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Bibliometric analysis on the structure and function of IL17

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Abstract

Background Interleukin17 (IL17) is an important cytokine in host defense at mucosal surfaces and also mediates many autoimmune diseases, including rheumatoid arthritis (RA). In recent years, many types of research relevant to the structure and function of IL17 have been identified. However, there is no bibliometric analysis in this research field. This study aims to explore the history, research hotspots, and emerging trends of IL17 from the perspective of the structure and function dynamics.

Methods Articles relevant to IL17 in the last two decades were retrieved through the Web of Science Core Collection (WoSCC) database. The bibliometric analysis was performed by VOSview.

Results A total of 882 papers in this research were analyzed from 65 countries, and the rate of published articles has increased from 2008 annually, with the USA, China, and Germany leading the research effort. Frontiers in Immunology has significantly impacted research in this field and the University of Pittsburgh was the leading institution. Gaffen, Sarah L. from the University of Pittsburgh was the most productive researcher in this field and Papp Ka from the Probity Medical Research Incorporate of Canada is the most co-cited author. The analysis of keywords showed that inflammation, expression, Th17 cells, and cytokines were the main hotspots and frontier directions of IL17. The trend of clinical application in the future is the development of new therapy drugs based on the structure of IL17 or IL17 signaling pathway molecular.

Conclusions Our research summarized the developments and research trends of IL17 and would help researchers understand the research status of IL17 and provide a reference for future researchers as soon as possible.

Keywords Bibliometric analysis, IL17, Structure and function, Autoimmune disease

Background

Interleukin-17 (IL17) discovered in 1999 from the joints of rheumatoid arthritis (RA) patients [1] is a highly versatile proinflammatory and T helper 17 (Th17) cytokines and is involved in host defense, tissue repair, cancer progression, and many autoimmune diseases [2]. In autoimmune-RA diseases, IL17 is involved in promoting the activation of fibroblast-like synoviocytes (FLS), osteoclastogenesis, and recruitment and activation of neutrophils, macrophages, and B cells [3].

IL17 is a glycoprotein containing 155 amino acids and contains 6 family members (IL17A-F) [4]. As IL-17RA is a receptor shared by the ligands of the IL-17 family, the receptor correspondingly has 5 family members (IL17RA-RE). IL-17A and IL-17F exist as homodimers or heterodimers, and various forms of cytokines induce downstream signals through specific dimeric IL-17RA and IL-17RC receptor complexes. IL17A was first discovered from a rodent T cell by Rouvier et al. in 1993 and contained a highly conserved cysteine-knot fold structure in the C-terminal [5]. Unlike IL17A detected in activated CD4 T

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cells, IL17B mainly expresses in neutrophils, chondrocytes, and native, memory, and germinal center B cells and was also detected in rheumatoid synovial tissues from rheumatic arthritis patients [6–10]. IL17B consists of 180 amino acids and assembles a non-covalent dimer glycoprotein [11]. IL17C was reported to bind to IL17RE and activate the NF-κB pathway. However, the ligands for IL17RD have yet to be identified. Meanwhile, the heterodimer consisting of IL17RA and IL17RB serves as a receptor for IL17E. Variants of IL17 and their potential role are summarized and shown in Table 1. IL17R contains a conserved extracellular fibronectin III-like domain and SEFIR (similar expression to fibroblast growth factor genes and IL17R) domain which recruits the cytoplasmic adaptor protein Act1 via SEFIR-SEFIR interaction [12].

Recently, structure-based drug design was used to guide the optimization of a series of selective IL17 or IL17R inhibitors in preclinical development. IL17 inhibitors have been studied to therapy clinical diseases such as psoriatic (PSO), psoriatic arthritis (PSA), and ankylosing spondylitis (AS) [13]. Secukinumab and ixekizumab are both antibodies of IL17A but are not effective on IL17F [14, 15]. Brodalumab targets IL17R which can neutralize IL17RA with high affinity [16]. Besides biological therapy, small molecule inhibitors targeting IL17A signaling ligand also have been developed and some studies have been vindicated that some macrocycles may more efficiently interfere with the IL17A binding with IL17RA compared to that of antibodies [17].

The bibliometric analysis focuses on the publications in a specific research field and can visually depict the distribution, research status, hotspots, and development trend to allow researchers to easily access relevant scientific information and serve as a useful reference or guide [18–20]. Up to now, the study of IL17 structure and function has not been analyzed by bibliometric analysis. Our study provides a comprehensive understanding of the current state and trends in the field purposing to promote the development of IL17 study in various diseases.

