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Original Article

A bibliometrics analysis and visualization of osteoimmunology on osteoarthritis studies

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Abstract: Background: Osteoarthritis (OA), the most prevalent form of arthritis, which affects up to 15% of the adult population. The work presented in this paper focuses on the analysis of the publications on osteoimmunology of OA. The purpose of this paper is to provide inspiration for future research on osteoimmunology of OA. Methods: We extracted all of the English publications relevant to osteoimmunology of OA published from 1991-2020 from the Web of Science. SPSS, GraphPad Prism, Citespace, and VOSviewer were utilized to collect and analyze the publication trends in osteoimmunology of OA. Results: We identified a total number of 1,004 publications with a total number of citations of 35,675 by October 31, 2020. Most publications came from China (26.8%). The United States ranked second, but its average number of citations and H index ranked best (10,130 citations and 55 H-index). Shandong University is the main center of institutional cooperation. Most papers related to osteoimmunology of OA were published in the journal of *Osteoarthritis and Cartilage*. In this field, TAK PP published the most papers (15), while Kotake, S's article was cited the most frequently (1,195). As presented in Figure 6, the 70 keywords, defined as terms that appeared more than 50 times in all papers, were classified into four clusters molecular research, human research, animal research and cell research. Research on cytokines and pathways is the new trend in Molecular research. Conclusion: The current status and global trend of osteoimmunology of OA revealed by this study indicates that there is a strong possibility that the number of papers will increase in the coming year, and the research on cytokines as well as pathways would be the next hot topic.

Keywords: Bibliometrics, osteoimmunology, osteoarthritis, immune cell, osteoclast, osteoblast

Introduction

Osteoarthritis, known as degenerative arthritis, is the most common arthritis worldwide [1]. It is characterized by pain, cartilage degeneration, chronic inflammation and loss of mobility. Numerous risk factors for osteoarthritis have been identified, including age, obesity, genetic basis and previous joint damage [2]. Osteoarthritis has become an important global health concern due to aging populations, with estimates indicating that 250 million individuals are living with the disease at present [3].

There is currently no effective treatment available for OA, only those that delay OA progression: symptomatic treatment and joint replacement [4, 5]. Therefore, there is an urgent needed to study its in-depth mechanism of pathogenesis and to develop new therapeutic approaches. Extensive research has shown that the immune system is crucial to the development of osteoarthritis [6]. It is thought that cartilage antigen-induced autoimmunity contributes significantly to the pathogenesis of chronic inflammatory polyarthritis. Yuan et al. found that antigen exposure promotes the release of cytokines and chemokines when the cartilage is exposed to mechanical stress [7]. The chronic inflammation of the joints eventually results in cartilage damage and total joint destruction [8]. In recent years, synovial pathology has been highlighted as a crucial factor in osteoarthritis initiation and progression. The most abundant infiltrating immune cells in the synovial membrane are monocyte-derived macrophages, followed by mast cells and T cells [9]. It has been accepted that macrophages play important roles in the development of osteoar-

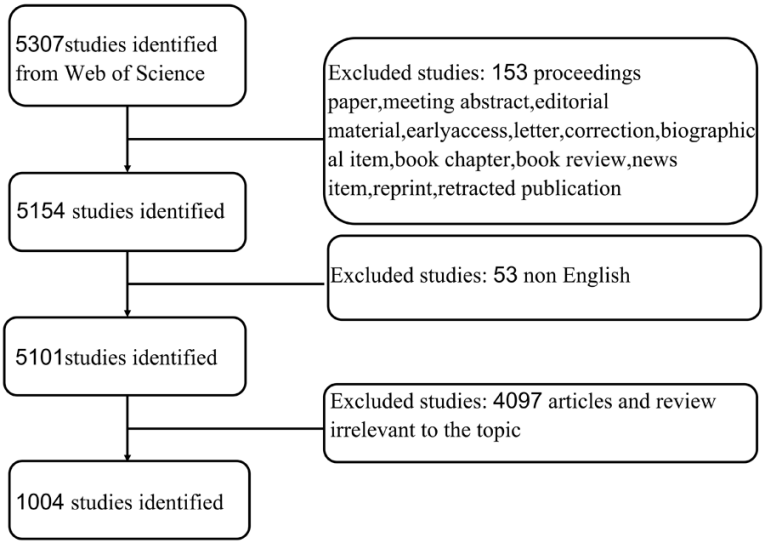


Figure 1. Flow diagram of the inclusion process. The detailed process of screening and enrollment.

thritis. In previous studies, different cytokines were shown to induce different macrophage polarizations (M1 or M2) [10]. Liu et al. found that symptom severity of osteoarthritis is related to macrophage M1/M2 imbalances [11]. Researchers recently reported that the number of synovial mast cells correlates positively with cartilage damage in patients with osteoarthritis, and that mast cells might be responsible for the development of the disease [12]. Qian et al. discovered that the IgE/FcεRI/Syk axis mediates mast cell activation and degranulation, promoting inflammation and releasing pro-fibrotic mediators, leading to osteoarthritis [13]. The role of T cells in osteoarthritis development has received increasing attention in recent years. Osteoclasts are stimulated by Th17 cells through the production of IL-17, and Th1 and Th2 cells inhibit osteoclasts with IFN-γ and IL-4 [14, 15]. Moreover, osteoimmunology, as a new concept, has been a research hot spot in recent years. In osteoarthritis, activated macrophages are required to produce an inflammatory response, indicating that we may be able to treat osteoarthritis specifically by targeting activated macrophages [16]. Hence, we can develop new methods and targets for treating OA through exploring osteoimmunology. Currently, we can modulate bone immunity by influencing the bone microenvironment, such as by affecting osteoclast differentiation and activation, or by altering chondrocyte function [14, 15]. As the expansion of research about the treatment of OA has increased, there have been many papers published each year, and there is an urgent need to summarize these studies.

