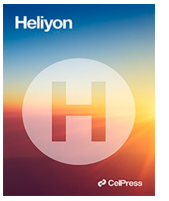
Heliyon 9 (2023) e19761

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Global scientific trends update on macrophage polarization in rheumatoid arthritis: A bibliometric and visualized analysis from 2000 to 2022

Jun Yuan, Tong Feng, Yanding Guo, Kun Luo, Qiaofeng Wu, Shuguang Yu, Haiyan Zhou *

Acupuncture and Tuina School, Chengdu University of Traditional Chinese Medicine, Chengdu 610075, China

ARTICLE INFO

Keywords:
bibliometrics
Rheumatoid arthritis
Macrophage polarization
CiteSpace
VOSviewer

ABSTRACT

The goal of this work was to use bibliometric analysis to help guide future research on macrophage polarization in RA. We looked for studies on macrophage polarization in RA published between January 1, 2000, and December 31, 2022, in the WoSCC database. Research trends and hotspots were shown and assessed using VOSviewer and CiteSpace. A total of 181 articles were gathered. Belgium was among the early adopters of the field. Chinese institutes have produced the most research. Researchers such as Angel Luis Corb, Amaya Puig-Kröger, and Lizbeth Estrada-Capetillo have made major contributions to the field. *Frontiers in Immunology* has published the most study findings. According to VOSviewer, the most investigated immune cells, biomarkers, and signaling pathways in the previous three years have been "T cells", "gm-csf", and "nf-κb" in that order. We discovered that the most often used terms in the previous three years were "pathway", "oxidative stress", "extracellular capsule" and "nlrp3 inflammasome" using Citespace. We emphasize these concepts in our findings, presenting the exact mechanisms of pathophysiology related to macrophage polarization in RA, as well as current breakthroughs in therapy strategies.

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterized by macrophage activation [1]. Synovial inflammation and joint erosion are the major symptoms. Immunologic processes may occur many years before symptoms of joint inflammation are detected. One of the recently proposed theories is that citrulline action results in the formation of anti-citrullinated protein antibodies. Rheumatoid factor (rf) is another antibody that enhances pathological autoimmunity. Based on the presence of these two antibodies, RA can be categorized into two types (seropositive and seropositive). Immunological pathophysiological mechanisms are based on the involvement of synovial macrophages in the release of cytokines such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-alpha), and interleukin-6 (IL-6), which have been associated with inflammatory pathways, stimulation of osteoclast activity, and stimulation of fibroblast-like synoviocytes (FLS). Upon activation, matrix metalloproteinase (MMP) is formed and receptor activation receptor nuclear factor-kB ligand (RANKL) is up-regulated, with effects on T cells. Complex interactions at the molecular level result in cartilage and bone destruction and increased angiogenesis [2]. Multiple cell types, including macrophages, T

* Corresponding author.
E-mail address: zhouhaiyan@cdutcm.edu.cn (H. Zhou).

https://doi.org/10.1016/j.heliyon.2023.e19761
Received 16 March 2023; Received in revised form 22 August 2023; Accepted 31 August 2023
Available online 9 September 2023

cells, B cells, and dendritic cells, invade the joint in active rheumatoid arthritis to increase inflammation and bone damage [3]. In 40% of patients, the inflammatory infiltrate is mostly composed of macrophages. Macrophages are generated cytokines that promote inflammation and contribute to cartilage damage [4]. Multiple stimuli may cause macrophage plasticity to polarize toward distinct profiles. The capacity of classically activated M1 macrophages to remove harmful bacteria distinguishes them. This is related to M1 macrophages' propensity to generate substantial amounts of pro-inflammatory cytokines such as interleukin-1β (IL-1β), IL-12, tumor necrosis factor-α (TNF-α), and inducible nitric oxide synthase (iNOS). When the organism is exposed to external pathogenic microbial stimuli, Alternative activation of macrophages (M2) occurs. M2 Macrophages can produce high quantities of the anti-inflammatory mediators IL-10 and tumor growth factor-β (TGF-β) while also expressing cell surface markers including mannose receptor (MR/CD206) and clearance receptor (SR/CD163). They primarily suppress the inflammatory response and participate in tissue remodeling and repair [5]. There is a transition from pro-inflammatory to anti-inflammatory macrophages, with significant flexibility between states [6]. This can result in the advancement of several illnesses, including RA. Understanding the function of macrophage polarization, as represented by the M1 type and M2 type, is critical for understanding the pathogenesis of RA and finding early biomarkers and potential treatment targets. As a result, a scientific review of current research outcomes on this topic can assist researchers in swiftly understanding the field's present condition and identifying prospective future directions.

Bibliometrics originally appeared around the turn of the twentieth century, and by 1969 it had evolved into a distinct subject that was frequently utilized for document performance analysis and visualization [7]. Bibliometric analysis is a quantitative tool for assessing and surveying the existing literature on a certain topic. Detailed information such as authors, keywords, publications, countries/regions, institutes, references, and so on may be acquired throughout the analysis process [8]. Thus, the bibliometric analysis may be used to determine the evolution of a field. Modern computer technology, graphics, and visual findings can be used to augment the bibliometric analysis. CiteSpace, VOSviewer, UCINET, gCLUTO, SciMAT, Pajek, and Bicomb are examples of popular bibliometric software [9–11]. There is, however, no agreement on which software is the best. CiteSpace and VOSviewer were used for the bibliometric analysis of this study, taking into account their respective characteristics and combined with our practical needs. The growing interest of researchers in macrophage polarization in rheumatoid arthritis in recent years. The gradual abundance of information in this field of study has demonstrated the need for original research bibliometric studies of the scientific literature to validate the current state of knowledge in the field and to emphasize the importance of accurately filtering and interpreting the many manuscripts in the field.

As a result, we gathered qualitative and quantitative data on this field's publications and evaluated the status of countries/regions, institutes, financing, journals, authors, citation literature, and keywords. To the best of our knowledge, this is the first thorough bibliometric investigation of RA macrophage polarization in the last 22 years. The goal is to give researchers who have entered or will enter the subject insights into the present state of research, new trends, and prospective research hotspots in RA macrophage polarization.

2. Metarials & methods

2.1. Data collection

The Web of Science Core Collection (WoSCC) was chosen as the study's data source. WOS is recognized by scholars as an excellent database for bibliometrics. Many academics regard WoSCC as a high-quality digital literary resource database, and it is regarded as the best database for bibliometric analysis [12]. Search and download pertinent data from the WoSCC database's Science Citation Index Expanded (SCI-Expanded). The following is the search strategy: TS = ((“macrophage polarization”) AND (“Rheumatoid Arthritis” OR “Arthritis, Rheumatoid”)); Publication date: “2000-01-01” to “2022-12-31”; The language restriction was English, while the article type restriction was Article or Review. The retrieval results were chosen in the form of “Full Record and Cited References” and downloaded in the “Plain Text” document format. Meanwhile, no ethical approval was required for this investigation because data were simply downloaded and exported from the WoSCC database. To avoid changes caused by daily database updates, searches are only performed on the same day. Articles having just online publishing dates were eliminated to ensure that all publications have a definite publication date for further analysis. Two investigators conducted the initial data search independently and reviewed any discrepancies.

Keywordsare an important part of the content of a manuscript and are specifically directed to the field of the article itself, the purpose of the study, the research questions and the objectives. They are an important component of bibliometric analysis and are significant in the process of literature retrieval. Search engine algorithms and indexers use keywords as a way to find relevant documents. Therefore, a useful information strategy for assessing conceptual understanding and practical application is to analyze keywords [13].

2.2. Visualization

All valid data obtained was loaded into VOSviewer (version 1.6.17) (Centre for Science and Technology Studies, Leiden University, Leiden, the Netherlands) and CiteSpace (version 6.1.6) (Chaomei Chen, Drexel University, Philadelphia, PA) for visual analysis. VOSviewer visualizes collaborative networks across countries/regions, institutes, funds, journals, authors, references, and keyword clusters. Nodes indicate a country/region, institution, journal, author, citation, or keyword. The weight of the element determines the size of a node. Each node is assigned a color, and the same color signifies the same cluster, which is a group of things in the network with comparable qualities. The linkages between nodes represent the correlation between items, while the width of the links reflects

the strength of the relationships [14]. CtieSpace is data visualization software written in Java. Because the "download *.txt" file format was only recognized by CiteSpace, the downloaded files were renamed after it. Use CiteSpace to explore the change in the keyword hotspot distribution map over time and evaluate the field's trend [15]. Fig. 1 depicts the detailed search strategy.

3. Results

3.1. Basic quantitative data

This study's 181 articles were produced by 1305 authors from 330 organizations in 30 countries, published in 103 journals, and mentioned 11254 references from 1842 journals.

3.2. Number of publications

The number of publications (NP) in a particular period can objectively and quantitatively indicate the general trajectory of a field. Between January 1, 2000, and December 31, 2022, there were 134 (74.03%) articles and 47 (25.97%) reviews of the 181 SCI-indexed works on macrophage polarization in RA. Despite occasional volatility, the NP increased from 1 on January 1, 2009, to 181 on December 31, 2022 (Fig. 2). Over the last 22 years, the growth rate has been pretty consistent (0.35 ± 0.16). The annual NP increased

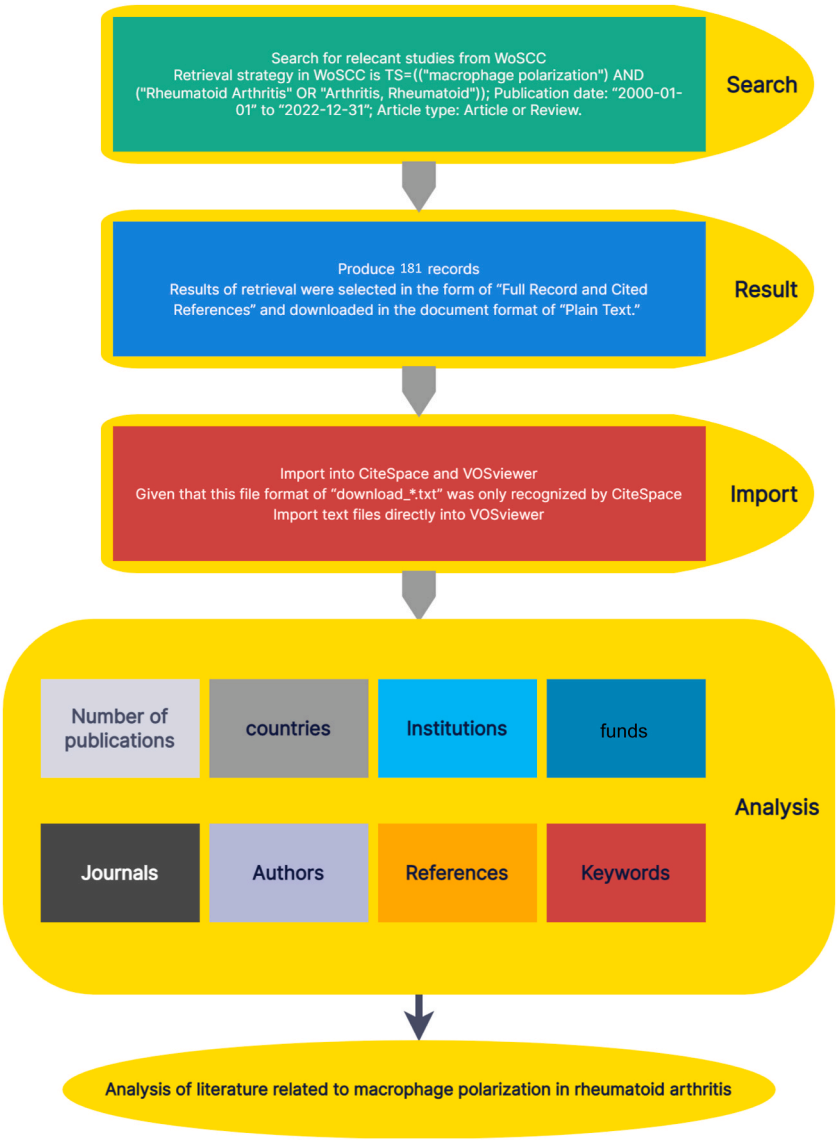


Fig. 1. Study flow diagram.

and was strongly associated with the year of publication ($R^2 = 0.9136$).

