Heliyon 10 (2024) e32832

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Bibliometric analysis of the top 100 most cited articles on Th17/Treg balance and rheumatoid arthritis

Xinru Liu [a,*,1], Yilan Wang [b,1], Quan Wen [a,**]

[a] Chengdu Eighth People's Hospital (Geriatric Hospital of Chengdu Medical College), Chengdu, China
[b] Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China

ARTICLE INFO

Keywords:
Th17
Treg
Rheumatoid arthritis
Top 100 most cited articles
Bibliometric analysis

ABSTRACT

Objective: Rheumatoid arthritis (RA) is an autoimmune disease. The role of Th17/Treg balance in RA pathogenesis has been increasingly emphasized. In this study, bibliometric and visualization analyses of the top 100 most cited articles on Th17/Treg balance in the field of RA were conducted.

Methods: By searching the Web of Science Core Collection database, the top 100 most cited articles of related studies were included, and the authors, countries, institutions, journals, keywords and other information were extracted for analysis using VOSviewer software.

Results: The top 100 most cited papers had a total of 7185 citations, with an average citation frequency of 72 (range 21–730). All of them were published between 2011 and 2022. The most influential paper, with 730 citations, was written by "Komatsu, Noriko" in 2014 and published in NATURE MEDICINE. The author with the highest output was "Cho, Mi-La" (n = 24). China was the country with the highest number of publications (n = 42). Catholic University of Korea was the institution with the highest number of publications (n = 24). ARTHRITIS AND RHEUMATISM (n = 7), ARTHRITIS & RHEUMATOLOGY (n = 7) and INTERNATIONAL IMMUNOPHARMACOLOGY (n = 7) were the journals that published the most literature. "Expression" (cytokines and transcription factors, etc) and "differentiation" (T cells, Treg cells, and Th17 cells) were the themes of the research. "Mechanisms", "gut microbiota", "STAT3", "interleukin-6", "synovial fibroblasts" were the hot spots of research in recent years.

Conclusions: For the first time, the top 100 most cited articles were analyzed using bibliometric methods. We aimed to grasp the current development and research trends of RA and Th17/Treg-related studies. It is hoped that this study will provide direction and support for future research.

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic, erosive polyarthritis. Its main pathological features are synovitis and cartilage destruction, and clinical manifestations are joint pain, swelling, and limitation of movement [1,2]. The pathogenesis of RA has not yet formed a unified consensus, and is related to a variety of factors. Some studies have suggested that

* Corresponding author.
** Corresponding author.
E-mail addresses: liuxinru@stu.cdutcm.edu.cn (X. Liu), 381338886@qq.com (Q. Wen).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2024.e32832
Received 15 February 2024; Received in revised form 8 June 2024; Accepted 10 June 2024
Available online 14 June 2024

immune disorders lead to the development of disease due to an imbalance between pro-inflammatory and anti-inflammatory factors [3,4].

With the rapid development of immunology, lymphocyte subsets are of great significance in the immune mechanism of RA. T helper cell 17 (Th17) secretes pro-inflammatory factors such as interleukin-17 (IL-17) and is a subset of $CD4^+$ T cells [5]. Regulatory T cell (Treg), another subpopulation of $CD4^+$ T cells, has significant immunosuppressive properties. It mainly secretes interleukin-10 (IL-10), transforming growth factor-β (TGF-β), and other pro-inflammatory factors [6]. Excessive differentiation of Th17 cells promotes the development of RA, and Treg cells subpopulations can mitigate autoimmune inflammatory responses by inhibiting Th17 cells expression [7]. Functional imbalance between Th17 cells and Treg cells is expressed as Th17 up-regulation and/or Treg down-regulation [8], which is one of the important pathogenic mechanisms leading to RA.

Bibliometrics is a scientific quantitative analysis method that integrates bibliography, mathematics and statistics. The method is used to analyze the distribution structure, quantitative relationship and patterns of change of scientific literature information [9]. Bibliometrics can aid in understanding how a field has developed by obtaining detailed information about authors, journals, countries, organizations, keywords, references, etc [10]. Bibliometrics has been widely used in medicine and more recently in the field of RA [11–13].

VOSviewer is a commonly used analytical tool for bibliometrics. VOSviewer is a software for analyzing and visualizing collaborations. It presents large networks visually, thus effectively avoiding the coverage of important nodes and emphasizing the display of the main information of the dataset [14]. In the network diagram generated by VOSviewer, larger circles indicate more frequent occurrences, and thicker lines indicate stronger associations. A cluster's color is represented by an element's color, and different colors correspond to distinct clusters. Usually, items in the same cluster indicate stronger collaborative relationships [15].

In recent years, studies on Th17/Treg in RA have become a hot topic, and the role of Th17/Treg balance in RA pathogenesis has been increasingly emphasized. No bibliometric studies on Th17/Treg and RA have been reported so far. Regulation of Th17/Treg balance is essential for understanding disease pathogenesis, prognostic assessment and treatment. This study's aim is to examine the research dynamics, hotspots, and trends of Th17/Treg balance in RA through bibliometric methods and the visualization function of VOSviewer. It is hoped to provide more targets for the treatment of RA and to provide theoretical basis and references for future research.

2. Materials and methods

2.1. Search strategy

The Web of Science Core Collection database (SCIE and SSCI) were selected as the source of literature. Search subject terms included "Rheumatoid arthritis" "Th17 Cells" "T Helper Cell 17" "Treg Cells" "Regulatory T Cell" "Th17/Treg". Select "Article" and "Review" for Document Type. The language of literature was "English". The literature search was completed on 6/29/2023.

2.2. Data collection

The retrieved documents were sorted from highest to lowest number of citations. After manually excluding irrelevant literature (no

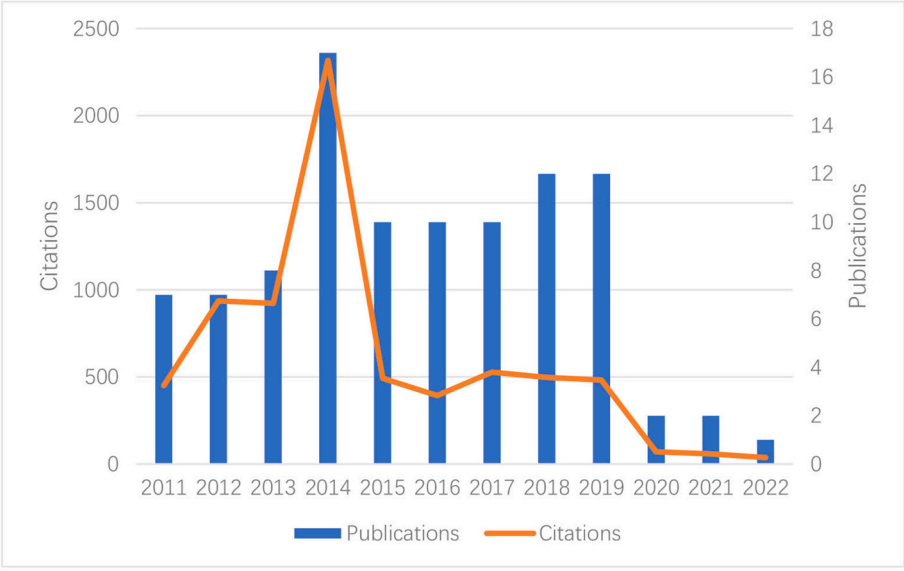

Fig. 1. The top 100 most cited articles published in 2011–2022.