Methods

Data collection and statistics

The data were collected from the Web of Science Core Collection (WoSCC) database (https://www.webofscience.com/wos/woscc/basic-search). This paper set ("IL17" OR "Interleukin-17" OR "IL-17 receptor" OR "IL17R") AND ("Structure*" OR "Structural" OR "Structure–function" OR "Structure-targeting" OR "Targeting") as the retrieval condition, with a time interval of 1998–2023 and literature types selected as "Article" and "Review Article". Analyses were conducted on Jun 13, 2023. Then 882 literature records were retrieved, downloaded, and saved as a plain text file in the format of "Full Record and Cited References".

Data analysis

The data obtained from WoSCC were processed and analyzed by the bibliometric analysis software VOSviewer. The different nodes in the figure map represent items such as countries, institutions, authors, and hotspots; the size of the nodes indicates the number of these elements; and the lines between nodes show the degree of cooperation or co-cited of the project. The quantitative analysis of publications distribution was analyzed by Microsoft Office Excel 2009.

Results

Quantitative analysis of annual publications distribution

The annual research outputs from 1998 to 2023 are shown in Fig. 1A. 1998 was the first year that an IL17-related gut epithelial paper was published. The number of publications was relatively small between 2000 and 2007. Overall, annual publications about IL17 increased rapidly since 2008. Moreover, Frontiers In Immunology ranked the top in the number of published (34), followed by Plos

Table 1 Different variants of IL17 and their potential role

IL17 variants	The role of IL17 variants
IL17A	Regulates the activity of NF-κB and mitogen-activated protein kinase, stimulates the expression of IL6 and cyclooxygenase-2, and promotes the production of NO.
IL17B	Promotes neutrophil migration, stimulates the release of TNF-α and IL1ß, and plays an important role in cancer progression, angiogenesis, and inflammatory arthritis.
IL17C	Stimulates the release of cytokines and is associated with autoimmune disorders and bacterial infections.
IL17D	Induces classical pro-inflammatory cytokine responses and a potential target for tumor immunotherapy
IL17E	Inhibits of Th17 cell-mediated autoimmunity and induces expression of IL1, IL6, and IL23
IL17F	Regulates the expression of chemokines such as CXCL8 and CXCL10, recruits APCs (antigen-presenting cells) such as DC(Dendritic cells) and macrophages, and inflammatory cells such as neutrophils and monocytes, and directly acts on NK (Natural killer) cells to up-regulate the production of cytokines such as IFN-γ and TNF-α to enhance immune response.

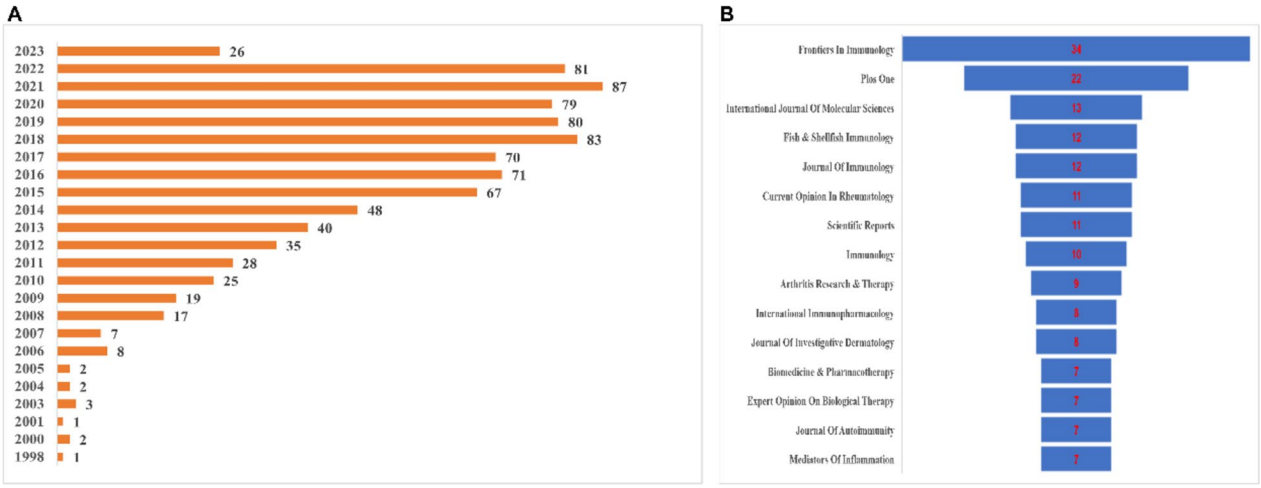

Fig. 1 **A** Annual number of publications in structure and function research of IL17 from 1998 to 2023. **B** The top 15 fruitful journals. Numbers represent the publication's quantity

One (22) and International Journal Of Molecular Sciences (13) as shown in Fig. 1B.