3.3. Distribution of country/region

These publications are from 30 different countries/regions (Fig. 3A). In terms of NP, the top ten countries/regions produced 98.34% (178/181) of the publications, with China (45.86%, 83/181), the United States (14.36%, 26/181), and Spain (6.63%, 12/181) leading the way (Table 1). China (1756), the United States (737), and Spain (601) have the highest number of citations (NC) (Fig. 3B). South Korea (69.88), Germany (58.30), and Spain (50.08) have the highest average number of citations (AC) ratings (Fig. 3B). Australia, Scotland, Ireland, and Belgium were early pioneers in this sector (Fig. 3C), while China and the United States have the largest number of joint publications (Fig. 3C). Early on in the field's development, Japan and France began to collaborate significantly with other nations, and more recently, the Czech Republic has begun to focus on collaborative inter-country research (Fig. 3C) (Supplementary Table 1).

3.4. Distribution of institutes and funds

330 institutes participated in this domain, with 17 of them publishing at least three publications, color-coded into 13 clusters. According to the clustering results, the Chinese Academy of Sciences and the University of Jinan; Centro de Investigaciones Biológicas Margarita Salas and Gregorio Maranon University General Hospital; Anhui Medical University and Sun Yat-sen University; Sichuan University and Southwest Medical University have all collaborated on studies in this field (Fig. 4A). Anhui Medical University (2.73%, 9/330); Sichuan University (1.82%, 6/330); Shanghai Jiao Tong University (1.82%, 6/330) are the top three NP-ranked universities worldwide (Table 2). Centro de Investigaciones Biológicas Margarita Salas (70.00); Gregorio Maranon University General Hospital (36.40); University of Amsterdam(35.40) had the greatest AC (Table 2). Centro de Investigaciones Biológicas Margarita Salas and Gregorio Maranon University General Hospital have partnered less often than Chinese institutes, but have done early exchange research in this sector (Fig. 4B) (Supplementary Table 2).

Financial assistance is critical to scientific development. The study "Macrophage Polarization in Rheumatoid Arthritis" has received funding from 200 different sources. National Natural Science Foundation Of China (28.50%, 57/200); National Institutes of Health (9.00%, 18/200); United States Department Of Health & Human Services(9.00%, 18/200) were the top three funding sources (Table 3). Overall, the National Natural Science Foundation Of China and the Natural Science Foundation Of Anhui Province provide the majority of funding for RA-macrophage polarization research in China. Three of the top ten were supported by Japanese research institutes (Fig. 4C).

3.5. Distribution of journals

There are 103 journals with papers on this topic. Thirteen journals provided at least three papers each. The top ten journals published around 35.91% (65/181) of the publications. The top three journals in the top 10 are all about immunity and inflammation. There are three publishers in of each the United States and the Netherlands (Table 4). *Frontiers In Immunology* was the most productive magazine (12.71%, 23/181), publishing a considerable number of such publications in recent years (Fig. 5A and B). The journal with the highest AC was *Journal Of Immunology* (91.00), followed by *Biomaterials* (51.40) and *Scientific Reports* (44.25). In 2022, Biomaterials had the highest IF (15.304), followed by Frontiers In Immunology (8.786) and Cells (7.666). The majority of these publications were published in the Q1 and Q2 journals (Table 4).

When two papers from separate journals are mentioned in the same piece, they are deemed linked. 112 of 1842 mentioned co-cited journals were referenced at least 20 times (Fig. 5C and D). The five most often referenced journals (94.30%, 1737/1842) were *Journal Of Immunology* (544), *Annals of Rheumatic Diseases* (329), *Arthritis & Rheumatology* (317), *Frontiers in Immunology* (308) and *Arthritis Research and Therapy* (239).

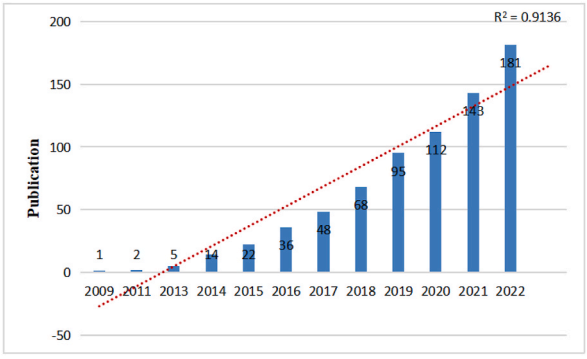


Fig. 2. The number of publications from 2000 to 2022. The bar chart depicts the total number of publications in the field up to the current year. The red dashed line depicts a linear relationship between the year of publication and the overall number of publications.

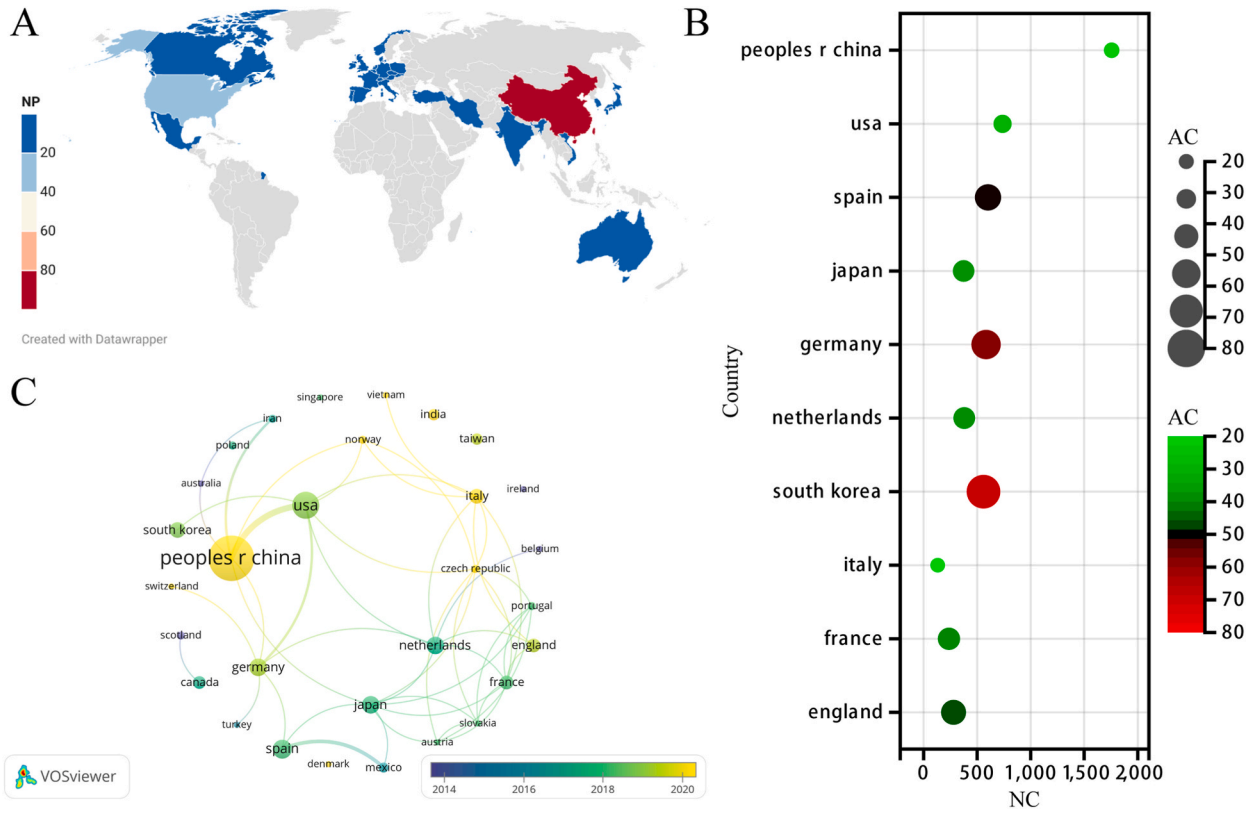


Fig. 3. Contributions from various nations/regions to the investigation of macrophage polarization in RA. (A) Regional map of the RA macrophage polarization studies' global spread. Different nations are represented by various hues depending on the number of articles published. More articles have been published when the color is redder; fewer articles have been published when the color is bluer. Because the map program cannot search for specific regions, we have provided the country in which the area is located directly. **(B)** Bubble charts in NC and AC for the top 10 nations/regions. The bubble's size and color signify AC; the larger and redder the bubble, the higher the AC; the smaller and greener the lower AC. The horizontal axis stands for NC. **(C)** A network diagram based on the study of country/regional collaboration and time-course-visualized using VOSviewer. NP: number of publications; NC: number of citations; AC: average number of citations per item.

Table 1
Number of publications (NP) in the top 10 countries/regions, number of citations (NC) and average number of citations (AC).

Ranking	Country	NP	NC	AC
1	China	83	1756	21.16
2	USA	26	737	28.35
3	Spain	12	601	50.08
4	Japan	10	373	37.30
5	Germany	10	583	58.30
6	Netherlands	10	379	37.90
7	South Korea	8	559	69.88
8	Italy	7	131	18.71
9	France	6	236	39.33
10	England	6	279	46.50

3.6. Distribution of authors

There have been 1305 writers that have contributed to the field. An examination of the writers of the literature reveals information about the key researchers and core research capabilities in this field. Half of the articles on the same topic are written by a group of exceptionally prolific authors [18]. According to Price's law, the minimum number of publications for a core author in a field is $M = 0.749 \times \sqrt{Nmax} \approx 1.67$ (according to Vosviewer, $Nmax = 5$, N represents the total number of authors, and M represents the minimum number of publications for core authors), so authors with more than two publications (including two) are considered core authors. A total of 73 key writers wrote 165 articles, accounting for 91.16% of all publications and satisfying half of Price's (50%) criteria. Hence, in the fields of rheumatoid arthritis macrophage polarization big data and rheumatoid arthritis data mining, a solid collaborative group