RA, or no Treg, or no Th17), the top 100 papers were selected for analysis. The export was in plain text and tab-delimited file format. The record was a "full record with cited references", including authors, countries, institutions, titles, publication years, citations, journals and other information.

2.3. Bibliometric analysis

VOSviewer (Version 1.6.19) was used to perform collaborative network analysis of authors, countries, institutions and keywords co-occurrence analysis. The specific operation was as follows: after opening VOSviewer, selected "Create a map based on bibliographic data", then selected "Read data from bibliographic database files", and imported the plain text data of the top 100 most cited articles downloaded from the Web of Science Core Collection database. In this study, we used "Co-authorship" and "Co-occurrence" analysis. "Co-authorship" included the analysis of authors, institutions and countries. "Co-occurrence" was used for the keywords co-occurrence analysis, and selected "All keywords".

3. Results

3.1. Overall analysis of publications

A total of 1081 articles were retrieved through the search formula. There were 1049 articles after being excluded by the literature type and literature language. The top 100 most cited articles were published in 2011–2022 (Fig. 1), including 90 treatises (90 %) and 10 reviews (10 %). These 100 articles were cited 7185 times in total, with an average citation frequency of 72 (range 21–730). Among them, the largest number of articles (n = 17) was published in 2014 with 2317 citations. The most influential article with the highest citation (730) was published by "Komatsu, Noriko" in 2014 in the journal NATURE MEDICINE. There were 2 articles with citation

Table 1
The top 5 cited articles in terms of the total citations of publications.

Rank	Title	Author	Journal	Total Citations	Year	Significance
1	Pathogenic conversion of Foxp3 (+) T cells into T(H)17 cells in autoimmune arthritis	Komatsu, Noriko	NATURE MEDICINE	730	2014	The presence of exFoxp3 TH17 cells serves as a biomarker for RA and helps to predict responsiveness to anti-IL-6 therapies. Further characterization of the mechanisms of transformation and function of plastic Foxp3+ T cells will provide new insights into the maintenance and restoration of self-tolerance, which in turn will facilitate the development of new therapeutic strategies for autoimmune diseases.
2	Th17 and regulatory T cell balance in autoimmune and inflammatory diseases	Noack, Melissa	AUTOIMMUNITY REVIEWS	608	2014	The balance between inflammation (Th17 cells) and tolerance (Treg cells) may influence the pathology or disease outcome of autoimmune diseases, including RA and MS. Novel therapies could be developed to maintain an appropriate balance of Th17/Treg to prevent the development and expansion of autoimmune and inflammatory diseases.
3	CD19(+)CD24(hi)CD38(hi) B Cells Maintain Regulatory T Cells While Limiting T(H)1 and T(H)17 Differentiation	Flores-Borja, Fabian	SCIENCE TRANSLATIONAL MEDICINE	483	2013	In patients with active RA, $CD19^{+}CD24hiCD38hi$ B cells with regulatory functions may not be able to prevent the onset of auto-reactive responses and inflammation, leading to autoimmunity. The data presented here provide new insights into the biology of $CD19^{+}CD24hiCD38hi$ B cells with regulatory functions in human health and autoimmune diseases.
4	Brief Report: Inhibition of interleukin-6 function corrects Th17/Treg cell imbalance in patients with rheumatoid arthritis	Samson, Maxime	ARTHRITIS AND RHEUMATISM	267	2012	This study demonstrates for the first time that inhibition of IL-6 function by tocilizumab in vivo restores the physiologic balance of Th17/Treg cells in RA patients. This study opens a potential new avenue for the treatment of RA and other autoimmune diseases that may involve IL-6, Treg cells and/or Th17 cells or for monitoring current anti-cytokine therapies.
5	Disturbed Th17/Treg balance in patients with rheumatoid arthritis	Niu, Qian	RHEUMATOLOGY INTERNATIONAL	178	2012	Th17/Treg imbalance has a potential role in the pathogenesis and progression of RA. Therefore, blockade of key cytokines in vivo, especially IL-6 and IL-23, or administration of exogenous TGF-β1 may promote recovery in RA patients by restoring Th17/Treg balance.

frequency >500 and 13 articles with citation frequency >100. Table 1 lists the top 5 cited articles.

3.2. Authors

The top 100 most cited publications contained a total of 656 authors. Table 2 lists the five most prolific authors with more than nine publications. The author with the highest number of publications was "Cho, Mi-La", with a total of 24 papers. The author with the highest citation was also" Cho, Mi-La" with 1202 citations. The author with the highest average citation was "Kim, Eun-Kyung" (54.43). Fig. 2 illustrates the authors collaboration network diagram.

3.3. Countries

The top 100 most cited articles involved a total of 19 countries. As shown in Table 3, the top 5 countries in terms of publications were China (n = 42), South Korea (n = 26), USA (n = 13), France (n = 9), and England (n = 5). China had both the most publications and total citations, but the average number of citations was low. The highest average citation was England with 159.8 citations. Fig. 3 illustrates the collaborative network relationships between countries.

3.4. Institutions

154 institutions contributed to the top 100 most cited articles. Table 4 lists the top 4 institutions with the highest number of articles, which were Catholic University of Korea, Sun Yat Sen University, Jiangsu University, and China Pharmaceutical University. Catholic University of Korea had the highest number of articles and the highest total citations, which was the main contributing institution of the study. The institution with the highest average citation frequency was Jiangsu University (88.60). Fig. 4 illustrates the collaborative network of institutions.

