[32] Meng F, Xue L, Wang X, et al. Study on variation and correlation of LTβ4 and CD4+CD25+ regulatory T cell in peripheral blood of children with Henoch-Schonlein purpura nephritis. J Clin Transfus Lab Med 2011;13:108–10.

[33] Mao J, Zhou J, Peng X, et al. Expression and significance of Th17 Cells and IL-17 in children with Henoch-Schonlein purpura. Jangsu Med J 2014;49:102–4.

[34] Tan X, Yang B, Zhang L, et al. Effects of IL-10+B cells on Th17/Treg imbalance in Henoch-Schonlein purpura. Immunol J 2017;33:133–40.

[35] Wang Q, Shi Y, Cao M, et al. Role of Imbalance between Th17 cells and Treg cells in the pathogenesis of children with Henoch-Schonlein purpura. J Exp Hematol 2015;23:1391–6.

[36] Wang X, Liang Q, Zhang Y, et al. Regulation of CD4 T cell subsets on pathogenic mechanism in children with Henoch-Schonlein purpura. Chin J Appl Clin Pediatr 2015;30:1614–1616.1618.

[37] Xiao J, Liu J, Zhang Q. Influence of compound glycyrrhizin on functions of Treg and TH17 cells in children with Henoch-Schonlein purpura. Acta Academicae Medicinae Qingsdao Universitatis 2014;50:315–20.

[38] Xiao Q, Yin Q, Lin D. Effect of leflunomide on Th17 cells in patients with HSPN and its clinical efficacy. J Med Res 2014;43:142–5.

[39] Xing C, Shao M, Chen H, et al. Significance and changes of Th17, Th22 and Treg cells in peripheral blood of children patients with Henoch-Schonlein Purpura. Chin J Health Lab Tec 2017;27:1432–4.

[40] Yang J, Li C, Zu Y, et al. Role of regulatory T cells in pathogenesis of Henoch-Schonlein purpura in children. Chin J Pediatr 2006;44:411–4.

[41] Zhang L. Research on imbalances of peripheral blood Th17 cells and Treg cells in Anaphylactoid purpura children. Chin J Immun 2015;31:1494–6.

[42] Zhang T, Ji X, Li S, et al. Detection of Th17, Treg cells and IL-17, IL-23 levels in children with Henoch-Schonlein purpura. Chin J Immun 2016;32:1801–14.

[43] Zi G, Fu Y, Chen X, et al. Expression of TLR6 protein in peripheral blood mononuclear cells and the balance of Th1, Th2 and Th17 in children with Schoenlein-Henoch purpura. Chin J Clinicians (Electronic Edition) 2014;8:3789–94.

[44] Besbas N, Szatcz U, Ruzac S, et al. The role of cytokines in Henoch Schonlein purpura. Scand J Rheumatol 1997;26:456–60.

[45] Yu YH, Pan KI. Role of cytokines in Henoch-Schonlein purpura nephritis. Zhongguo Dang Dai Er Ke Za Zhi 2009;11:869–72.

[46] Yang L, Anderson DE, Baschier-Allan C, et al. IL-21 and TGF-β are required for differentiation of human TH17 cells. Nature 2008;454:330.

[47] Korn T, Hetteli E, Gao W, et al. IL-21 initiates an alternative pathway to induce proinflammatory T(H)17 cells. Nature 2007;448:484–7.

[48] Castro G, Liu X, Ngo K, et al. DORgammat and RORalpha signature genes in human Th17 cells. PLoS One 2017;12:e0181865.

[49] Bettelli E, Oukka M, Kuchroo VK. TH17 cells in the circle of immunity and autoimmunity. Nat Immunol 2007;8:345–50.

[50] Khoury SJ. Th17 and Treg balance in systemic sclerosis. Clin Immunol 2011;139:231–2.

[51] Kolls JK, Linden A. Interleukin-17 family members and inflammation. Immunity 2004;21:467–76.

[52] Mekala DJ, Alii RS, Geiger TL. IL-10-dependent infectious tolerance after the treatment of experimental allergic encephalomyelitis with redrected CD4+CD25+ T lymphocytes. Proc Natl Acad Sci U S A 2005;102:11817–22.

[53] Mekala DJ, Geiger TL. Immunotherapy of autoimmune encephalomyelitis with redrected CD4+CD25+ T lymphocytes. Blood 2005;105:2090–2.

[54] Bettelli E, Carrier Y, Gao W, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature 2006;441:235–8.

[55] Niu Q, Cai B, Huang ZC, et al. Disturbed Th17/Treg balance in patients with rheumatoid arthritis. Rheumatol Int 2012;32:2731–6.

[56] Kang KY, Kim YK, Yi H, et al. Metformin downregulates Th17 cells differentiation and attenuates murine autoimmune arthritis. Int Immunopharmacol 2013;16:85–92.

[57] Lee SY, Lee SH, Yang EJ, et al. Metformin ameliorates inflammatory bowel disease by suppression of the stat3 signaling pathway and regulation of the between Th17/Treg balance. PLoS One 2015;10:e0135858.

[58] Son HJ, Lee J, Lee SY, et al. Metformin attenuates experimental autoimmune arthritis through reciprocal regulation of Th17/Treg balance and osteoclastogenesis. Mediators Inflamm 2014;2014:973986.