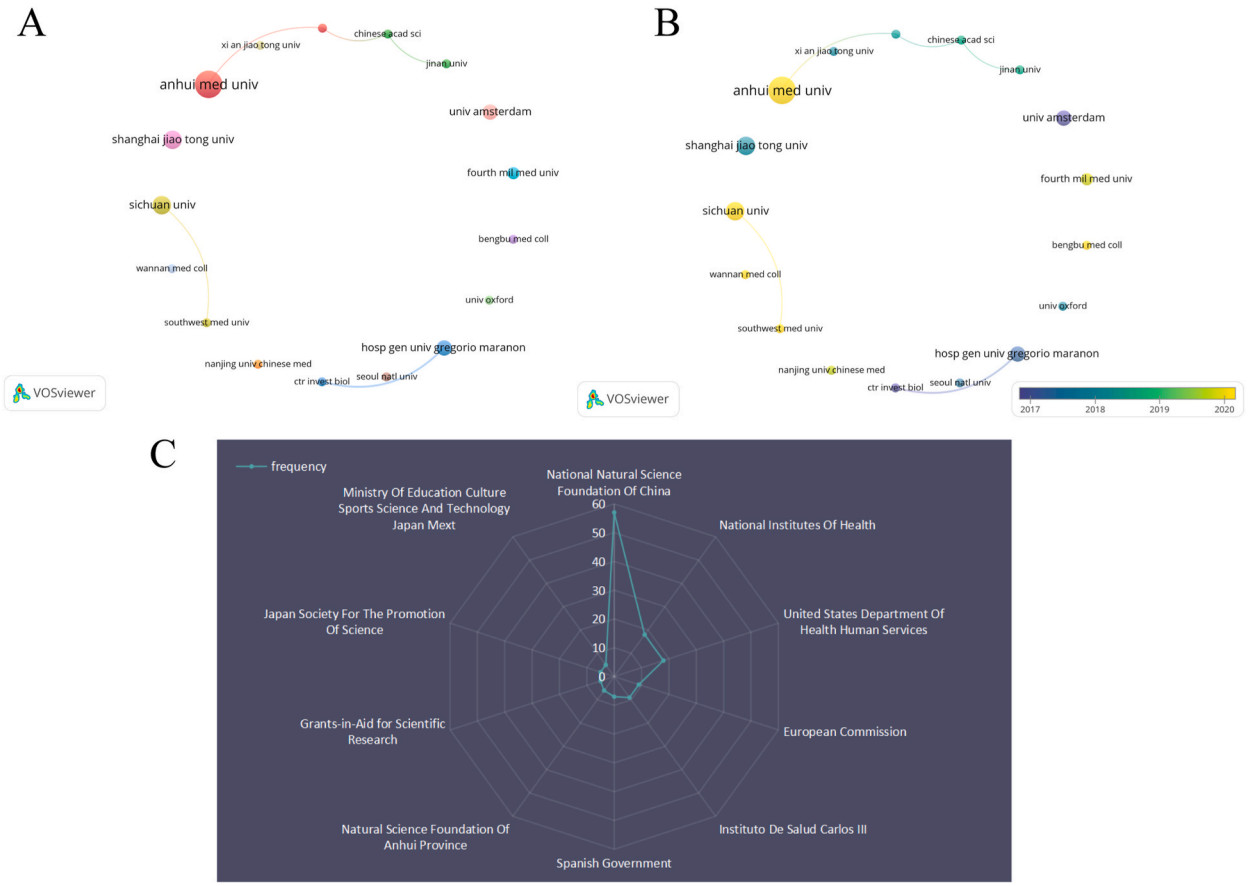


Fig. 4. Visual analysis of institutes and funds. (A) Visualization of the frequency of publications at each university. Each institution published at least three publications. The node size reflects the frequency of institutes, the curve represents the cooperative connection of institutes, and nodes of the same color represent the same cluster. **(B)** The time evolution of publications from various institutes. **(C)** Frequency radar map of the top ten funds.

Table 2
Top ten research institutes in terms of frequency of research findings. NP: Number of publications. NC: Number of citations. AC: Average number of citations.

Ranking	Institutes	Country	NP	NC	AC
1	Anhui Medical University	China	9	132	14.67
2	Sichuan University	China	6	137	22.83
3	Shanghai Jiao Tong University	China	6	159	26.50
4	Gregorio Maranon University General Hospital	Spain	5	182	36.40
5	University of Amsterdam	Netherlands	5	177	35.40
6	Fourth Military Medical University	China	4	43	10.75
7	Chinese Academy of Sciences	China	3	39	13.00
8	Centro de Investigaciones Biológicas Margarita Salas	Spain	3	210	70.00
9	Sun Yat-sen University	China	3	54	18.00
10	University of Jinan	China	3	63	21.00

of writers has been developed. These researchers were color-coded into 16 clusters, mainly centered on Amaya Puig-Kröger and Lizbeth Estrada-Capetillo in Spain (Fig. 6A), with the Spanish cluster having conducted research in this area earlier (Fig. 6B) (Supplementary Table 3). The author with the greatest H index (54) and the most publications (NP = 5, NC = 430) was Angel Luis Corb of Centro de Investigaciones Biológicas Margarita Salas. Concha Nieto of the same institution got the highest AC (126.33), followed by Angel Luis Corbí (88.40) and Amaya Puig-Kröger (75.50) of Instituto de Investigación Sanitaria Gregorio Marañón (Table 5).

Co-cited writers are two or more authors who are referenced in one or more articles at the same time. Of the 9125 authors co-cited, 64 (6 clusters) received at least 10 citations (Fig. 6C and D). Iain B McInnes from the Institute of Infection, Immunity and Inflammation, University of Glasgow, UK, was the highest-ranked NP (57) with an H-index of 110. This is followed by Peter J Murray (45), of the Max-

Table 3
The top 10 funding sources for articles.

Ranking	funding source	Headquarters	frequency
1	National Natural Science Foundation Of China	China	57
2	National Institutes Of Health	USA	18
3	United States Department Of Health Human Services	USA	18
4	European Commission	Brussels and Luxembourg	9
5	Instituto De Salud Carlos III	Spain	9
6	Spanish Government	Spain	7
7	Natural Science Foundation Of Anhui Province	China	6
8	Grants-in-Aid for Scientific Research	Japan	5
9	Japan Society For The Promotion Of Science	Japan	5
10	Ministry of Education, Culture, Sports, Science and Technology	Japan	5

Table 4
Top 10 Most Productive Journals. The categories of Impact Factor (IF) [16] and Journal Citation Reports (JCR) [17] are used to measure the quality of scientific content. IF is the average number of citations per journal article produced in the previous two years. JCR allocates each scientific publication to its relevant IF and ranks them according to specific areas of expertise (Q1, Q2, Q3 and Q4). International Standard Serial Number (ISSN) is a serial publication's unique identifier applied to diverse content and carrier types. NP: Number of publications. NC: Number of citations. AC: Average number of citations.

Ranking	Source	JCR [17]	Country	ISSN	IF(2022) [16]	NP	NC	AC
1	*Frontiers in Immunology*	Q1	Switzerland	1664–3224	8.786	23	539	23.43
2	*International Immunopharmacology*	Q1	Netherlands	1567–5769	5.714	9	140	15.56
3	*Journal of Immunology*	Q2	USA	0022–1767	5.426	6	546	91.00
4	*Cells*	Q2	Switzerland	2073–4409	7.666	5	46	9.20
5	*Biomaterials*	Q1	Netherlands	0142–9612	15.304	5	257	51.40
6	*International Journal of Molecular Sciences*	Q1	USA	1422–0067	6.208	4	73	18.25
7	*Scientific Reports*	Q2	England	2045–2322	4.996	4	177	44.25
8	*European Journal of Pharmacology*	Q2	Netherlands	0014–2999	5.195	3	54	18.00
9	*Inflammation*	Q3	USA	0360–3997	4.657	3	64	21.33
10	*Arthritis Research & Therapy*	Q1	England	1478–6354	5.606	3	73	24.33

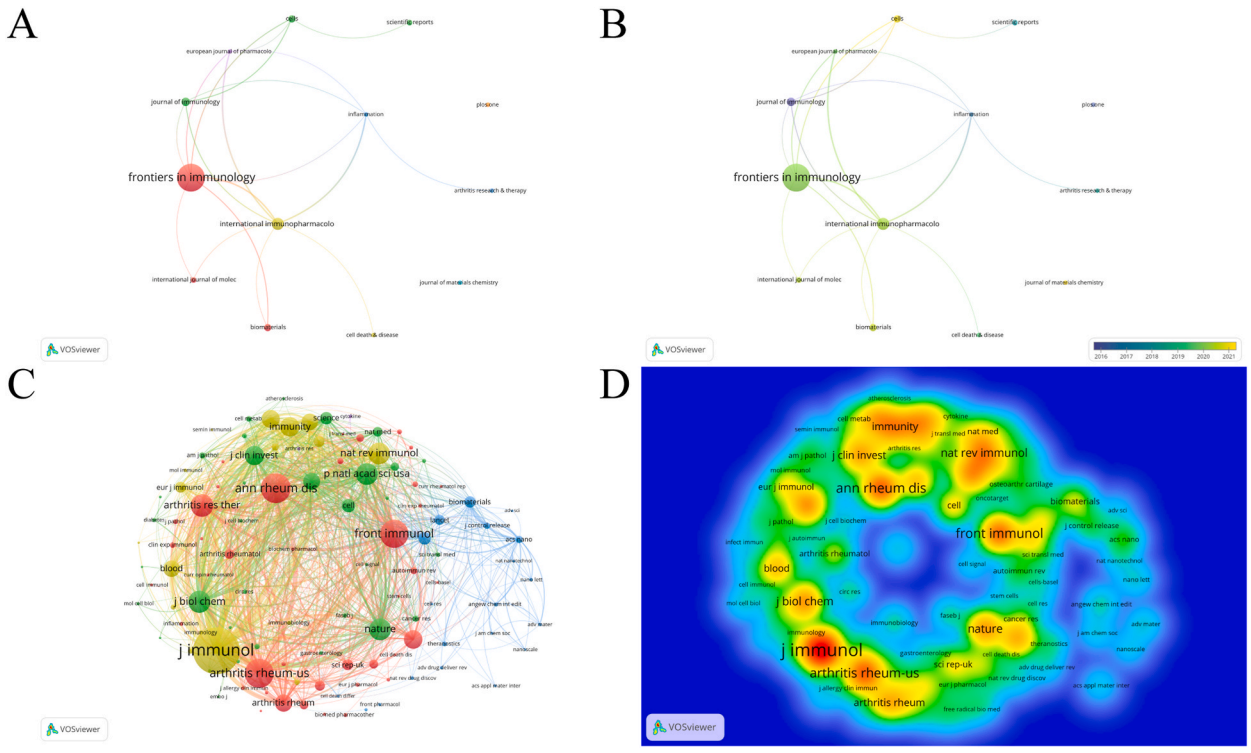


Fig. 5. Visual analysis of journals. (A) Visual analysis of journals published at least three publications in each journal. **(B)** The evolution of several journal publications. **(C)** Visualization of co-cited journals that have been cited at least 20 times. **(D)** Density map of co-cited journals.