3.5. Journals

The top 100 most cited articles were published in 50 journals. The nine journals that published more than two papers were listed in Table 5. Among them, the most prolific journals were ARTHRITIS AND RHEUMATISM (n = 7), ARTHRITIS & RHEUMATOLOGY (n = 7) and INTERNATIONAL IMMUNOPHARMACOLOGY (n = 7). ARTHRITIS AND RHEUMATISM had the highest number of citations with 838. However, ARTHRITIS AND RHEUMATISM has ended its publication and this journal is not included in the latest Journal Citation Reports. The journal with the highest average citation was AUTOIMMUNITY REVIEWS (223). The 2 journals with the highest IF were AUTOIMMUNITY REVIEWS and ARTHRITIS & RHEUMATOLOGY with IF 13.6 and 13.3 respectively.

3.6. Keywords

After merging the synonyms, co-occurrence analysis was performed for keywords with ≥4 occurrences. A total of 54 nodes and 3614 links were generated and presented by both overlay and density visualization. The high-density keywords in the top 100 most cited articles were "rheumatoid arthritis", "Th17 cells", "Treg cells", "collagen-induced arthritis", "expression", "differentiation", "T-cells", "inflammation", etc (Fig. 5A). Table 6 lists the top 10 most frequent keywords.

The color of the nodes in the overlay view can indicate the average time of occurrence of the keywords. The earlier the keyword appears, the closer the color is to purple; and conversely, the closer it is to yellow [16]. As can be seen from Fig. 5B, the active topics related to Th17/Treg and RA in recent years included "mechanisms", "gut microbiota", "signal transducers and activators of transcription 3 (STAT3)", "interleukin-6 (IL-6)", "synovial fibroblasts", etc.

4. Discussion

4.1. Research status of Th17/Treg and RA from 2011 to 2022

The analysis based on the number of citations is a common method of bibliometric research. It is generally recognized that the more times a paper is cited, the greater its academic value and the more innovative it is [17].

It is evident that there were higher publications in 2011–2019. Citations showed an increasing trend from 2011 to 2014. Most

Table 2
The five most prolific authors with more than nine publications.

Rank	Author	Publications	Citations	Average Citations
1	Cho, Mi-La	24	1202	50.08
2	Park, Sung-Hwan	18	941	52.28
3	Kim, Eun-Kyung	14	762	54.43
4	Kim, Ho-Youn	13	666	51.23
5	Park, Jin-Sil	10	519	51.90

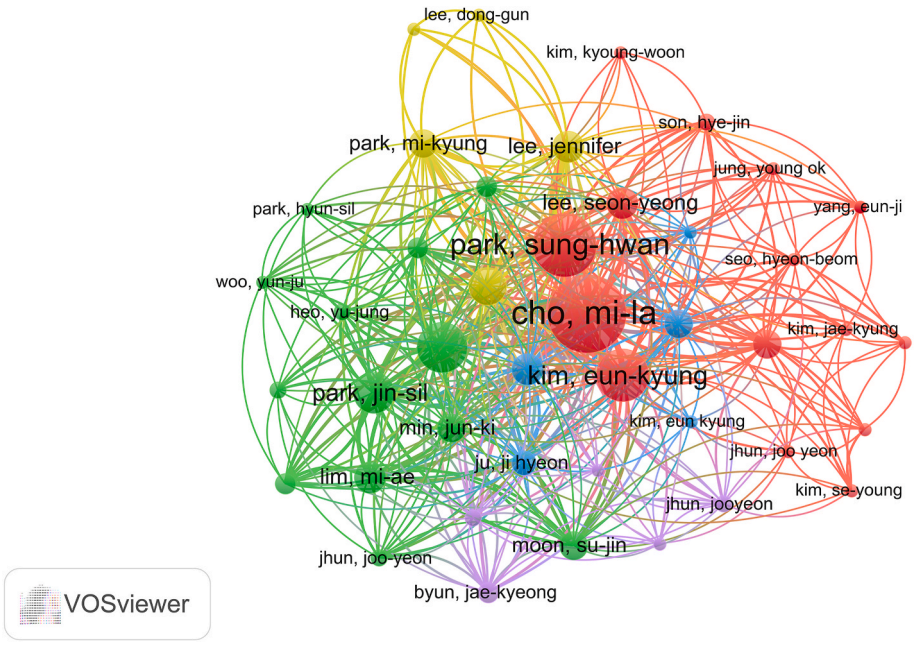

Fig. 2. The collaboration network diagram of authors.

Table 3
The top 5 countries in terms of publications.

Rank	Publications	Country	Citations	Average Citations
1	42	China	2327	55.40
2	26	South Korea	1277	49.12
3	13	USA	1483	114.08
4	9	France	1372	152.44
5	5	England	799	159.80

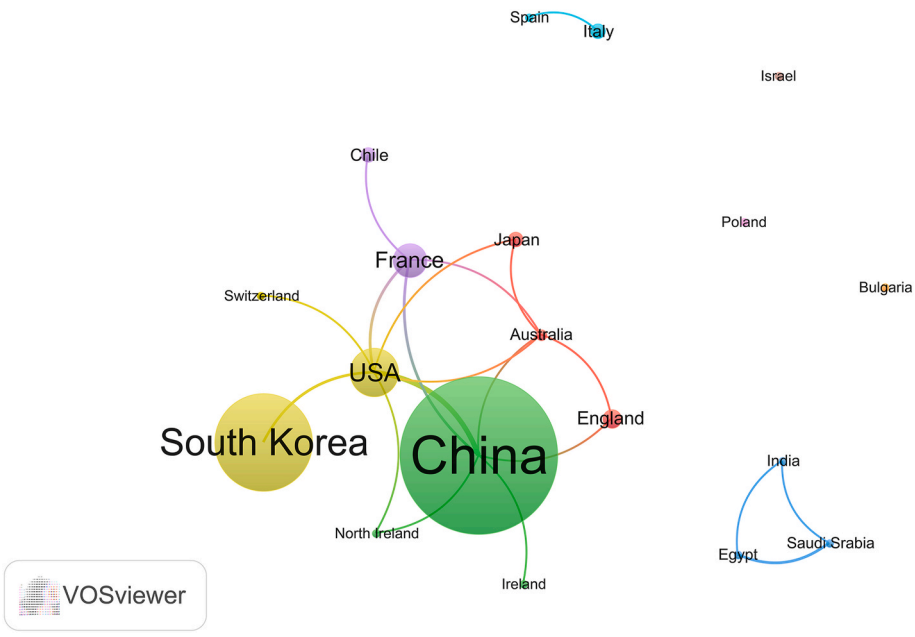

Fig. 3. The collaboration network diagram of countries.