Distribution characteristics of countries/regions and institutions

Between 1998 and 2023, 65 countries published studies related to the structure and function of IL17. The top ten countries with the highest number of publications are distributed in North America, Asia, and Europe. Among the top 10 countries (Table 2), the USA had the highest number of publications ($n=300$), followed by China ($n=216$), and Germany ($n=70$). As shown in Fig. 2A, the network nodes of the USA, China, and Germany are located at the center of the cooperation relationship map with multiple links with the other major issuing countries. The top ten institutions are in the USA and China (Table 2 right (from the institution line)). The collaboration network between institutions was also analyzed by VOSviewer (Fig. 2B). The top 10 contributing institutions published 855 articles, accounting for 97%. And the University of Pittsburgh in Southwestern of Pennsylvania, USA, contributed the most to the body of knowledge ($n=16$), followed by the University of Lyon ($n=14$), Chinese Academy Sciences ($n=13$), and Fudan University ($n=13$).

Analysis of top authors and co-cited authors

A collaboration between authors was shown in Fig. 3A and the top 10 authors was tabulated in Table 3 based on the authors' published papers. Gaffen, Sarah L. and Kolls, Jay K. from the University of Pittsburgh focused on the structure and function of IL17R, and the receptors of IL17 family members bind with [21–24]. Pierre Miossec, Marije I. Koenders, and Erik Lubberts from the

Table 2 The Top10 countries and institutions contributing to publications in IL17

Rank	Country	Publications	Citations	Proportion	Institutions	Publications	Citations
1	The USA	300	19,072	34.01%	University of Pittsburgh	16	2876
2	China	216	5383	24.49%	University of Lyon	14	585
3	Germany	70	3443	7.94%	Chinese Academy Sciences	13	1315
4	Italy	48	1958	5.44%	Fudan University	13	164
5	France	43	2581	4.88%	Shanghai Jiao Tong University	12	647
6	Japan	43	2083	4.88%	Sun Yat-sen University	12	228
7	England	39	2304	4.42%	Genentech incorporated	11	1422
8	Netherlands	35	1731	3.97%	University of Michigan	11	1417
9	Canada	34	1297	3.85%	Harvard Medical School	10	229
10	South Korea	27	1284	3.06%	Stanford University	10	1209

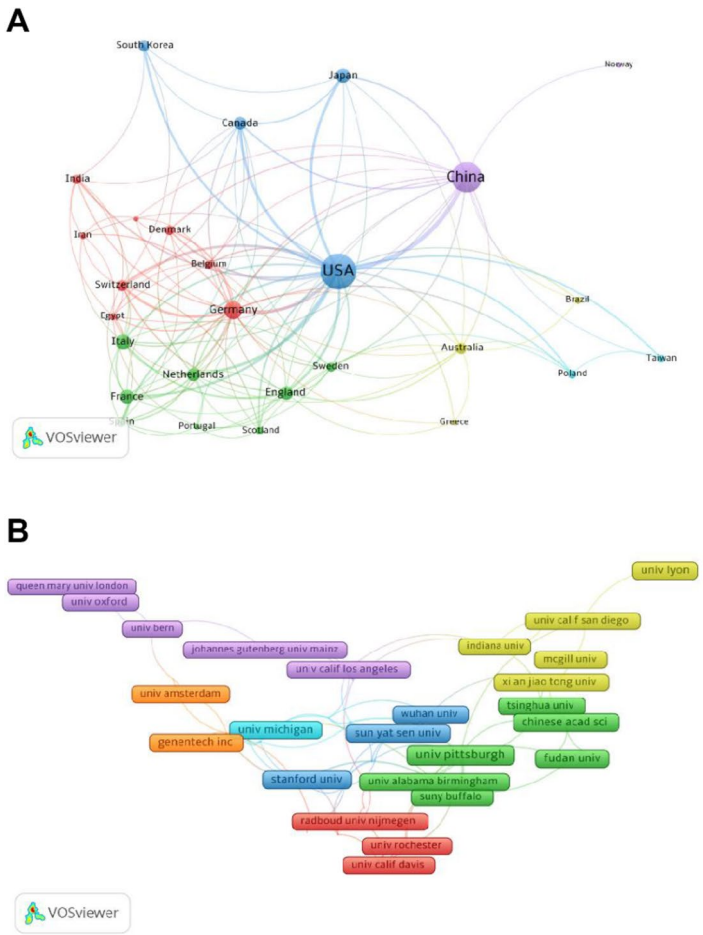

Fig. 2 Main countries and institutions related to the structure and function research of IL17. **A** A visualization network of collaboration between countries in the structure and function research of IL17. **B** A visualization network of collaboration among institutions in the structure and function research of IL17

University of Lyon focused on the mechanism and targeting function of IL17 in various diseases [1, 25, 26].