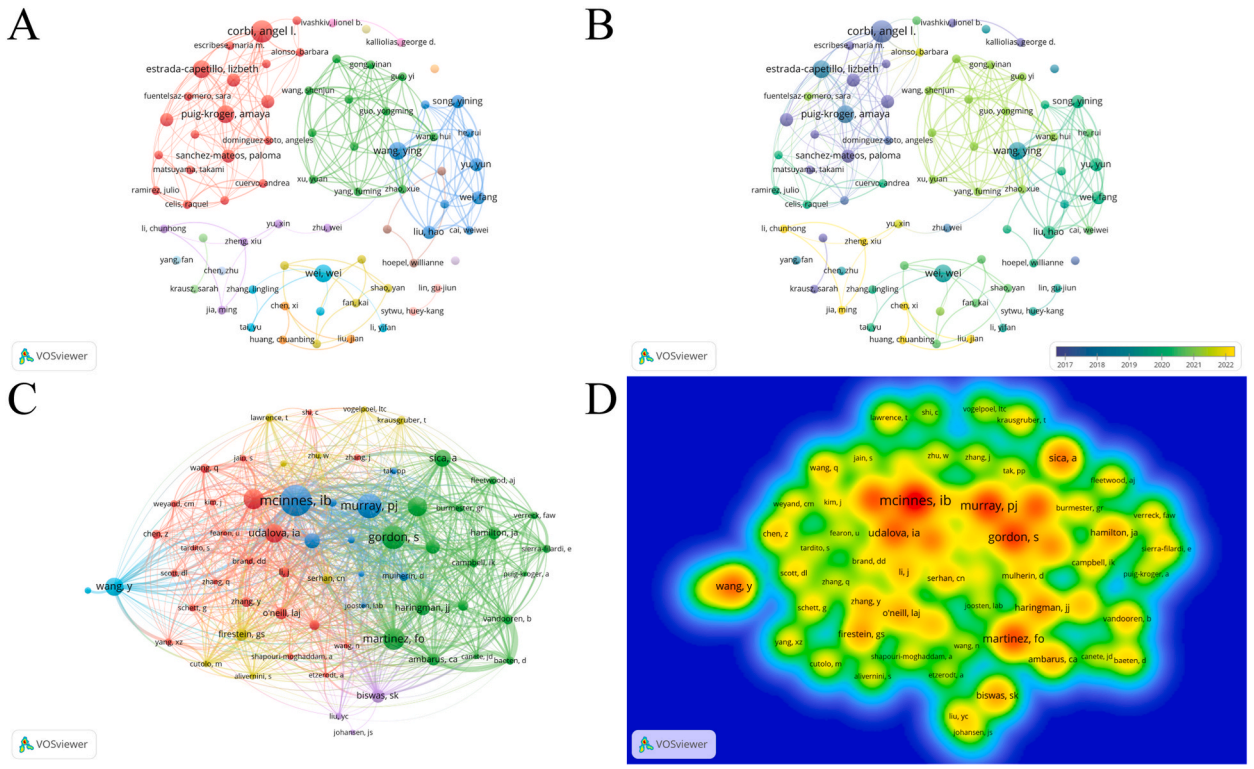


Fig. 6. Visual analysis by the authors. (A) Visual analysis of the authors, with a minimum of two publications per author. **(B)** The evolution of output results from different scholars. **(C)** Visualization of co-cited authors that have been cited at least 10 times. **(D)** Density map of co-cited authors.

Table 5
The top ten most productive authors. Scopus was used to obtain the authors' H-index (Elsevier BV, Amsterdam, The Netherlands). H-index [19] is defined as a researcher's number of h publications published, with each article having at least h citations. It is frequently used to assess a researcher's scientific output and academic status. NP: Number of publications. NC: Number of citations. AC: Average number of citations.

Ranking	Author	Affiliations	Country	H-index [19]	NP	NC	AC
1	Angel Luis Corbí	Centro de Investigaciones Biológicas Margarita Salas	Spain	54	5	442	88.40
2	Ying Wang	Anhui Engineering Technology Research Center of Biochemical Pharmaceutical	China	5	4	104	26.00
3	Amaya Puig-Kröger	Instituto de Investigación Sanitaria Gregorio Marañón	Spain	27	4	302	75.50
4	Lizbeth Estrada-Capetillo	Hospital General Universitario Gregorio Marañon	Spain	11	4	142	35.50
5	Wei Wei	Anhui Medical University	China	54	4	109	27.25
6	Hao Liu	Bengbu Medical College	China	28	3	64	21.33
7	Yining Song	Anhui Engineering Technology Research Center of Biochemical Pharmaceutical	China	3	3	64	21.33
8	Fang Wei	Anhui Engineering Technology Research Center of Biochemical Pharmaceutical	China	10	3	64	21.33
9	Yun Yu	Bengbu Medical College	China	6	3	64	21.33
10	Concha (Concepción) Nieto	Centro de Investigaciones Biológicas Margarita Salas	Spain	25	3	379	126.33

Planck-Institut für Biochemie, Planegg, Germanys, who has an H-index of 74. Siamon Gordon (43), from the Sir William Dunn School of Pathology, United Kingdom, has an H-index of 139.

3.7. Distribution of references

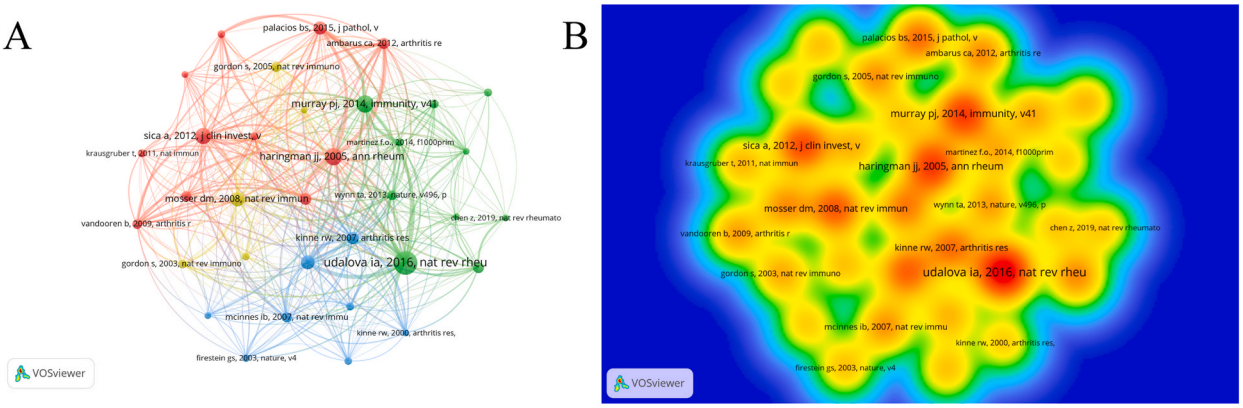
Of the 11,254 references referenced, 34 papers were cited at least ten times (Fig. 7A). In 2016, Irina A Udalova ranked top with a paper with a maximum NC of 34, followed by Jasper J Haringman (25) and Peter J Murray (25) (Fig. 7B) (Supplementary Table 4). Research by Irina A Udalova investigates the characteristics of monocyte-derived infiltrating and tissue-resident macrophages [4].

Furthermore, Jasper J Haringman et al. demonstrated that alterations in sub-synovial macrophages may be utilized to predict anti-rheumatic therapy success [20]. Peter J Murray et al. proposed a uniform framework for naming macrophage activation [21].

The Burst detection tool detects big variations in the number of citations at a given moment. It is used to identify the decrease or increase of a certain citation or term [22]. The relevant references for macrophage polarization in RA research were extracted using a burst detection technique in this study. There were seven references with the most bursts (Fig. 7C). The bursts of references were uniformly spread across time, with no one year having a disproportionate amount of bursts. Peter J Murray et al. [21] had the greatest bursts of citations among these references. Antonio Sica [23] provided the second most powerful reference. The authors summarize the characterization of the molecular network of macrophage polarization in this review [23], detail the functional polarization found in vivo under normal and pathological settings, as well as the dynamic alterations and therapeutic targets of polarised inflammation. References written by Zhu Chen et al. after 2019 have considerable bursts [24]. The authors focused on establishing that cytokines involved in type 2 immunological responses and eosinophil activation, such as IL-4, IL-5, IL-13, and IL-33, cause Macrophage polarization toward an immune-regulatory phenotype. Anti-inflammatory pathway induction and inflammation regression are appealing therapy choices for RA patients seeking long-term disease control. This is an emerging trend in this field of study.

3.8. Distribution of keywords

The keywords are the heart and soul of a publication, and keyword co-occurrence analysis can uncover research hotspots in a scientific topic. Between 2000 and 2022, 1215 keywords were used, with 39 of them appearing at least seven times ($m = 0.749 \times \sqrt{n_{max}} \approx 7.27$). These keywords are organized into five clusters that represent the field's five primary study directions (Fig. 8A). Clusters 1 and 2 each feature 9 keywords, shown by red and green circles. Cluster 1 includes terms such as "macrophage polarization", "Rheumatoid Arthritis", "inflammation", and so on. Cluster 2 has "activation", "nf-kappa-b", "collagen-induced arthritis", and other terms. These researches focused on etiology, important inflammatory indicators, cytokines, and treatments, based on the distribution of hot issues in the field (Supplementary Table 5) (Supplementary Fig. 1). The top five keywords were "rheumatoid-arthritis"(94), "macrophage polarization"(87), "inflammation"(53), "rheumatoid arthritis"(53), "macrophages"(35). The most popular immune cell in this field is "T-cells" (19), especially "regulatory t-cells" (18), while the most common biomarker is "gm-csf" (10). The most interesting pathway is "nf-kb" (21). In addition, the keywords' average publication year is split between 2016 and 2020. In addition to the phrases "rheumatoid arthritis", "macrophage polarization", "inflammation", "expression", "activation", and others, the leading keywords in the average publishing year 2018–2020 are "nf-kappa-b" (21), "t-cells" (19), "gm-csf" (10), "oxidative stress" (7), and "regulatory t-cells" (7) (Fig. 8B) (Supplementary Table 5).



C

Top 7 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2009 - 2022
Sica A, 2012, J CLIN INVEST, V122, P787, DOI 10.1172/JCI59643, DOI	2012	5.11	**2014**	2017	
Sierra-Filardi E, 2011, BLOOD, V117, P5092, DOI 10.1182/blood-2010-09-306993, DOI	2011	3.6	**2014**	2016	
Murray PJ, 2014, IMMUNITY, V41, P14, DOI 10.1016/j.immuni.2014.06.008, DOI	2014	5.49	**2016**	2019	
Martinez F.O., 2014, F1000PRIME REP, V6, P13	2014	3.63	**2016**	2019	
Palacios BS, 2015, J PATHOL, V235, P515, DOI 10.1002/path.4466, DOI	2015	3.71	**2019**	2020	
Udalova IA, 2016, NAT REV RHEUMATOL, V12, P472, DOI 10.1038/nrrheum.2016.91, DOI	2016	4.07	**2020**	2022	
Chen Z, 2019, NAT REV RHEUMATOL, V15, P9, DOI 10.1038/s41584-018-0109-2, DOI	2019	3.93	**2020**	2022	

Fig. 7. Visual analysis of references. (A) A reference co-occurrence analysis. Each article was cited at least ten times. **(B)** Density map of preference. **(C)** The seven citations with the most intense bursts (sorted by year of bursts onset). The blue line represents the time when the citation appeared, and the red line is the time when the bursts happened.