Table 4
The top 4 institutions in terms of publications.

Rank	Institution	Country	Publications	Citations	Average Citations
1	Catholic University of Korea	South Korea	24	1145	47.71
2	Sun Yat Sen University	China	5	259	51.80
3	Jiangsu University	China	5	443	88.60
4	China Pharmaceutical University	China	5	201	40.20

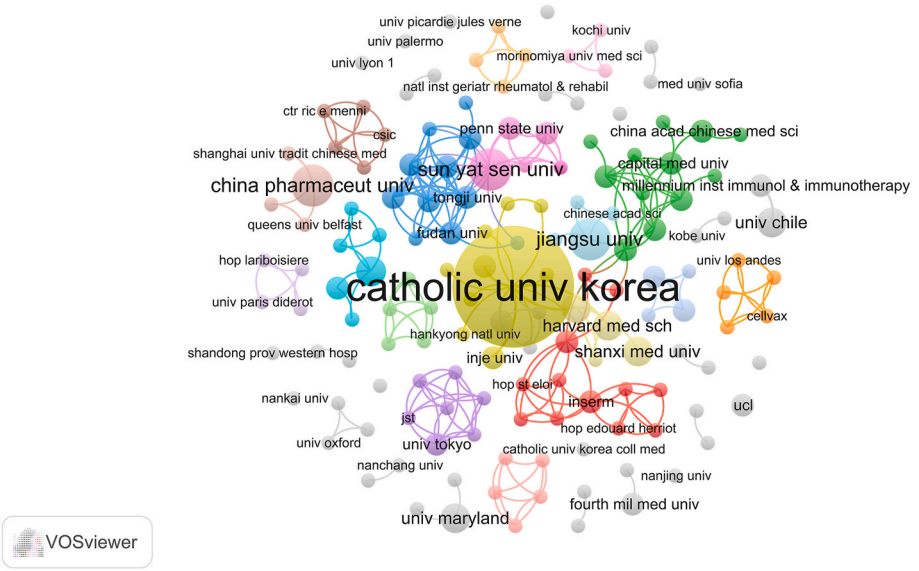

Fig. 4. The collaboration network diagram of institutions.

Table 5
The nine journals that published more than two papers.

Rank	Journal	Publications	Impact Factor (2022)	Citations	Average Citations
1	ARTHRITIS AND RHEUMATISM	7	–	838	119.71
2	ARTHRITIS & RHEUMATOLOGY	7	13.3	359	51.29
3	INTERNATIONAL IMMUNOPHARMACOLOGY	7	5.6	340	48.57
4	FRONTIERS IN IMMUNOLOGY	6	7.3	247	41.17
5	PLOS ONE	5	3.7	223	44.60
6	RHEUMATOLOGY INTERNATIONAL	4	4	395	98.75
7	MEDIATORS OF INFLAMMATION	4	4.6	287	71.75
8	SCIENTIFIC REPORTS	4	4.6	216	54
9	AUTOIMMUNITY REVIEWS	3	13.6	669	223

notable research outputs was in 2014 (most publications and citations). The cited frequency had shown a downward trend since 2014, and the number of publications and the citation were lower in 2020–2022. This may be due to the fact that citations take time to accumulate [18]. It has been reported that scientific works are usually cited for the first time one to two years after publication, and peak around ten years later [19]. Therefore, papers published in recent years do not have enough citations to be in the top 100, while articles published earlier may have more citations. The papers included in our study could attract more attention from researchers in the coming years.

The most cited article was the study on "Pathogenic conversion of Foxp3+ T cells into TH17 cells in autoimmune arthritis" by "Komatsu, Noriko [20]" published in 2014. They found that, in addition to the fact that Treg cells require Foxp3 for their suppressive effects, Foxp3 instability plays a vital role in the development of pathogenic Th17 cells in autoimmunity. It has been shown that CD25loFoxp3+CD4^{+} T cells lose Foxp3 expression (referred to here as exFoxp3 cells) and transdifferentiate into Th17 cells under arthritic conditions. The presence of exFoxp3 Th17 cells could serve as a biomarker for RA and could be used to predict responsiveness to anti-IL-6 therapy.

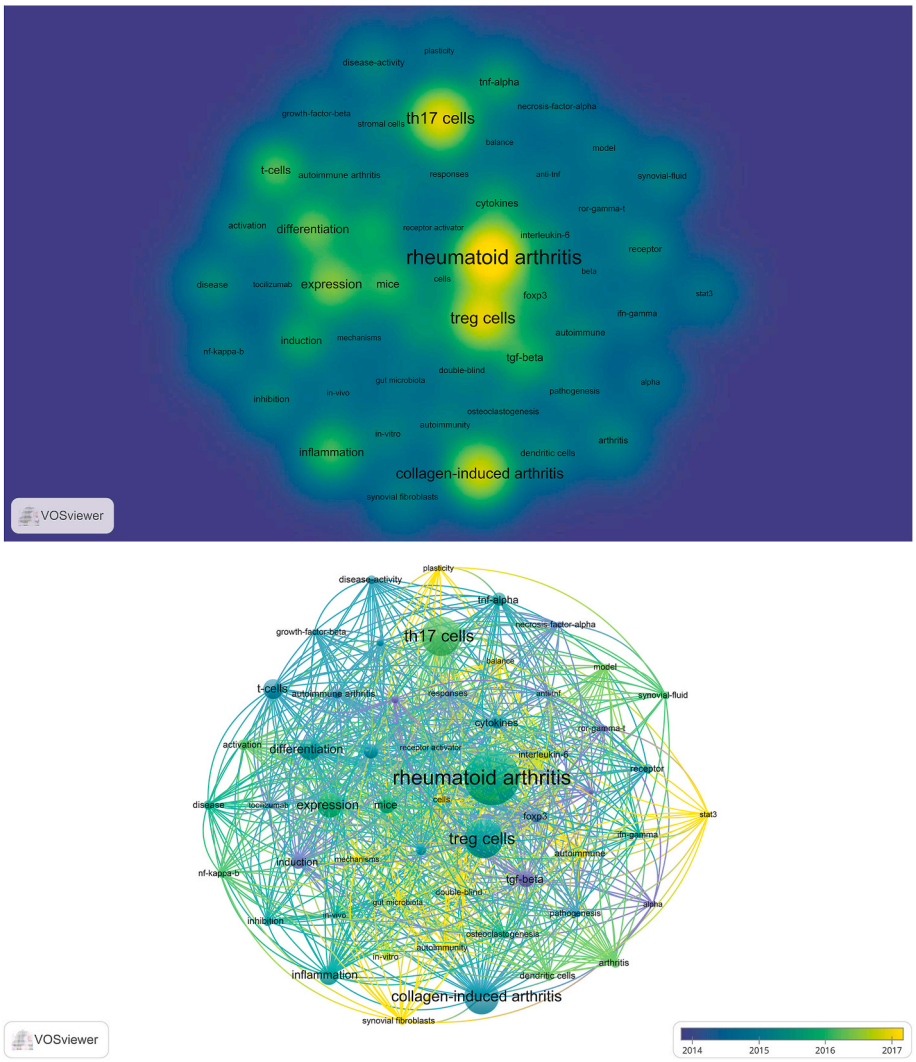

Fig. 5. A The density visualization diagram of keywords B The overlay visualization diagram of keywords.