The top 10 co-cited authors are shown in Table 3 (right (from the co-cited authors line)), and 302 authors (minimum co-citation number of an author equal to 20) were filtered to draw the co-citation network (Fig. 3B). Analysis showed that Papp Ka, Mease Pj, and Gaffen Sl et al. have an important influence in the structure and function research of IL17. Papp Ka from Probity Medical Research Incorporated of Canada is engaged in the targeting therapy of IL17 in various diseases [27, 28]. Mease Pj from the University of Washington (the USA) is studying the drug and mechanism for inhibiting IL17 in arthritis [29, 30]. Gaffen Sl from the University of Pittsburgh (the USA) is to explain the structure and signaling of IL17 [2, 31, 32].

Analysis of hotspots and frontiers

Hotspots is a key methodology in bibliometric analysis to point topic in a specific research area during a certain period of time. Keyword burst patterns were detected to reveal active contents in IL17 through the co-occurrence analysis of keywords. Following a previous study [33], keywords with similar meanings were merged, then for keyword analysis. The network visualization of keywords is shown in Fig. 4. The size of nodes mirrors the occurrence frequency of keywords and the distance between two nodes reflects the strength of their association. The top 20 high-frequency keywords are shown in Table 4.

Keywords with a closer distance were classified into the same cluster, which roughly reflects the main topics in the research area [34]. Among these keywords, "Inflammation", "Expression", "Th17 cells", and "Cytokines" appeared more than 200 times, representing the main research direction of IL17. The keywords "Rheumatoid arthritis", "Trial", and "Psoriatic spondylitis" are related to the role of IL17 in pathogenesis. As shown in Fig. 4A, the keywords in red clusters consist