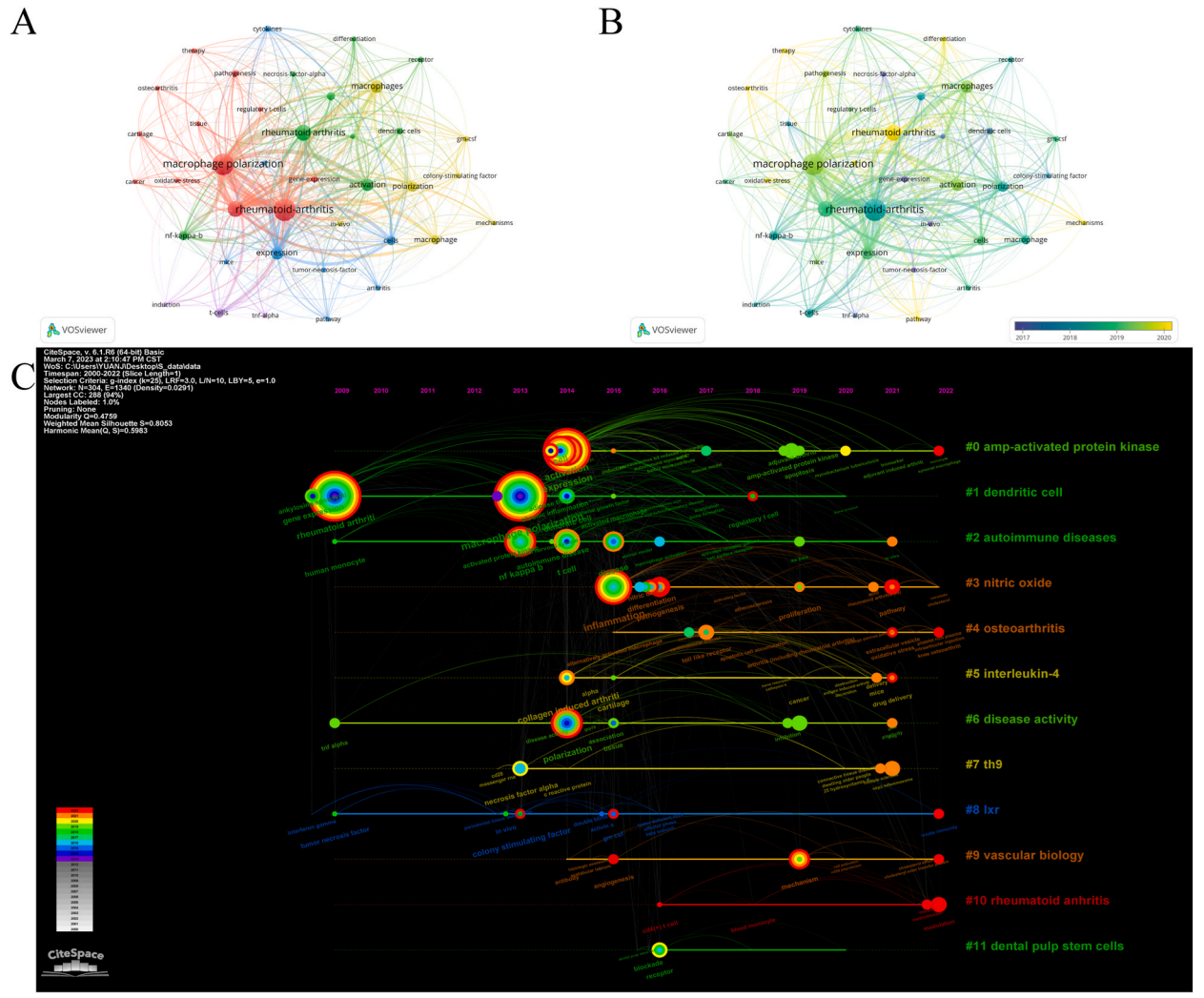


Fig. 8. Visual analysis of keywords. (A) Keywords co-occurrence analysis. Each keyword appeared at least 7 times. **(B)** Keyword evolution was created using VOSviewer based on the average year of publication. **(C)** Keywords timeline view generated by CiteSpace. Greater radius circles along the dotted lines connecting each cluster denote higher citation frequency, whereas warmer-colored yearly rings denote later citation dates.

At the same time, we built a keyword timeline display. The keywords were clustered using the log-likelihood ratio (LLR) approach. A cluster modularity value (Q) of more than 0.3 shows the presence of considerable cluster structure, while a mean profile value (S) greater than 0.5 suggests that the clusters are dependable [25]. There were nine clusters in all, with a Q value of 0.4759 and an S value of 0.8053 (Fig. 8C). From the moment they first emerged until 2022, the areas represented by #0, #3, #4, #8, #9, and #10 have piqued the curiosity of scholars. The milestone results for #0 appeared around 2014, while #3 occurred around 2015–2016. While the remaining clustered keywords did not exist in 2022, #1 appeared first, while #2 provided a considerable number of relevant results from 2013 to 2015. For the previous three years, the phrases "nlrp3 inflammasome", "oxidative stress", "extracellular vesicle" and "pathway" have all come up (Supplementary Table 6). They are essential to the field, appear often, and have research significance.

4. Discussion

4.1. General information

Our bibliometric study of 181 publications in the WoSCC database relating to macrophage polarization in RA from 2000 to 2022 reveals several intriguing and important insights. To begin with, this is an active field of study. Throughout these 22 years, the quantity of study findings in this field has continuously expanded globally. This field's popularity is predicted to rise further in 2023.

Another exciting aspect is the visualization of global trends. Countries that studied this area early on lay the groundwork for future advancement. The output of a huge number of research outcomes provides increased prospects for field development. A large number

of international collaborations suggest that research on macrophage polarization in RA has caught the interest of many individuals. It is worth mentioning, however, that several of the nations that have generated outcomes with substantial effect have produced very few research outputs, indicating that there is still room for future inquiry in this promising domain. Institutional and funding sources reflect research results in many ways and provide a crucial foundation for the field's development. Most of the institutions are from universities, which may indicate that the area is currently more focused on fundamental research and that translational medical research is still restricted. More hospitals are anticipated to do clinical research in the future, which will aid in addressing this worldwide issue. Despite having just two funding sources, China has the most articles backed by these funds, most likely owing to the vast number of researchers.

Journals are significant vehicles for the dissemination of research, and their quality and prestige thus play a vital influence in the diffusion of research results. Nine of the top 10 journals had high IFs (>5.000), with the great majority of these articles falling into the Q1 or Q2 categories. All of these shows that macrophage polarization in RA should be investigated further. Immunology journals are more focused than molecular biology or pharmacology journals on how macrophage polarization occurs in RA. Additionally, the IF of 15.304 for *Biomaterials* appears to imply that academics have great hopes for molecular research in this sector.

In terms of authorship, partnerships between high-level writers have made outstanding contributions to the field, notably in the areas of macrophage polarization and pro-inflammatory cytokines [26,27]. These powerful groups might be possible collaborators for field researchers. In general, writers who are regularly referenced are seen to have more impact than those who are less frequently quoted. Co-cited writers are likely to specialize in related fields of study. Iain B McInnes specializing in RA [28–30].Peter J Murray specializes in Macrophage polarization [21,31,32]. They have had a significant impact on the area of RA and macrophage polarization. These writers have worked on immunological and inflammatory research, summarizing changing hypotheses, etiology, related effects, and therapies.

The most cited papers in a certain period can indicate the foundation and context of knowledge and may be landmarks in the growth of a specific topic. Academics from the Academic Medical Centre/University of Amsterdam discovered in 2014 that alterations in sub-synovial macrophages might be utilized to predict the possible efficacy of the anti-rheumatic medication. Since then, nomenclature and experimental protocols for macrophage activation and polarization have been suggested [21]. The recommendations harmonized the description of macrophage activation and polarization, including the origin of macrophages, the definition of activators, and the indicators that indicate macrophage activity. The most prominent research on the subject has subsequently appeared [4]. This research investigates how macrophages influence disease development in RA as well as the heterogeneity of macrophages in RA. The study also shows that this molecular mechanism, which promotes macrophage differentiation into a pro-inflammatory or anti-inflammatory phenotype, may aid in the identification of signaling pathways that may affect future treatment approaches. These seminal results offer novel approaches to the treatment of RA and may be considered "groundbreaking" studies that have sparked more studies in the area.

4.2. Hotspots and frontiers

Keyword co-occurrences in bibliometrics can represent hot areas in the academic field, and timeline charts can demonstrate the evolution of new hot spots. Overall, the progressive growth in the number of keywords over the last 22 years implies that macrophage polarization in RA is an attractive study subject. The field first came to public attention in 2007. Scholars first concentrated on recognizing and analyzing the importance of macrophage polarization in RA as a separate subject. Since 2013, scholarly interest in this area has expanded, and the cognitive viewpoint has gotten broader, with some important keywords continuing to have an influence today. These keywords can reflect the focus of academic study on the topic of macrophage polarization in rheumatoid arthritis, and keywords from the last three years can largely represent the field's most recent research goals. We examined the keywords with the highest frequency of occurrence and research significance in the last three years based on the findings of the two software studies.

4.2.1. NF-κb participates in macrophage polarization in RA

The nuclear factor kappa-B (NF-κB) has long been recognized as a classic pro-inflammatory signaling pathway [33], as well as a crucial transcription factor regulating macrophage polarization and RA synovial fibroblasts. During the inflammatory phase, inflammatory cytokines control macrophage polarization by activating the NF-κB signaling pathway via cytokine receptors [34,35]. In RA, synovial tissue is abnormally invaded by macrophages and other cells, allowing pro-inflammatory cytokines to be overexpressed [36]. These cytokines are partly reliant on NF-κB activity [37]. According to a recent study, IL-26 significantly activates NF-κB and cJUN phosphorylation to enhance M1 macrophage differentiation [38]. One of the current hot spots in immunotherapy is targeted treatment against NF-κB. Mitogen-activated protein kinase (MAPK) and NF-κB pathways were blocked by SR9009, an agonist of the transcriptional repressor Nuclear receptor subfamily 1 group D member 1 (NR1D1), which inhibited M1 macrophage polarization and control of osteoclast formation and osteoclast-associated gene expression [39]. By pharmaceutical targeting of the NF-κB/MAPK pathway, inhibition of phosphorylation of IκBα, *p*-JNK, *p*-ERK and p-P38 in macrophages lowers the production of related inflammatory cytokines and repolarizes M1 macrophages to M2 [40–47]. As a result, determining the role of NF-κB in macrophage immune training is critical. Furthermore, the diagnostic significance of a biomarker via the NF-κB pathway has been favored by researchers. The adipokine nesfatin-1 has been linked to the development of inflammation in a variety of disorders. Its enhanced expression elevated CCL2 expression in human RASF and promoted monocyte migration via the MEK/ERK, p38, and NF-κB signaling pathways. The increase in CCL2 expression caused by nesfatin-1 improves M1 polarization [48]. Moreover, by activating the Cholinergic anti-inflammatory pathway (CAP) - Silent information regulator 1 (SIRT1) pathway in macrophages, a class of compounds suppresses NF-κB-mediated inflammation and M1 macrophage polarization [49]. This might imply that blocking the TLR4/NF-κB signaling

pathway is one of the potential strategies for slowing the advancement of macrophage polarization towards the M1 subpopulation in RA [41]. As a result, inhibiting the NF-κB signaling pathway is thought to be key in limiting the inflammatory response to RA [50].

4.2.2. GM-CSF is a promising biomarker of macrophage polarization in RA

Scholars have recognized the need for reliable biomarkers to provide predictive information about the diagnosis, treatment, and future risk of recurrence in RA in recent years. Granulocyte-macrophage colony-stimulating factor (GM-CSF) has recently emerged as a prominent topic in biomarker research. Despite substantial research over the last two decades, the involvement of GM-CSF in macrophage polarization in RA has caused scientists to reconsider its significance. GM-CSF was present in high expression in RA [51]. It enhances the synthesis of inflammatory mediators by bone marrow cells via GM-CSFR and promotes the activation of synovial fibroblasts. Synovial fibroblasts secrete GM-CSF when stimulated by inflammatory mediators, which stimulate monocyte migration and macrophage activation in the synovium [52]. GM-CSF promotes neutrophil and macrophage chemokine production of CCL3 and CCL2 [53], promoting macrophage survival and differentiation toward a pro-inflammatory phenotype. In individuals with RA, psoriatic arthritis, and all kinds of undifferentiated arthritis, GM-CSF and its activation of macrophage polarization are considered prospective therapeutic targets [54]. As a result, the researchers tried to prevent macrophages that polarize toward the M1 subpopulation by inhibiting GM-CSF and the M1 biomarker iNOS released in the synovium [41]. According to a recent study, GM–CSF–induced macrophage polarization results in cytokine-induced expression of SH2-containing protein (CIS), and CIS deficiency biases monocyte development towards the immunosuppressive M2 type [55]. Several researchers, however, argue that CSF-1 or GM–CSF–derived macrophages should not be classified as M1 or M2 [21,56]. Scientists are presently investigating a variety of promising biomarkers. Before these indicators can be employed in clinical practice, they must be rigorously validated in large cohort studies.