Table 6
The top 10 most frequent keywords.

Rank	keyword	occurrences	total link strength
1	Rheumatoid arthritis	71	383
2	Th17 cells	47	293
3	Treg cells	46	262
4	Collagen-induced arthritis	40	223
5	Expression	26	153
6	Differentiation	22	130
7	T-cells	20	95
8	Inflammation	19	102
9	Mice	17	100
10	Tgf-beta	16	102

South Korea and China were the two most contributing countries in the top 100 papers with the most citations (68 % of 100 publications). China was in the first place both publications (n = 42) and total citations (2327), but its average citation rank was low. This indicated that although relevant research had a high level of enthusiasm in China, there were relatively few high-quality outputs, and the overall quality and level of research still need to be improved. We observed that in the national cooperation network, China cooperated closely with Ireland and North Ireland; USA cooperated closely with South Korea and Switzerland; Australia cooperated closely with Japan and England; France cooperated closely with Chile; Israel, Poland, and Bulgaria had no cooperation with other

countries. Cooperation and exchanges between countries can still be further strengthened, with a view to obtaining more high-quality outputs.

From the perspective of issuing institutions, three of the top four research institutions in terms of publications were from China, but the number of articles issued by China was relatively small. Jiangsu University had the highest average citation although the number of articles issued was small, indicating that Jiangsu University had carried out high-level research in RA field in the past 10 years. Catholic University of Korea was the most prolific institution, reflecting excellence in RA research. The top 5 authors with the highest number of publications were all from Catholic University of Korea. The most prolific author, Cho, Mi-La, was mainly working on the improvement of experimental autoimmune arthritis through the modulation of Th17/Treg cells and the inhibition of osteoclastogenesis, which were mostly related to the inhibition of STAT3. For example, PTEN down-regulates STAT3 activation; AG490 blocks JAK2 (Janus Kinase 2)-STAT3; STA-21 is a promising STAT-3 inhibitor; and so on.

In addition to the 9 journals with the highest number of publications listed in Table 2, the top 100 most cited papers also included SCI journals with high impact factors: NATURE MEDICINE (n = 1, IF: 82.9), NATURE REVIEWS RHEUMATOLOGY (n = 1, IF: 33.7), ANNALS OF THE RHEUMATIC DISEASES (n = 2, IF: 27.4), CELLULAR & MOLECULAR IMMUNOLOGY (n = 1, IF: 24.1). Besides, there were also journals with impact factors greater than 10: EXPERIMENTAL AND MOLECULAR MEDICINE (n = 3, IF: 12.8), JOURNAL OF AUTOIMMUNITY (n = 2, IF: 12.8), SCIENCE TRANSLATIONAL MEDICINE (n = 1, IF: 17.1). It shows that this research area is becoming increasingly acknowledged by global mainstream medicine.

4.2. Research hot spots

With the continuous in-depth research on the pathogenesis of RA, attention has been paid to the role of T helper cells (Th) in CD4 + T cells in RA. The Th17/Treg balance as a target has become a hot spot in the current research. “Expression” and “differentiation” were important keywords. “Expression” included the expression of transcription factors and cytokines. “Differentiation” included the differentiation of T cells, Th17 cells and Treg cells.

RA is characterized by a chronic synovial inflammatory response dominated by infiltration of large numbers of CD4 + T cells [21]. The autoimmune response of CD4 + T cells against antigens, which are presented by antigen-presenting cells, has a significant impact on the pathogenesis of RA [22]. Initial $CD4^+$ T cells can differentiate in different directions after being stimulated by antigens, including Th17, Treg, etc [23]. The imbalance between Th17 cells and Treg cells (increased proportion of Th17 cells and decreased proportion of Treg cells) plays a key role in RA progression. Animal models of RA (collagen-induced arthritis, CIA) have been used in more and more studies on RA and Th17/Treg. The CIA model can accurately and comprehensively reflect the clinical symptoms and pathological manifestations of RA, and it is a commonly used animal model for the study of RA at present [24].

Th17 cells and Treg cells mutually constrain in the process of differentiation and functioning. They are regulated by a variety of cytokines and transcription factors to jointly maintain the immune balance of the body [25]. When some cytokines and transcription factors are overexpressed, they will affect the differentiation pattern of initial T cells and disrupt the Th17/Treg balance, thus triggering a series of inflammatory responses.

Retinoid acid receptor-related orphan receptor γt (RORγt) is a Th17-specific transcription factor, and STAT3 is an upstream regulator of RORγt [26]. RORγt promotes Th17 cells differentiation and IL-17 expression and inhibits Treg cells differentiation, mainly through the STAT3-mediated signaling pathway [22,27]. Foxp3, a crucial transcription factor and specific marker for Treg cells [28], is essential in maintaining Treg immunosuppressive function. RORγt/Foxp3 balance determines whether initial T cells differentiate toward Th17 or Treg after antigenic stimulation [27].

IL-6 contributes significantly to maintaining the differentiation and homeostasis of Th17 cells. IL-6 synergizes with TGF-β to initiate the differentiation of Th17 cells; but in the presence of TGF-β alone and in the absence of IL-6, initial CD4 + T cells differentiate into Treg cells [29]. In addition, Th17 differentiation requires Il-6-mediated STAT3 signaling, which is crucial in the pathogenesis of RA [30]. STAT3 is a key regulator of Treg and Th17 cells during the exercise of their biological functions [31]. By activating the STAT3 signal, IL-6 inhibits Foxp3 and promotes the expression of RORγt, which leads to the differentiation of initial $CD4^+$ T cells into Th17 cells and inhibits the generation of Treg [32,33]. Activated STAT3 increases RORyt expression, induces Th17 cells to secrete cytokines such as IL-6 and IL-17, and feedback activates the JAK/STAT pathway, thereby mediating the inflammatory cascade response in RA [34]. Activation of JAK/STAT signaling pathway is involved in the occurrence of RA, and T cells differentiation in inflammatory sites is mediated by activation of JAK/STAT signaling pathway [35]. Under the combined effect of IL-6 and TGF-β, initial $CD4^+$ T cells induce high expression of RORγt by activating the JAK-STAT3 signaling pathway. Induction of cytokines such as TGF-β and interleukin-2 (IL-2) upregulates Foxp3 expression through the JAK-STATs signaling pathway [36].