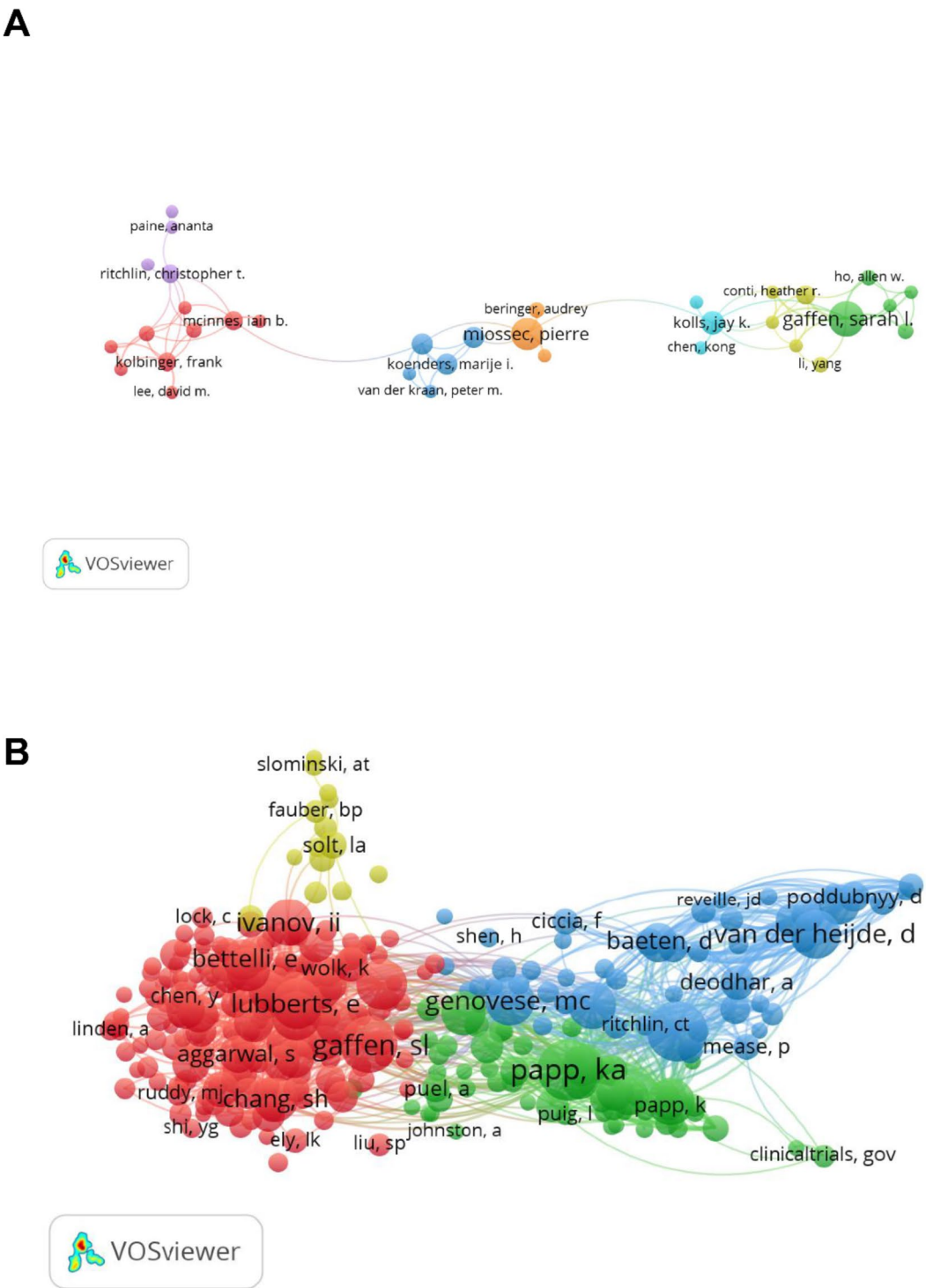

Fig. 3 Visualization of authors (**A**) and co-cited authors (**B**) in the structure and function research of IL17

of inflammation, expression, Th17 cells, and cytokines, in blue clusters consist of rheumatoid arthritis, and in green clusters consist of trial and psoriatic spondylitis. The overlay visualization of author keywords is presented in Fig. 4B. The keywords colored in yellow represent those that have appeared recently. Keywords, such

Table 3 Top 10 authors and co-cited authors on the research of IL17

Rank	Authors	Count	Co-cited authors	Citations
1	Gaffen, Sarah L	14	Papp, Ka	272
2	Miossec, Pierre	12	Mease, Pj	269
3	Kolls, Jay K	6	Gaffen, Sl	234
4	Koenders, Marije I	5	Lubberts, E	189
5	Lubberts, Erik	5	Miossec, P	185
6	Van Den Berg, Wim B	5	Van Der Heijde, D	176
7	Garg, Abhishek V	4	Chabaud, M	173
8	Kolbinger, Frank	4	Genovese, Mc	170
9	Mcinnes, Iain B	4	Mcinnes, Ib	167
10	Ritchlin, Christopher T	4	Reich, K	158

as "secukinumab", "mechanism", "plaque psoriasis", "psoriatic arthritis", and "ankylosing spondylitis" represent the main research direction in recent years. The keyword "secukinumab" associates with developing novel targeted drugs for IL17 and the keyword "mechanism" may be related to the signaling pathway of IL17 in various diseases and the interaction structure between IL17 and IL17R. The keywords "plaque psoriasis", "psoriatic arthritis", and "ankylosing spondylitis" implicate some autoimmune disease hotspots of IL17.

Analysis of reference with co-citation

Reference co-citation can be used to reflect the most-cited papers [35]. The co-citation network was drawn (Fig. 5) after filtering out references with a minimum number of co-citations is 60. The top 10 references that were co-cited were listed in Table 5. The reference "Park H, 2005, nat immunol, v6, p1133, https://doi.org/10.1038/ni1261" was co-cited up to 113 times [36].

Discussion

General information

Many high-quality studies on the structure and function of IL17 have been published. This bibliometric study analyzed the development of IL17 since it was first studied. Articles on IL17 showed a rapidly growing trend since 2008. Meanwhile, the number of articles about IL17 stationary fluctuated at 80 per year since 2018. Most of these articles were mainly published in journals *Frontiers in Immunology*, *Plos One*, and *International Journal of Molecular Sciences*.

Among the 65 countries contributing to the IL17 research, the USA led the way with the largest number of publications, citations, and link strength with other countries. Moreover, Gaffen, Sarah L. from the University of Pittsburgh in the USA mainly focused on the structure of IL17-IL17R and the downstream signaling pathway of IL17. China was the second most productive country where the institution—Chinese Academy Sciences having the most publications. Germany and Italy also contribute to the research of IL17. Miossec, Pierre from the University of Lyon published articles following Gaffen, Sarah L. mainly focuses on targeting therapy of IL17 in various diseases. Among the top 10 cited articles analyzed in this study, the key focus was inflammation response, expression in various diseases such as rheumatoid arthritis and psoriatic spondylitis and targeting drug of IL17 [14, 37, 38].