4.2.3. NLRP3 participates in macrophage polarization in RA

Nucleotide-binding domain-like receptor protein 3 (NLRP3) inflammasome is a multi-protein complex that includes NLRP3, apoptosis-associated speck-like protein (ASC), and caspase-1. It is mostly expressed in monocytes and macrophages [57]. NLRP3 signaling pathway activation recruits and activates caspase-1 to cleave IL-1 and IL-18 precursors, whereas the released mature cytokines IL-1β and IL-18 play important roles in systemic inflammation [58,59]. Prior research has demonstrated that lipopolysaccharide (LPS) increases NLRP3 protein expression in M1 macrophages but not in M2 type [60]. Later research indicated that inhibiting NLRP3 inflammasome caused microglia/macrophages to transition from promoting the M1 to the M2 phenotype [61,62]. Er Miao San (EMS) inhibited macrophage polarization to the M1 inflammatory phenotype in AA rats by downregulating the miRNA-33/NLRP3 pathway [63]. Human umbilical cord blood MSCs (hUCB-MSCs) suppress NLRP3 inflammasome and modify macrophage pro-inflammatory activity in mice, lowering excessive inflammatory responses [64]. As a result, for the future treatment of RA, novel medicines that target the suppression of NLRP3 inflammasome and promote macrophage polarization towards an anti-inflammatory phenotype seem appealing [65].

4.2.4. Oxidative stress significantly affects macrophage polarization in RA

Oxidative Stress (OS) is a condition in which there is an imbalance between oxidative and antioxidant action in the body. This condition causes neutrophil infiltration, increased protease secretion, and the creation of high quantities of oxidative intermediates [66]. Many studies have confirmed the significance of reactive oxygen species (ROS)-related oxidative stress in joint disease [67,68]. The activation of the M1 type might result in the generation of pro-inflammatory cytokines and ROS. Excess ROS production and metabolism can increase synovial cell senescence and excessive fibroblast proliferation, resulting in collagen deposition and subchondral bone erosion [69]. While ROS in macrophages is required for the clearance of dead cells, high amounts of ROS may be damaging to macrophages [70], and damaged macrophages are a major source of ROS [71], the two creating a circuit that continues RA worsening. The effects of oxidative stress on macrophage activity and polarization are significant. ROS-driven macrophage polarization has been a troublesome target for potential medicines due to a lack of selectivity. Recently developed manganese ferrite and ceria nanoparticle-anchored mesoporous silica nanoparticles (MFC-MSNs) may synergistically scavenge ROS, lower M1 macrophage levels, and stimulate M2 macrophages [72]. After that, another team of researchers encapsulated the MSNs with methotrexate (MTX) to create deep eutectic solvents (DES-MSNs) hydrogels. As a result, the MTX payload has a direct therapeutic impact, whereas nanoceria modifies the inflammatory milieu by triggering ROS clearance and macrophage phenotypic alteration [73]. This shows that clearing ROS by immunotherapy with a mix of medicines and their carriers might have a synergistic therapeutic impact on RA.

4.2.5. Treg-secreted IL-10 promotes macrophage polarization in RA

T-cells are formed from lymphatic stem cells in the bone marrow. It develops and matures in the thymus before being transported to immunological organs and tissues throughout the body via lymphatic and blood circulation. Recently, it was shown that the dynamic balance of Th1/Th2/Th17/Treg influences the immune response pattern of the tumor microenvironment and may potentially impact the efficacy of immunotherapy [74]. Treg cells are divided into three categories based on their origin and development. Natural Treg (nTreg) cells that originate from immature T lymphocytes during thymic development display CD25 and the nuclear transcription factor Foxp3. Mature nTreg cells are changed into acquired Treg (iTreg) cells, which include Tr1 and Th3 subpopulations, in response to peripheral antigen stimulation or induction by immunosuppressive agents. The former mostly secretes IL-10, whereas the latter primarily produces TGF-β [75]. Moreover, IL-10 is an endogenous cytokine generated by M2 macrophages, changing immune activation to tissue healing mode [76]. IL-10 signals through the Jak1/STAT3 pathway and is a key player in the modulation of inflammatory macrophage polarization by anti-TNF medications [77]. Its absence may enhance macrophage polarization towards the pro-inflammatory M1 phenotype, which contributes to the inflammatory response in RA [78]. IL-10 pDNA and the

chemotherapeutic medication dexamethasone sodium phosphate (DSP) were co-loaded into human serum albumin (HSA) in rats to prepare pDNA/DSP-NPs to actively target macrophages in synovial tissue to stimulate M1-M2 polarization [79]. Through activating the cJUN and NF-κB pathways, a novel member of the IL-10 family, IL-26, biases macrophage polarization towards the M1 phenotype [38]. IL-10 can also work in tandem with IL-18 to increase the synthesis of macrophage-derived mediators including bone-bridging protein (OPN) and thrombin, resulting in OPN production via thrombin cleavage, which works on integrin 4/9, increasing macrophage polarization and leading to angiogenic excess [80]. While IL-10 is an anti-inflammatory cytokine, our findings imply that class II cytokines or IL-10 synergistic pro-inflammatory cytokines can have pro-inflammatory effects in RA. Treg cells, as represented by IL-10, may be explored as a novel therapeutic target in the future.

4.2.6. EVs are effective drug delivery vehicles and participate in macrophage polarization in RA

Extracellular vesicles (EVs) are tiny membranous vesicles released by cells into the extracellular matrix. They are divided into ten subgroups: exosomes, microparticles, apoptotic vesicles, cancer vesicles and so forth [81]. It is found in a variety of cell types and bodily fluids, participates in signaling and intercellular information transmission, and is capable of passing information to other cells, thereby affecting the function of the receiving cell [82]. Several researchers have employed conventional nanoparticles to treat macrophage polarization in RA [79,83], but such nanoparticles are frequently difficult to produce, are swiftly removed from circulation by the mononuclear phagocyte system, and can have undesirable side effects [84,85]. The structure of EVs facilitates vesicles crossing the plasma membrane of receptor cells, which is a vital step in efficient local and systemic drug administration. Thus further, it's excellent biocompatibility and low immunogenicity, along with its superior loading capacity, make it a better drug delivery method than nano-formulations [86]. Encouragingly, medications packaged into tiny EVs can be administered more efficiently to target cells in therapeutic doses due to their low immunogenicity, high biocompatibility, and high efficiency [87]. In contrast to tiny chemical medicines with relatively short joint half-lives, M2-EVs had a longer retention period of about 3 days in the joints of mice with collagen-induced arthritis (CIA) models, according to a recent study. This allowed for the reprogramming of EV-directed in situ macrophages into anti-inflammatory M2 macrophages in joints, which alleviated RA with no evidence of systemic deleterious effects [88]. Small EVs generated from Mesenchymal stromal cells (MSCs) are less immunogenic and have a greater safety profile, according to clinical research, and MSC-EVs have a significant potential for boosting M2 macrophage polarization in inflammation-related disorders [89–92]. It induces apoptosis in T cells and promotes the proliferation of IL-10 and TGF-β expressed in RA [93,94]. An investigation has validated the mechanism of EV participation in RA, mainly through miRNA, based on the fact that EVs are capable of transferring information to receptor cells [95]. Recently, researchers encapsulated plasmid DNA encoding the anti-inflammatory cytokine interleukin-10 (IL-10 pDNA) and the chemotherapeutic medication betamethasone sodium phosphate (BSP) within the M2 Exo, a bionic vector produced from M2 macrophages, to create a co-delivery system for RA combination treatment. IL-10 pDNA and BSP promote M1—M10 macrophage polarization by reducing pro-inflammatory cytokine production (IL-1β, TNF-α) and increasing IL-2 cytokine expression [96]. The concern is that current researches are still at the pre-clinical stage, and additional clinical trials are needed to examine the safety, effectiveness, and durability of MSC-EVs in patients with RA. Overall, the study of vesicle-related functions has become a research hotspot and is predicted to aid in the early detection and novel treatment strategies of RA illness.

This study also has significant limitations due to the nature of bibliometrics. To begin, although the data were gathered from WoSCC, the most authoritative database generally used in scientometrics, some studies that were not included in WoSCC were omitted. Second, all information was extracted using bibliometric technologies based on machine learning and natural language processing, which may result in bias in other bibliometric research reporting. Nonetheless, we continue to give a plethora of impartial information and insights to scholars.

5. Conclusion

This bibliometric research looked at the global literature on macrophage polarization in RA. Throughout the last 22 years, research in this field has increased and will continue to be of interest in the future, although longitudinal studies and randomized controlled trials are required to corroborate existing findings. Ongoing research in this field is focused on developing more accurate early RA indicators as well as targeted and precise therapies. The main limitation of this study was the inability to manually check every paper in the study to avoid including false positives. This bibliometric approach can provide a time-saving method for researchers, scholars and students in identifying research topics and objectives, selecting and filtering the dense literature in the field of research, describing the scientific achievements in the field, providing a comprehensive overview of the current state of research, and searching for possible future directions of possible research. Our study can serve as a guide and reference for researchers when considering and deciding on their research options. All investigations seek to improve understanding of RA pathogenesis and to progress the development of RA diagnosis and therapy.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.>

Data availability statement

Data included in article/supplementary material/referenced in article.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e19761.