Th17 cells also autocrine interleukin-21 (IL-21) and interleukin-22 (IL-22), which positively activate STAT3. At the same time, IL-21 can stimulate the expression of interleukin-23 (IL-23) receptor, which makes the cells receive the stimulation of IL-23 [22]. After IL-23 binds to IL-23 receptor, it needs to be transduced by the JAK/STAT signaling pathway to phosphorylate STAT3 [37]. Inhibition of IL-10 secretion through STAT3 signaling promotes the stabilization of Th17 cells, and STAT3 function can only be realized after JAK2 phosphorylation [22]. Th17 cells differentiation requires IL-23 signaling, which in turn inhibits the transcriptional activity of Foxp3 and suppresses Treg cells differentiation [38].

Besides, IL-2 promotes the differentiation of initial $CD4^+$ T cells to Treg cells, affects the balance between Foxp3 and RORγt through the signal transducers and activators of transcription 5 (STAT5) pathway. Reduced RORγt expression and increased TGF-β-induced Foxp3 expression enhance Treg function, which is also an important mechanism by which Treg regulates Th17 differentiation [27].

Meanwhile, in the study of negative regulation of Th17 differentiation, suppressor of cytokine sig-naling 3 (SOCS3) and suppressor of cytokine signaling 1 (SOCS1) are important negative regulators. They regulate T cells homeostasis by inhibiting STAT3

phosphorylation and negatively regulating the JAK-STAT signaling pathway, respectively [39,40].

MicroRNAs (miRNAs) are important immune response regulators. They can regulate post-transcriptional target gene expression and participate in the regulation of CD4 + T cells subsets by promoting mRNA degradation or inhibiting the translation of transcription products [41]. MiR-21 is involved in the regulation of signaling sensor and activator of STAT3 and STAT5, which are regulators of Th17 and Treg differentiation, respectively [42]. Decreased miR-21 levels increase STAT3 expression and activation while decreasing STAT5 expression and activation. This promotes Th17 cells differentiation, inhibits Treg cells development, and induces Th17/Treg imbalance [41].

In addition to "STAT3" and "IL-6", "gut microbiota" and "synovial fibroblasts" have also been the focus of research on the mechanism of Th17/Treg in RA in recent years.

Recently, the study of gut microbiota in RA has received increasing attention. The disturbance of gut microbiota can affect the differentiation of cells, thus disrupting the auxiliary Th17/Treg balance and leading to RA [43]. For example, segmented filiable bacillus promotes the differentiation of $CD4^+$ T lymphocytes to Th17 cells through dendritic cell antigen and amyloid A in intestinal epithelial cells. At the same time, dendritic cells can secrete IL-23, increase the secretion of IL-6 and IL-22 through the innate lymphocyte channel, increase the expression of amyloid A. This enhances the secretion of IL-17, which acts on the RORγt receptor and promotes differentiation to Th17 cells [44]. Faecalibacterium prausnitzii can directly stimulate and activate the expression of Foxp3+ receptors to promote the differentiation of initial T cells to nTreg cells [45]. Bacteroides thetaiotaomicron can interfere with the intrinsic immune system and initial T-cells differentiation by regulating antimicrobial peptide activity through Toll-like receptors in intestinal mucosal cells [46]. They can also influence differentiation towards Treg cells by regulating the intra-nucleolar shuttling of peroxisome proliferators-activated receptors (PPARs) [47]. Podoplanar polysaccharide A from Bacterooides fragilis induces T cells differentiation towards Treg cells, down-regulates inflammation through activation of Foxp3 and subsequent production of IL-10, and inhibits the secretion and effects of pro-inflammatory factors [48].

RA synovial fibroblasts are the main effector cells of synovial proliferation and invasion, and play an important role in the pathological development of RA [49]. The large number of immune cells present in RA synovial tissues is dominated by $CD4^+$ T cells, which secrete Th17 cells that are abnormally active, and predominantly secrete IL-17 [50]. Receptor activator of nuclear factor-κB ligand (RANKL) plays a key role in osteoclast formation and bone erosion [51]. IL-17 stimulates RANKL expression in synovial fibroblasts, resulting in increased osteoclastogenesis [52]. In addition, IL-17 up-regulates IL-6 expression and induces the release of matrix metallopeptidase 1 (MMP1) and matrix metallopeptidase 3 (MMP3) from fibroblast-like synoviocytes, thereby promoting tissue destruction. Synergistically with tumor necrosis factor-α (TNF-α) and Interleukin-1β (IL-1β), IL-17 also directly induces osteoclastogenesis and inhibits osteoblastogenesis, which disrupts the balance between osteogenesis and bone destruction, leading to cartilage damage and bone erosion [53]. Another pro-inflammatory cytokine, IL-23, is involved in the pathogenesis of RA. It induces the expression of RANKL in RA fibroblast-like synoviocytes through the nuclear factor-kappa B (NF-κB) and STAT3 signaling pathways [41]. Osteoprotegerin (OPG) is secreted by osteoblasts. IL-10 secreted by Treg can up-regulate OPG expression and down-regulate RANKL expression, thereby regulating RANKL/OPG balance and inhibiting bone resorption [54].

Localized joint hypoxia is also one of the pathogenic mechanisms of RA [55]. Hypoxia-inducible factor-1α (HIF-1α) is an important regulator of hypoxia in tissue cells. It can induce Foxp3 ubiquitination or proteasomal degradation, and inhibit differentiation toward Treg cells. It can also positively regulate the differentiation of initial CD4 + T cells toward Th17 cells through the STAT3 pathway [44]. Hypoxia in RA-affected joints leads to upregulation of HIF-1α expression in synovial tissues. Hypoxia is also one of the triggers for elevated IL-6 expression in RA synovial fibroblasts, exacerbating the pathological process of RA [55].

4.3. Limitations

This study has several restrictions. First, we only looked for the literature in the Web of Science, and different databases may have different results. Second, some newly published high-quality papers do not have enough time to accumulate citations, resulting in low citations. These papers may not be included in the top 100 most cited articles. In the future, it is hoped that we can carry out more databases, and more comprehensive studies of emerging high-quality papers.