Research basis

In 1998, recombinant hIL17 was first cloned from a Pichia pastoris expression to study the structure and function of IL17 [39]. Following, the binding signaling pathway of IL17 and targeting therapy were revealed in autoimmune disease. The common pathway is the IL17 recruited to their receptors (IL17R) through specificity heterotypic interactions between the SEFIR domain (CC′ loop motif) of Act1 and that of IL17R [40]. Secukinumab, ixekizumab, and Brodalumab which are recombinant fully human monoclonal anti-IL17A antibody enable the effects of IL17A inhibition in multiple autoimmune diseases [41–43]. As IL17 arises directly from Th17 cells and targeting IL17 alone is not sufficient to improve clinical endpoints, targeting the IL17 and Th17 cell lineage may be superior to blocking a single effector cytokine [44].

IL17A is associated with RA due to IL17A expression in RA synovial fluid. RA is a systemic poly-articular autoimmune pathology [45] and affects an average of 1% of the adult population worldwide [46]. The common damage in rheumatoid arthritis is joints and extra-articular organs [47]. Although the etiology of RA is not yet fully understood, researchers have studied that IL17 induces downstream cytokine production through NF-κB and PI3K/Akt-dependent pathways [48]. Targeting IL17 and Th17 pathway therapy has been experimented with in RA model [26, 49]. Currently, many nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids (SAIDs), and analgesics have been used to decrease inflammatory and immunosuppressive effects during RA treatment [50]. Although the above agents have mitigated the RA pain [51], it is still needed to research and explore new methods to achieve the maximum therapeutic effectiveness.

Ankylosing spondylitis is a chronic inflammatory disease involving the axial spine which can manifest with