References

[1] M.-A. Boutet, et al., Novel insights into macrophage diversity in rheumatoid arthritis synovium, Autoimmun. Rev. 20 (3) (Mar. 2021), 102758, https://doi.org/10.1016/j.autrev.2021.102758.
[2] A.-F. Radu, S.G. Bungau, Management of rheumatoid arthritis: an overview, Cells 10 (11) (Oct. 2021) 2857, https://doi.org/10.3390/cells10112857.
[3] I.B. McInnes, G. Schett, The pathogenesis of rheumatoid arthritis, N. Engl. J. Med. 365 (23) (Dec. 2011) 2205–2219, https://doi.org/10.1056/NEJMra1004965.
[4] I.A. Udalova, A. Mantovani, M. Feldmann, Macrophage heterogeneity in the context of rheumatoid arthritis, Nat. Rev. Rheumatol. 12 (8) (Aug. 2016) 472–485, https://doi.org/10.1038/nrrheum.2016.91.
[5] S.K. Biswas, A. Mantovani, Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm, Nat. Immunol. 11 (10) (Oct. 2010) 889–896, https://doi.org/10.1038/ni.1937.
[6] A. Paoletti, et al., Restoration of default blood monocyte-derived macrophage polarization with adalimumab but not etanercept in rheumatoid arthritis, Front. Immunol. 13 (2022), 832117, https://doi.org/10.3389/fimmu.2022.832117.
[7] L. Waltman, A.F.J. van Raan, S. Smart, Exploring the relationship between the engineering and physical sciences and the health and life sciences by advanced bibliometric methods, PLoS One 9 (10) (2014), e111530, https://doi.org/10.1371/journal.pone.0111530.
[8] F. Tang, W.-B. Dai, X.-L. Li, D. Turghun, H. Huang, Y.-Q. Fan, Publication trends and hot spots in femoroacetabular impingement research: a 20-year bibliometric analysis, J. Arthroplasty 36 (8) (Aug. 2021) 2698–2707, https://doi.org/10.1016/j.arth.2021.03.019.
[9] J. Long, Y. Zhang, X. Liu, M. Pan, Q. Gao, Exosomes in the field of neuroscience: a scientometric study and visualization analysis, Front. Neurol. 13 (2022), 871491, https://doi.org/10.3389/fneur.2022.871491.
[10] X. Gao, et al., Global research trends in catheter ablation and surgical treatment of atrial fibrillation: a bibliometric analysis and science mapping, Front Surg 9 (2022), 1048454, https://doi.org/10.3389/fsurg.2022.1048454.
[11] Q. Li, W. Yang, J. Li, Z. Shan, Emerging trends and hot spots in autoimmune thyroiditis research from 2000 to 2022: a bibliometric analysis, Front. Immunol. 13 (2022), 953465, https://doi.org/10.3389/fimmu.2022.953465.
[12] D. Xia, R. Yao, S. Wang, G. Chen, Y. Wang, Mapping trends and hotspots regarding clinical research on COVID-19: a bibliometric analysis of global research, Front. Public Health 9 (2021), 713487, https://doi.org/10.3389/fpubh.2021.713487.
[13] A.-F. Radu, S.G. Bungau, P.A. Negru, M.F. Marcu, F.L. Andronie-Cioara, In-depth bibliometric analysis and current scientific mapping research in the context of rheumatoid arthritis pharmacotherapy, Biomed. Pharmacother. 154 (Oct. 2022), 113614, https://doi.org/10.1016/j.biopha.2022.113614.
[14] N.J. van Eck, L. Waltman, Software survey: VOSviewer, a computer program for bibliometric mapping, Scientometrics 84 (2) (2010) 523–538, https://doi.org/10.1007/s11192-009-0146-3.
[15] C. Chen, Searching for intellectual turning points: progressive knowledge domain visualization, Suppl 1, no. Suppl 1, Proc Natl Acad Sci U S A 101 (2004) 5303–5310, https://doi.org/10.1073/pnas.0307513100. Apr.
[16] P.S. Kamath, G. Bologna, Impact factor: misused and overhyped? Hepatology 49 (6) (Jun. 2009) 1787–1789, https://doi.org/10.1002/hep.23040.
[17] X.-F. Wu, Q. Fu, R. Rousseau, On indexing in the Web of Science and predicting journal impact factor, Jul, J. Zhejiang Univ. - Sci. B 9 (7) (2008) 582–590, https://doi.org/10.1631/jzus.B0840001.
[18] D.J. Price, And others, Little science, big science... and beyond, in: Columbia University Press vol. 480, New York, 1986.
[19] L. Engqvist, J.G. Frommen, The h-index and self-citations, Trends Ecol. Evol. 23 (5) (May 2008) 250–252, https://doi.org/10.1016/j.tree.2008.01.009.
[20] J.J. Haringman, et al., Synovial tissue macrophages: a sensitive biomarker for response to treatment in patients with rheumatoid arthritis, Ann. Rheum. Dis. 64 (6) (Jun. 2005) 834–838, https://doi.org/10.1136/ard.2004.029751.
[21] P.J. Murray, et al., Macrophage activation and polarization: nomenclature and experimental guidelines, Jul, Immunity 41 (1) (2014) 14–20, https://doi.org/10.1016/j.immuni.2014.06.008.
[22] J. Kleinberg, Bursty and hierarchical structure in streams, Data Min. Knowl. Discov. 7 (4) (Oct. 2003) 373–397, https://doi.org/10.1023/A:1024940629314.
[23] A. Sica, A. Mantovani, Macrophage plasticity and polarization: in vivo veritas, Mar, J. Clin. Invest. 122 (3) (2012) 787–795, https://doi.org/10.1172/JCI59643.
[24] Z. Chen, A. Bozec, A. Ramming, G. Schett, Anti-inflammatory and immune-regulatory cytokines in rheumatoid arthritis, Nat. Rev. Rheumatol. 15 (1) (Jan. 2019) 9–17, https://doi.org/10.1038/s41584-018-0109-2.
[25] T. Liu, L. Yang, H. Mao, F. Ma, Y. Wang, Y. Zhan, Knowledge domain and emerging trends in podocyte injury research from 1994 to 2021: a bibliometric and visualized analysis, Front. Pharmacol. 12 (2021), 772386, https://doi.org/10.3389/fphar.2021.772386.
[26] E. Sierra-Filardi, et al., CCL2 shapes macrophage polarization by GM-CSF and M-CSF: identification of CCL2/CCR2-dependent gene expression profile, J. Immunol. 192 (8) (Apr. 2014) 3858–3867, https://doi.org/10.4049/jimmunol.1302821.
[27] B. Soler Palacios, et al., Macrophages from the synovium of active rheumatoid arthritis exhibit an activin A-dependent pro-inflammatory profile, J. Pathol. 235 (3) (Feb. 2015) 515–526, https://doi.org/10.1002/path.4466.
[28] J.S. Smolen, D. Aletaha, I.B. McInnes, Rheumatoid arthritis, Lancet 388 (10055) (Oct. 2016) 2023–2038, https://doi.org/10.1016/S0140-6736(16)30173-8.
[29] J.S. Smolen, et al., EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update, Ann. Rheum. Dis. 79 (6) (Jun. 2020) 685–699, https://doi.org/10.1136/annrheumdis-2019-216655.
[30] I.B. McInnes, G. Schett, Pathogenetic insights from the treatment of rheumatoid arthritis, Jun, Lancet 389 (10086) (2017) 2328–2337, https://doi.org/10.1016/S0140-6736(17)31472-1.
[31] P.J. Murray, T.A. Wynn, Obstacles and opportunities for understanding macrophage polarization, J. Leukoc. Biol. 89 (4) (Apr. 2011) 557–563, https://doi.org/10.1189/jlb.0710409.
[32] P.J. Murray, T.A. Wynn, Protective and pathogenic functions of macrophage subsets, Nat. Rev. Immunol. 11 (11) (Oct. 2011) 723–737, https://doi.org/10.1038/nri3073.
[33] T. Lawrence, The nuclear factor NF-kappaB pathway in inflammation, Cold Spring Harb Perspect Biol 1 (6) (Dec. 2009) a001651, https://doi.org/10.1101/cshperspect.a001651.
[34] S.S. Makarov, NF-kappa B in rheumatoid arthritis: a pivotal regulator of inflammation, hyperplasia, and tissue destruction, Arthritis Res. 3 (4) (2001) 200–206, https://doi.org/10.1186/ar300.
[35] Y. Hu, Y. Wang, T. Chen, Z. Hao, L. Cai, J. Li, Exosome: function and application in inflammatory bone diseases, Oxid. Med. Cell. Longev. 2021 (2021), https://doi.org/10.1155/2021/6324912.

[36] E.H. Choy, G.S. Panayi, Cytokine pathways and joint inflammation in rheumatoid arthritis, N. Engl. J. Med. 344 (12) (Mar. 2001) 907–916, https://doi.org/10.1056/NEJM200103223441207.

[37] M. Feldmann, S.R.N. Maini, Role of cytokines in rheumatoid arthritis: an education in pathophysiology and therapeutics, Jun, Immunol. Rev. 223 (2008) 7–19, https://doi.org/10.1111/j.1600-065X.2008.00626.x.

[38] Y.-H. Lin, et al., Interleukin 26 skews macrophage polarization towards M1 phenotype by activating cJUN and the NF-κB pathway, Cells 9 (4) (Apr. 2020) 938, https://doi.org/10.3390/cells9040938.

[39] H. Liu, et al., NR1D1 modulates synovial inflammation and bone destruction in rheumatoid arthritis, Feb, Cell Death Dis. 11 (2) (2020) 129, https://doi.org/10.1038/s41419-020-2314-6.

[40] Z. F, et al., Kinsenoside attenuates osteoarthritis by repolarizing macrophages through inactivating NF- κ B/MAPK signaling and protecting chondrocytes, Sep, Acta Pharm. Sin. B 9 (5) (2019), https://doi.org/10.1016/j.apsb.2019.01.015.

[41] Y. Cao, et al., Wilforlide A ameliorates the progression of rheumatoid arthritis by inhibiting M1 macrophage polarization, J. Pharmacol. Sci. 148 (1) (Jan. 2022) 116–124, https://doi.org/10.1016/j.jphs.2021.10.005.

[42] C. Han, et al., Glaucocalyxin B inhibits cartilage inflammatory injury in rheumatoid arthritis by regulating M1 polarization of synovial macrophages through NF-κB pathway, Aging (Albany NY) 13 (18) (Sep. 2021) 22544–22555, https://doi.org/10.18632/aging.203567.

[43] J. Han, et al., Sesquiterpene lactones-enriched fractions from Xanthium mongolicum Kitag alleviate RA by regulating M1 macrophage polarization via NF-κB and MAPK signaling pathway, Front. Pharmacol. 14 (2023), 1104153, https://doi.org/10.3389/fphar.2023.1104153.

[44] B. Zhou, et al., Therapeutic effects of a novel BAFF blocker on arthritis, Signal Transduct Target Ther 4 (2019) 19, https://doi.org/10.1038/s41392-019-0051-z.

[45] Y. Cheng, et al., Bone erosion in inflammatory arthritis is attenuated by Trichinella spiralis through inhibiting M1 monocyte/macrophage polarization, iScience 25 (3) (Mar. 2022), 103979, https://doi.org/10.1016/j.isci.2022.103979.

[46] W. Lin, et al., Wutou decoction attenuates the synovial inflammation of collagen-induced arthritis rats via regulating macrophage M1/M2 type polarization, J. Ethnopharmacol. 301 (Jan. 2023), 115802, https://doi.org/10.1016/j.jep.2022.115802.

[47] S. Liu, L.-P. Song, R.-B. Li, L.-H. Feng, H. Zhu, Iguratimod promotes transformation of mononuclear macrophages in elderly patients with rheumatoid arthritis by nuclear factor-κB pathway, World J Clin Cases 9 (10) (Apr. 2021) 2181–2191, https://doi.org/10.12998/wjcc.v9.i10.2181.

[48] J.-W. Chang, et al., Nesfatin-1 stimulates CCL2-dependent monocyte migration and M1 macrophage polarization: implications for rheumatoid arthritis therapy, Int. J. Biol. Sci. 19 (1) (Jan. 2023) 281–293, https://doi.org/10.7150/ijbs.77987.

[49] W.-G. Chen, et al., α-Mangostin treats early-stage adjuvant-induced arthritis of rat by regulating the CAP-SIRT1 pathway in macrophages, Drug Des Devel Ther 16 (Feb. 2022) 509–520, https://doi.org/10.2147/DDDT.S348836.

[50] Q. Wang, et al., Polyphyllin I ameliorates collagen-induced arthritis by suppressing the inflammation response in macrophages through the NF-κB pathway, Front. Immunol. 9 (2018) 2091, https://doi.org/10.3389/fimmu.2018.02091. Sep.

[51] A.L. Bell, M.K. Magill, W.R. McKane, F. Kirk, A.E. Irvine, Measurement of colony-stimulating factors in synovial fluid: potential clinical value, Rheumatol. Int. 14 (5) (1995) 177–182, https://doi.org/10.1007/BF00262295.

[52] B. Becher, S. Tugues, M. Greter, GM-CSF: from growth factor to central mediator of tissue inflammation, Nov, Immunity 45 (5) (2016) 963–973, https://doi.org/10.1016/j.immuni.2016.10.026.

[53] H. Shinohara, S. Yano, C.D. Bucana, I.J. Fidler, Induction of chemokine secretion and enhancement of contact-dependent macrophage cytotoxicity by engineered expression of granulocyte-macrophage colony-stimulating factor in human colon cancer cells, J. Immunol. 164 (5) (Mar. 2000) 2728–2737, https://doi.org/10.4049/jimmunol.164.5.2728.