5. Conclusion

In this study, the first bibliometric analysis of RA and Th17/Treg related research was conducted. Influential countries, institutions, authors, and journals were analyzed through the top 100 most cited articles, with a view to grasping the current status of development and trends in the study of RA and Th17/Treg. "Expression" (cytokines and transcription factors, etc) and "differentiation" (T cells, Treg cells, and Th17 cells) were the themes of the research. "Mechanisms", "gut microbiota", "STAT3", "interleukin-6", "synovial fibroblasts" were the hot spots of research in recent years. It is hoped that this study will provide direction and support for future research.

Ethics approval and consent to participate

Not applicable.

Funding

This study received no external funding.

Data availability

Data will be made available on request.

CRediT authorship contribution statement

Xinru Liu: Writing – original draft, Visualization, Software, Methodology, Data curation, Conceptualization. **Yilan Wang:** Visualization, Validation, Data curation. **Quan Wen:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e32832.

References

[1] H. Ying, et al., Treating rheumatoid arthritis based on theory of "Yang transforming Qi and Yin Shaping body", Acta Chinese Medicine 38 (2023) 684–689.
[2] S. Jian, et al., Clinical efficacy of Warm Meridian Remitting Paralysis Soup on patients with rheumatoid arthritis with cold-damp paralysis syndrome, Chin. Tradit. Pat. Med. 45 (3) (2023) 1036–1039.
[3] W. Jinfeng, et al., Research status of traditional Chinese medicine regulating Th17/Treg balance in the treatment of rheumatoid arthritis, China Pharm. 34 (6) (2023) 763–768.
[4] Y. Tianning, et al., Research progress of Chinese Herbal Intervention on Th17/Treg cell imbalance and related factors in rheumatoid arthritis, Tradit. Chin. Drug Res. Clin. Pharmacol. 34 (4) (2023) 564–570.
[5] H. Park, et al., A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17, Nat. Immunol. 6 (11) (2005) 1133–1141.
[6] N. Lane, et al., Regulation in chronic obstructive pulmonary disease: the role of regulatory T-cells and Th17 cells, Clinical Science 119 (2) (2010) 75–86.
[7] J.M. Fletcher, et al., CD39+Foxp3+ regulatory T cells suppress pathogenic Th17 cells and are impaired in multiple sclerosis, J. Immunol. 183 (11) (2009) 7602–7610.
[8] H.M. Knochelmann, et al., When worlds collide: Th17 and Treg cells in cancer and autoimmunity, Cell. Mol. Immunol. 15 (5) (2018) 458–469.
[9] Z. Zehua, et al., Bibliometric analysis of COVID - 19 based on CiteSpace, Chin. J. Hosp. Pharm. 40 (19) (2020) 2029–2035.
[10] G. Abramo, C.A. D'Angelo, F. Viel, The field-standardized average impact of national research systems compared to world average: the case of Italy, Scientometrics 88 (2) (2011) 599–615.
[11] Y. Dong, et al., Relationship between gut microbiota and rheumatoid arthritis: a bibliometric analysis, Front. Immunol. 14 (2023) 1131933.
[12] R. Huang, et al., Global trends in research of fibroblasts associated with rheumatoid diseases in the 21st century: a bibliometric analysis, Front. Immunol. 14 (2023) 1098977.
[13] J. Liu, et al., Bibliometric and visualization analysis of mesenchymal stem cells and rheumatoid arthritis (from 2012 to 2021), Front. Immunol. 13 (2022) 1001598.
[14] N.J. van Eck, L. Waltman, Software survey: VOSviewer, a computer program for bibliometric mapping, Scientometrics 84 (2) (2009) 523–538.
[15] A.-F. Radu, et al., In-depth bibliometric analysis and current scientific mapping research in the context of rheumatoid arthritis pharmacotherapy, Biomed. Pharmacother. 154 (2022) 113614.
[16] Rongna Zhang, et al., Bibliometric analysis of COVID-19 related literature, based on Web of science Core collection, Disease Surveillance 37 (2022) 734–739.
[17] M. Fanxing, Study on the challenge and future development of research system in China———based on the analysis of academic level of SCI papers, Science and Technology Management Research 18 (2011) 237–240.
[18] K. Vishwanathan, S.B.S. Kambhampati, R. Vaishya, Top 100 cited articles on diabetes mellitus and Covid-19: a bibliometric analysis, Diabetes Metabol. Syndr.: Clin. Res. Rev. 15 (4) (2021) 102160.
[19] X. Tang, et al., Top-cited articles in digestive system disease from 1950 to 2013, J. Gastroenterol. Hepatol. 31 (1) (2016) 107–111.
[20] N. Komatsu, et al., Pathogenic conversion of Foxp3+ T cells into TH17 cells in autoimmune arthritis, Nat. Med. 20 (1) (2013) 62–68.
[21] H. Feng, et al., Mechanistic studies of Th17/treg imbalance influenced by exogenous wind-cold-damp pathogens on the development of rheumatoid arthritis, Journal of Hunan University of Chinese Medicine 41 (11) (2021) 1657–1662.
[22] X. Yaoyao, Effects of Ursolic Acid on Arthritis and Regulation of Peripheral Blood Th17/Treg Cell Imbalance in CIA Rats, Hunan University of Chinese Medicine, 2019.
[23] X.X. Li, Regulation of CD4+ T Cell Directed Differentiation to Th17 and Treg in MRL/lpr Lupus Mice by Compound Shengdi Synthetics, Shanghai University of Chinese Medicine, 2020.
[24] M. Dimitrijević, et al., Collagen-induced arthritis in Dark Agouti rats as a model for study of immunological sexual dimorphisms in the human disease, Exp. Mol. Pathol. 105 (1) (2018) 10–22.
[25] P. Xunlei, F. Sujuan, Treg/Th17 differentiation imbalance and inflammatory bowel disease, Med. Recapitulate 17 (1) (2011) 53–55.
[26] J.N. Ihle, STATs: signal transducers and activators of transcription, Cell 84 (3) (1996) 331–334.
[27] L. Zhou, et al., TGF-β-induced Foxp3 inhibits TH17 cell differentiation by antagonizing RORγt function, Nature 453 (7192) (2008) 236–240.
[28] C. Shuangshuang, et al., Effect of qufeng xiaoyan decoction on expression of transcription factors RORγt and Foxp3 in synovial tissue Th17/treg cell of rats with rheumatoid arthritis, Journal of Sichuan of Traditional Chinese Medicine 38 (3) (2020) 85–88.
[29] C. Lina, et al., Combined treatment of etanercept and MTX reverses Th1/Th2, Th17/Treg imbalance in patients with rheumatoid arthritis, J. Clin. Immunol. 31 (4) (2011) 596–605.