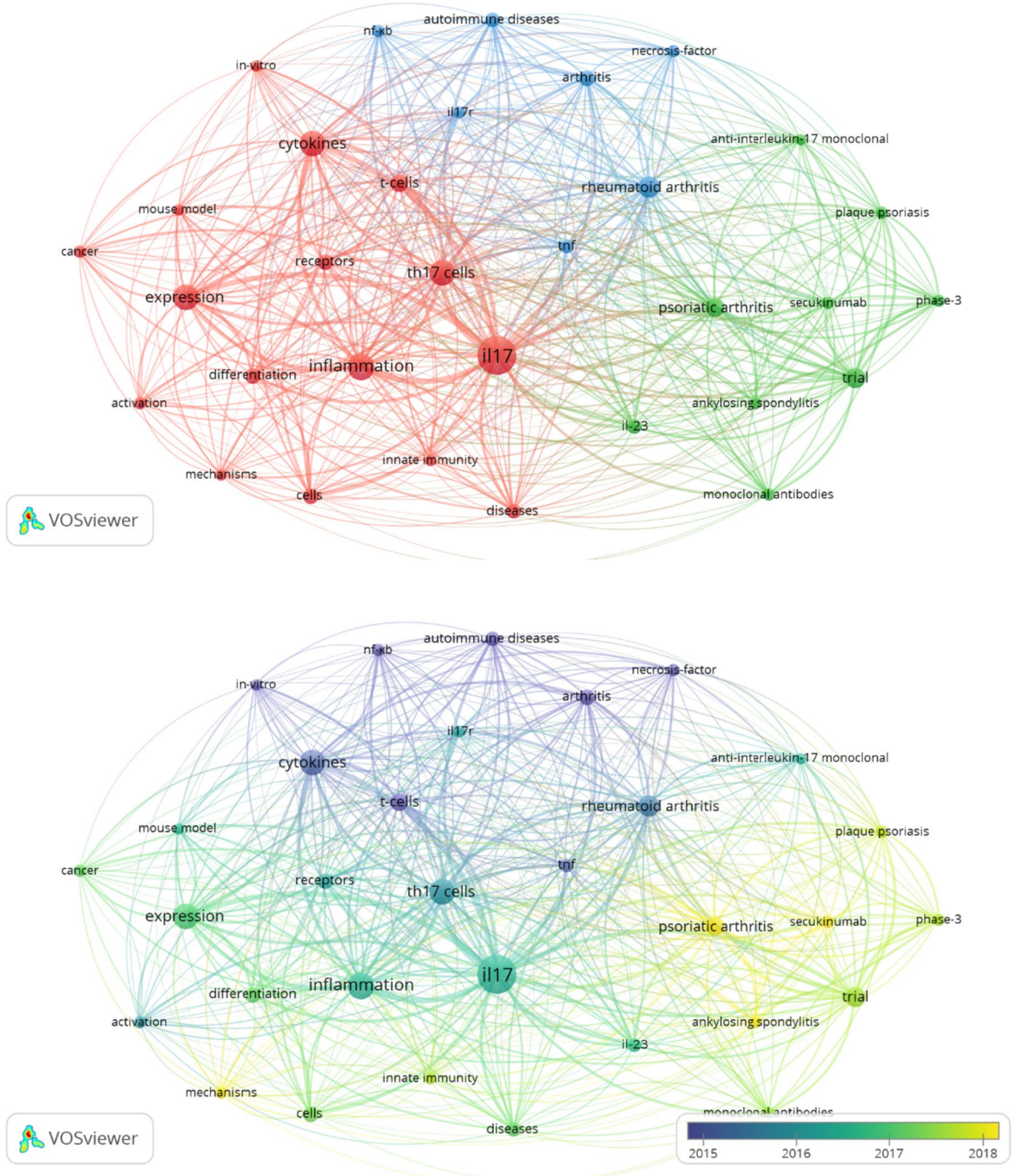

Fig. 4 Analysis of the research hotspots of IL17, **A** network visualization of author keywords and **B** overlay visualization of author keywords

various clinical signs and symptoms [52]. IL17A antagonists such as Secukinumab and ixekizumab have been explored to treat ankylosing spondylitis [53]. Recently, netakimab, a novel IL17 inhibitor in clinical trials, has established a therapeutic dose in patients with active ankylosing spondylitis [54] and Iguratimod, a novel small molecule drug, also has shown efficacy treatment [55]. Psoriatic spondylitis belongs to the family of ankylosing spondylitis, and novel nonbiological small molecules, such as Janus kinase (JAK) inhibitors, are being evaluated in clinical trials for this disease [56, 57]. Together, these findings clarify the critical role of IL17 in

Table 4 Top 20 keywords on the research of IL17

Rank	Keywords	Counts	Rank	Keywords	Counts
1	IL17	513	11	Cells	87
2	Inflammation	242	12	Receptors	87
3	Expression	229	13	Arthritis	83
4	Th17 cells	224	14	Diseases	78
5	Cytokines	220	15	Autoimmune diseases	70
6	Rheumatoid arthritis	153	16	IL23	70
7	Trial	142	17	TNF	65
8	Psoriatic spondylitis	128	18	cancer	58
9	T cells	111	19	IL17R	58
10	Differentiation	92	20	Plaque psoriasis	58

pathogenesis and targeted therapy research in a variety of diseases.

Future directions

Secukinumab, the first antibody against IL-17A, was approved in 2015 for the treatment of plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis, followed by ixekizumab and brodalumab for clinical trials in psoriasis and other IL-17 or IL-17R inhibitors. However, multiple clinical trials of secukinumab and brodalumab in IL-17-related diseases were discontinued due to no or limited clinical effect [58–60]. Recently, studies found that targeting Act1-SHP2 which is the downstream signaling molecule of IL17 inhibits IL17-related diseases resistant to anti-IL17 therapy (an autonomous activation of interleukin-17 receptor signaling sustains inflammation and promotes disease progression) [61]. This may indicate that the downstream molecule of IL17 can be a target for drug discovery and various autoimmune diseases may exist an autonomous activation of receptor signaling which suggests a new therapeutic research idea.

In conclusion, this study provides insight into the research trends and developments of IL17 by bibliometrics analysis, which may guide new directions for further study.

Conclusion

Drug target IL17 has been mostly studied for the treatment of various autoimmune diseases, such as RA and PSO in recent years. We report about the history, research hotspots, and emerging trends of IL17 from