[54] S. Fuentelsaz-Romero, et al., GM-CSF expression and macrophage polarization in joints of undifferentiated arthritis patients evolving to rheumatoid arthritis or psoriatic arthritis, Front. Immunol. 11 (2020), 613975, https://doi.org/10.3389/fimmu.2020.613975.

[55] S. Zhang, et al., CIS controls the functional polarization of GM-CSF-derived macrophages, Cell. Mol. Immunol. 20 (1) (Jan. 2023) 65–79, https://doi.org/10.1038/s41423-022-00957-z.

[56] F.O. Martinez, S. Gordon, The M1 and M2 paradigm of macrophage activation: time for reassessment, Mar, F1000Prime Rep 6 (2014) 13, https://doi.org/10.12703/P6-13.

[57] T. Murakami, et al., Critical role for calcium mobilization in activation of the NLRP3 inflammasome, Proc Natl Acad Sci U S A 109 (28) (Jul. 2012) 11282–11287, https://doi.org/10.1073/pnas.1117765109.

[58] H. Guo, J.B. Callaway, J.P.-Y. Ting, Inflammasomes: mechanism of action, role in disease, and therapeutics, Jul, Nat Med 21 (7) (2015) 677–687, https://doi.org/10.1038/nm.3893.

[59] J.-M. Dayer, F. Oliviero, L. Punzi, A brief history of IL-1 and IL-1 Ra in Rheumatology, Front. Pharmacol. 8 (2017) 293, https://doi.org/10.3389/fphar.2017.00293.

[60] F. Awad, et al., Impact of human monocyte and macrophage polarization on NLR expression and NLRP3 inflammasome activation, PLoS One 12 (4) (2017), e0175336, https://doi.org/10.1371/journal.pone.0175336.

[61] Y. Ye, et al., Meisoindigo protects against focal cerebral ischemia-reperfusion injury by inhibiting NLRP3 inflammasome activation and regulating microglia/macrophage polarization via TLR4/NF-κB signaling pathway, Front. Cell. Neurosci. 13 (2019) 553, https://doi.org/10.3389/fncel.2019.00553.

[62] J. Lu, S. Xie, Y. Deng, X. Xie, Y. Liu, Blocking the NLRP3 inflammasome reduces osteogenic calcification and M1 macrophage polarization in a mouse model of calcified aortic valve stenosis, Atherosclerosis 347 (Apr. 2022) 28–38, https://doi.org/10.1016/j.atherosclerosis.2022.03.005.

[63] M. Liu, et al., Effect of Er Miao San on peritoneal macrophage polarisation through the miRNA-33/NLRP3 signalling pathway in a rat model of adjuvant arthritis, Pharm. Biol. 60 (1) (Dec. 2022) 846–853, https://doi.org/10.1080/13880209.2022.2066700.

[64] T.-H. Shin, et al., Human umbilical cord blood-stem cells direct macrophage polarization and block inflammasome activation to alleviate rheumatoid arthritis, Cell Death Dis. 7 (12) (Dec. 2016) e2524, https://doi.org/10.1038/cddis.2016.442.

[65] D. Wu, et al., Suppression of macrophage activation by sodium danshensu via HIF-1α/STAT3/NLRP3 pathway ameliorated collagen-induced arthritis in mice, Feb, Molecules 28 (4) (2023) 1551, https://doi.org/10.3390/molecules28041551.

[66] M. Herb, M. Schramm, Functions of ROS in macrophages and antimicrobial immunity, Feb, Antioxidants 10 (2) (2021) 313, https://doi.org/10.3390/antiox10020313.

[67] E. Balogh, et al., Oxidative stress impairs energy metabolism in primary cells and synovial tissue of patients with rheumatoid arthritis, Arthritis Res. Ther. 20 (1) (May 2018) 95, https://doi.org/10.1186/s13075-018-1592-1.

[68] S. Mateen, S. Moin, A. Zafar, A.Q. Khan, Redox signaling in rheumatoid arthritis and the preventive role of polyphenols, Clin. Chim. Acta 463 (Dec. 2016) 4–10, https://doi.org/10.1016/j.cca.2016.10.007.

[69] V.L. Souliotis, N.I. Vlachogiannis, M. Pappa, A. Argyriou, P.A. Ntouros, P.P. Sfikakis, DNA damage response and oxidative stress in systemic autoimmunity, Dec, Int. J. Mol. Sci. 21 (1) (2019) 55, https://doi.org/10.3390/ijms21010055.

[70] N. Dey, et al., Caspase-1/ASC inflammasome-mediated activation of IL-1β-ROS-NF-κB pathway for control of Trypanosoma cruzi replication and survival is dispensable in NLRP3-/- macrophages, PLoS One 9 (11) (2014), e111539, https://doi.org/10.1371/journal.pone.0111539.

[71] H.-Y. Tan, N. Wang, S. Li, M. Hong, X. Wang, Y. Feng, The reactive oxygen species in macrophage polarization: reflecting its dual role in progression and treatment of human diseases, Oxid. Med. Cell. Longev. 2016 (2016), 2795090, https://doi.org/10.1155/2016/2795090.

[72] J. Kim, et al., Synergistic oxygen generation and reactive oxygen species scavenging by manganese ferrite/ceria Co-decorated nanoparticles for rheumatoid arthritis treatment, ACS Nano 13 (3) (Mar. 2019) 3206–3217, https://doi.org/10.1021/acsnano.8b08785.

[73] M. Li, et al., Deep eutectic solvents-Hydrogels for the topical management of rheumatoid arthritis, J Control Release 354 (Jan. 2023) 664–679, https://doi.org/10.1016/j.jconrel.2023.01.050.

[74] E. Sifnaios, et al., Gestational diabetes and T-cell (Th1/Th2/Th17/treg) immune profile 33 (1) (2019) 31–40, https://doi.org/10.21873/invivo.11435.

[75] Y. Carrier, J. Yuan, V.K. Kuchroo, H.L. Weiner, Th3 cells in peripheral tolerance. II. TGF-beta-transgenic Th3 cells rescue IL-2-deficient mice from autoimmunity, J. Immunol. 178 (1) (Jan. 2007) 172–178, https://doi.org/10.4049/jimmunol.178.1.172.

[76] M.H. Abdelaziz, et al., Alternatively activated macrophages; a double-edged sword in allergic asthma, Feb, J. Transl. Med. 18 (1) (2020) 58, https://doi.org/10.1186/s12967-020-02251-w.
[77] Y. Degboé, et al., Polarization of rheumatoid macrophages by TNF targeting through an IL-10/STAT3 mechanism, Jan, Front. Immunol. 10 (2019) 3, https://doi.org/10.3389/fimmu.2019.00003.
[78] L. Ye, et al., Interleukin-10 attenuation of collagen-induced arthritis is associated with suppression of interleukin-17 and retinoid-related orphan receptor γt production in macrophages and repression of classically activated macrophages, Apr, Arthritis Res. Ther. 16 (2) (2014) R96, https://doi.org/10.1186/ar4544.
[79] X. Zheng, et al., Targeted co-delivery biomimetic nanoparticles reverse macrophage polarization for enhanced rheumatoid arthritis therapy, Drug Deliv. 29 (1) (Dec. 2022) 1025–1037, https://doi.org/10.1080/10717544.2022.2057616.
[80] T. Kobori, et al., Interleukin-18 amplifies macrophage polarization and morphological alteration, leading to excessive angiogenesis, Front. Immunol. 9 (2018) 334, https://doi.org/10.3389/fimmu.2018.00334.
[81] B. Wang, Z. Tan, F. Guan, Tumor-derived exosomes mediate the instability of cadherins and promote tumor progression, Jul, Int. J. Mol. Sci. 20 (15) (2019) 3652, https://doi.org/10.3390/ijms20153652.
[82] M. Yáñez-Mó, et al., Biological properties of extracellular vesicles and their physiological functions, J. Extracell. Vesicles 4 (2015), 27066, https://doi.org/10.3402/jev.v4.27066.
[83] Y. Yang, et al., Targeted silver nanoparticles for rheumatoid arthritis therapy via macrophage apoptosis and Re-polarization, Biomaterials 264 (Jan. 2021), 120390, https://doi.org/10.1016/j.biomaterials.2020.120390.
[84] M.J. Mitchell, M.M. Billingsley, R.M. Haley, M.E. Wechsler, N.A. Peppas, R. Langer, Engineering precision nanoparticles for drug delivery, Nat. Rev. Drug Discov. 20 (2) (Feb. 2021), https://doi.org/10.1038/s41573-020-0090-8. Art. no. 2.
[85] K.W. Witwer, J. Wolfram, Extracellular vesicles versus synthetic nanoparticles for drug delivery, Nat. Rev. Mater. 6 (2) (Feb. 2021) 103–106, https://doi.org/10.1038/s41578-020-00277-6.
[86] T. Limongi, et al., Lipid-based nanovesicular drug delivery systems, Nanomaterials 11 (12) (Dec. 2021) 3391, https://doi.org/10.3390/nano11123391.
[87] Q. Hu, et al., Clinical applications of exosome membrane proteins, Precis Clin Med 3 (1) (Feb. 2020) 54–66, https://doi.org/10.1093/pcmedi/pbaa007.
[88] H. Kim, et al., Extracellular vesicle-guided in situ reprogramming of synovial macrophages for the treatment of rheumatoid arthritis, Biomaterials 286 (Jul. 2022), 121578, https://doi.org/10.1016/j.biomaterials.2022.121578.
[89] C. Lo Sicco, et al., Mesenchymal stem cell-derived extracellular vesicles as mediators of anti-inflammatory effects: endorsement of macrophage polarization, Mar, Stem Cells Transl Med 6 (3) (2017) 1018–1028, https://doi.org/10.1002/sctm.16-0363.
[90] S. Zhao, et al., Tumor-derived exosomal miR-934 induces macrophage M2 polarization to promote liver metastasis of colorectal cancer, Nov, J. Hematol. Oncol. 13 (1) (2020) 156, https://doi.org/10.1186/s13045-020-00991-2.
[91] M.T. Harting, et al., Inflammation-stimulated mesenchymal stromal cell-derived extracellular vesicles attenuate inflammation, Stem Cell. 36 (1) (Jan. 2018) 79–90, https://doi.org/10.1002/stem.2730.
[92] Y. Wang, et al., Mesenchymal stem cell-secreted extracellular vesicles carrying TGF-β1 up-regulate miR-132 and promote mouse M2 macrophage polarization, J. Cell Mol. Med. 24 (21) (Nov. 2020) 12750–12764, https://doi.org/10.1111/jcmm.15860.
[93] A. Del Fattore, et al., Immunoregulatory effects of mesenchymal stem cell-derived extracellular vesicles on T lymphocytes, Cell Transplant. 24 (12) (2015) 2615–2627, https://doi.org/10.3727/096368915X687543.
[94] W. Chen, et al., Immunomodulatory effects of mesenchymal stromal cells-derived exosome, Aug, Immunol. Res. 64 (4) (2016) 831–840, https://doi.org/10.1007/s12026-016-8798-6.
[95] Z. Chen, H. Wang, Y. Xia, F. Yan, Y. Lu, Therapeutic potential of mesenchymal cell-derived miRNA-150-5p-expressing exosomes in rheumatoid arthritis mediated by the modulation of MMP14 and VEGF, J. Immunol. 201 (8) (Oct. 2018) 2472–2482, https://doi.org/10.4049/jimmunol.1800304.
[96] H. Li, et al., M2-type exosomes nanoparticles for rheumatoid arthritis therapy via macrophage re-polarization, J Control Release 341 (Jan. 2022) 16–30, https://doi.org/10.1016/j.jconrel.2021.11.019.