[30] J.-S. Park, et al., JAK2-STAT3 blockade by AG490 suppresses autoimmune arthritis in Mice via reciprocal regulation of regulatory T cells and Th17 cells, J. Immunol. 192 (9) (2014) 4417–4424.
[31] J.-S. Park, et al., STA-21, a promising STAT-3 inhibitor that reciprocally regulates Th17 and Treg cells, inhibits osteoclastogenesis in mice and humans and alleviates autoimmune inflammation in an experimental model of rheumatoid arthritis, Arthritis Rheumatol. 66 (4) (2014) 918–929.
[32] Z. Jinghui, Molecular Mechanism Study of Oxymatrine on Regulating Th17/Treg Cells axis to Alleviate RA through IL-6/STAT3 Signaling Pathway, Ningxia Medical University, 2022.
[33] W. Tao, et al., Research progress in the Th17/Treg cell imbalance involved in pathogenesis of rheumatoid arthritis, Chin. J. Osteoporos. 28 (11) (2022) 1629–1633.
[34] W. Tiefeng, et al., Study on the role and mechanism of trichothecenes in regulating Th17/Treg balance against rheumatoid arthritis, Chinese Clinical Pharmacology and Therapeutics 28 (2) (2023) 138–146.
[35] A. Krause, et al., Rheumatoid arthritis synoviocyte survival is dependent on Stat3, J. Immunol. 169 (11) (2002) 6610–6616.
[36] P. Bing, IL-38 Regulates Th17/Treg Balance through SIRT1/HIF-1α Signaling Pathway and Inhibits Inflammatory Response in Collagen-Induced Arthritis Rats, China Medical University, 2021.
[37] K. Hu, et al., JAK2 and STAT3 polymorphisms in a han Chinese population with behçet's disease, Investigative Opthalmology & Visual Science 53 (1) (2012) 538–541.
[38] S.K. Tripathi, R. Lahesmaa, Transcriptional and epigenetic regulation of T-helper lineage specification, Immunol. Rev. 261 (2014) 62–83.
[39] P.V. Kasperkovitz, Activation of the STAT1 pathway in rheumatoid arthritis, Ann. Rheum. Dis. 63 (3) (2004) 233–239.
[40] D. Wenzhe, L. Jian, D. Shujie, Xinfeng capsule improves the imbalance of Th17/Treg in patients with rheumatoid arthritis by regulating SOCS1/STAT3/miR326, IMMUNOLOGICAL JOURNAL 34 (6) (2018) 499–506.
[41] L. Fan, et al., Progress of CD4+ T cell subsets in the pathogenesis of rheumatoid arthritis, Chin. Remedies Clin. 18 (10) (2018) 1721–1723.
[42] H. Ye, H. Mingzhi, H. Panxin, Up-regulation of miR-21 by naringin on ameliorating Treg/Th17 imbalance in rats with rheumatoid arthritis, Journal of New Chinese Medicine 52 (15) (2020) 11–15.
[43] Y. Maeda, K. Takeda, Role of gut microbiota in rheumatoid arthritis, J. Clin. Med. 6 (6) (2017) 60.
[44] L. Sihui, W. Qiaofeng, The progress of the roles of gut flora in Th17/Treg axis balance and inflammatory bowel diseases, Immunological Journal 35 (8) (2019) 722–726.
[45] C.B. Larmonier, et al., T lymphocyte dynamics in inflammatory bowel diseases: role of the microbiome, BioMed Res. Int. 2015 (2015) 1–9.
[46] C.G. Yu, Q. Huang, Recent progress on the role of gut microbiota in the pathogenesis of inflammatory bowel disease, Journal of Digestive Diseases 14 (10) (2013) 513–517.
[47] A. Luo, et al., The microbiota and epigenetic regulation of T helper 17/regulatory T cells: in search of a balanced immune system, Front. Immunol. 8 (2017) 417.
[48] L. Hui-lin, L. Hong-bin, Intestinal flora and rheumatoid arthritis, Chin J Allergy Clin Immunol 17 (1) (2023) 45–49.
[49] K. Wei, et al., Notch signalling drives synovial fibroblast identity and arthritis pathology, Nature 582 (7811) (2020) 259–264.
[50] W. Yuhan, et al., Mechanism of osteoclast activation and its predictors in rheumatoid arthritis, Chemistry of Life 40 (3) (2020) 378–383.
[51] H. Takayanagi, Osteoimmunology: shared mechanisms and crosstalk between the immune and bone systems, Nat. Rev. Immunol. 7 (4) (2007) 292–304.
[52] R. Ganesan, M. Rasool, Interleukin 17 regulates SHP-2 and IL-17RA/STAT-3 dependent Cyr61, IL-23 and GM-CSF expression and RANKL mediated osteoclastogenesis by fibroblast-like synoviocytes in rheumatoid arthritis, Mol. Immunol. 91 (2017) 134–144.
[53] P. Yang, et al., Th17 cell pathogenicity and plasticity in rheumatoid arthritis, J. Leukoc. Biol. 106 (6) (2019) 1233–1240.
[54] S. Hori, T. Nomura, S. Sakaguchi, Control of regulatory T cell development by the transcription FactorFoxp3, Science 299 (5609) (2003) 1057–1061.
[55] Y. Ru, Mechanism of Hypoxia-Induced Autophagy in Synovial Fibroblasts of Rheumatoid Arthritis to Promote Immune Response, Soochow University, 2017.

Abbreviations

CIA: Collagen-induced arthritis
HIF-1α: Hypoxia-inducible factor-1α
IL-10: Interleukin-10
IL-17: Interleukin-17
IL-2: Interleukin-2
IL-21: Interleukin-21
IL-22: Interleukin-22
IL-23: Interleukin-23
MMP: Matrix metallopeptidase
NF-κB: Nuclear factor-kappa B
OPG: Osteoprotegerin
PPARs: Peroxisome proliferators-activated receptors
RA: Rheumatoid arthritis
RANKL: Receptor activator of nuclear factor-κB ligand
RORγt: Retinoid acid receptor-related orphan receptor γt
SOCS: Suppressor of cytokine signaling
STAT: Signal transducers and activators of transcription
TGF-β: Transforming growth factor-β
Th17: T helper cell 17
TNF-α: Tumor necrosis factor-α
Treg: Regulatory T cell