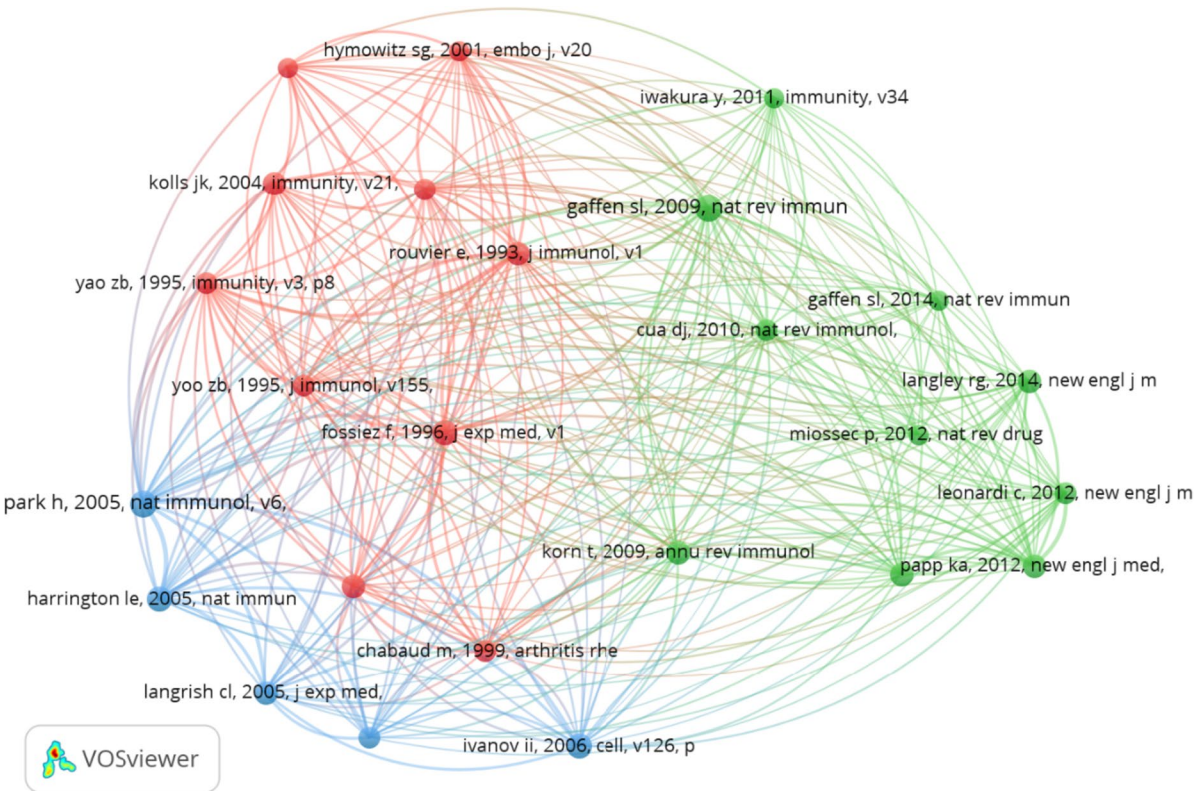

Fig. 5 Visualization of co-cited references on the research of IL17

Table 5 Top 10 co-cited references on the research of IL17

Rank	References	Citations
1	Park H, 2005, nat immunol, v6, p1133, https://doi.org/10.1038/ni1261	113
2	Gaffen Sl, 2009, nat rev immunol, v9, p556, https://doi.org/10.1038/nri2586	110
3	Ivanov Ii, 2006, cell, v126, p1121, https://doi.org/10.1016/j.cell.2006.07.035	107
4	Harrington Le, 2005, nat immunol, v6, p1123, https://doi.org/10.1038/ni1254	106
5	Fossiez F, 1996, j exp med, v183, p2593, https://doi.org/10.1084/jem.183.6.2593	104
6	Korn T, 2009, annu rev immunol, v27, p485, https://doi.org/10.1146/annurev.immunol.021908.132710	89
7	Rouvier E, 1993, j immunol, v150, p5445	87
8	Kolls Jk, 2004, immunity, v21, p467, https://doi.org/10.1016/j.immuni.2004.08.018	86
9	Langley Rg, 2014, new engl j med, v371, p326, https://doi.org/10.1056/nejmoa1314258	86
10	Langrish Cl, 2005, j exp med, v201, p233, https://doi.org/10.1084/jem.20041257	83

the perspective of the structure and function dynamics in the last two decades with bibliometric methods. IL17 has been extensively studied in rheumatism, and biologic therapy targeting IL17 antibodies is expected to be a new approach to the treatment of rheumatoid arthritis. Our research summarized the developments and research trends of IL17 and would help researchers understand the research status of IL17 and provide a reference for future researchers as soon as possible.

Abbreviations

APCs	Antigen-presenting cells
AS	Ankylosing spondylitis
DC	Dendritic cells
FLS	Fibroblast-like synoviocytes
IL17	Interleukin 17
JAK	Janus kinase
NK	Natural killer
NSAIDs	Nonsteroidal anti-inflammatory drugs
PSA	Psoriatic arthritis
PSO	Psoriatic
RA	Rheumatoid arthritis
SAIDs	Corticosteroids
SEFIR	Similar expression to fibroblast growth factor genes and IL17R
Th17	T helper 17
WoSCC	Web of Science Core Collection

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Authors' contributions
Liyun Zhang conceived and directed the study. Minglu Li contributed to literature search. Wenxia Yan designed and analyzed the data and wrote the manuscript.

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Availability of data and materials
We approve the availability of our data upon request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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