The bibliometric study uses publication indicators such as journals, authors, institutions and countries to give a general overview of the research field and identify the most influential research in this area [17]. Visualizing the publication data with bibliometric mapping makes it easier to understand the data and highlights the most influential research [18]. Although Xing Dan et al. also reported the research status and hotspots of osteoarthritis by bibliometric analysis, there was no previous bibliometric research on the immune response of osteoarthritis [19]. To explore a comprehensive review of current trends and progress in osteoimmunology, we conducted a bibliometric study, and current trends in osteoarthritis immunity were also discussed in this paper to guide future studies.

Materials and methods

Data sources and search strategies

Web of Science is the world's largest and most comprehensive academic information resource. Publications were obtained from the online database Science Citation Index-Expanded of WOS [20]. The whole process of searching was completed in one day, October 31, 2020, to prevent bias from the rapid updating of the databases. The search strategies were set as follows: TS = (Osteoarthritides OR Osteoarthrosis OR Osteoarthroses OR Arthritis, Degenerative OR Arthritides, Degenerative OR Degenerative Arthritides OR Degenerative Arthritis OR Arthrosis OR Arthroses OR Osteoarthrosis Deformans OR osteoarthritis) AND (macrophage OR neutrophil OR (NK cell) OR (natural killer cell) OR (dendritic cell) OR DC OR (innate lymphoid cells) OR ILCs OR (T cell) OR (T lymphocyte) OR (B cell) OR (B lymphocyte) OR (regulatory T cell) OR (Treg) OR (monocyte) OR (immune dysfunction) OR (immune response)) AND "Language = English". The detailed screening of manuscripts is shown in **Figure 1** [21].

Data collection

The authors (WY and ZPY) independently extracted relevant data from all eligible publications, including titles, keywords, authors, nationalities, publication dates, journals, H-index, the sum of citations, affiliations, and so on. The term relative research interest (RRI) was defined as the proportion of the number of weighted publications per year of the research filed in the collection of all weighted publications per year in web of science, which can better reflect the activity of the research field. Based on the information provided by the Journal Citation Reports (JCRs) published in 2020, the impact factor (IF) has been calculated. The index of H means that a scholar or a country has published H papers at least, and each paper has been cited in other publications at least H times. In this way, the H-index can be used to measure the quality and quantity of researchers' academic output and play a significant role in determining a country's research impact. Considering the limitations of other traditional bibliometrics, it is well suited to evaluating small collections of papers [22]. Meanwhile, the latest information of the gross domestic product (GDP) was retrieved from the websites of the World Bank.

Bibliometric analysis

Descriptive statistical analyses were mainly used. Data from WOS were exported to Microsoft Excel 2013 and then to the Statistical Package for the Social Sciences (SPSS, version 24, IBM Corporation, USA) for analysis. The statistical analysis of the distribution of countries published was performed on Microsoft Excel 2013. The trend analysis was carried out by trend estimation in Nonlinear regression analysis of Statistical Package for the Social Sciences (SPSS, version 24, IBM Corporation, USA). The analysis of cooperation between countries was carried out by using online website (http://bibliometric.com/). GraphPad Prism 8 software was used to plot graphics. Meanwhile, the latest information on the gross domestic product (GDP) was retrieved from the websites of the World Bank.

We used bibliometric indicators, Zipf's law, Price's and Bradford's laws, participation indices for languages and journals to measure the increase or distribution of scientific literature. CiteSpace is a scientific knowledge mapping software. We use links between nodes in the map to visualize bibliometric features such as references, institutions, authors and terms. Then, we use the co-occurrence of keywords to study hotspots and analyze research frontiers in this field. Using the Java programming language, VOSviewer software can generate a variety of graphs based on bibliometric relationships, including organization diagrams and keyword co-occurrence diagrams [23].

Results

Distribution of countries published

In total, 1,004 articles dating from 1991 to 2020 were considered. China ranked first in the number of publications with 270 (26.8%) articles, followed by the USA with 211 (21.0%) and Japan with 109 (10.8%) (**Figure 2A**). Although China has the greatest number of publications, its number of citations is relatively small (2468). The United States has the highest H-index (56) and total citations (10,272). By comparing the number of papers published per year, we found that the largest number of publications was in 2020, with 227 publications (22.6%). We also visualized the cooperation between countries through visualization software (the Online Analysis Platform of Literature Metrology and VOSviewer), and found that the United States had the closest relations with other countries (**Figure 3**).

Trends in global publications

As shown in **Figure 4**, the global cumulative publication numbers and the top 5 countries, as well as the corresponding model fitting curves, have been compiled. The growth curves also revealed that publications worldwide are on a fast trajectory and are expected to continue in the next decade, including in China, the USA and Japan (**Figure 4A-C**). It's worth noting that a decade ago, very few articles were published in China, but China showed an obviously faster growth curve in publications in this field compared to other countries (**Figure 4A**). Moreover, the RRI value in 2018-2020 is rising at a faster pace than that in 2009-2018 (**Figure 2B**). This shows that global interest in osteoimmunology on OA research increased rapidly between 2018 and 2020.

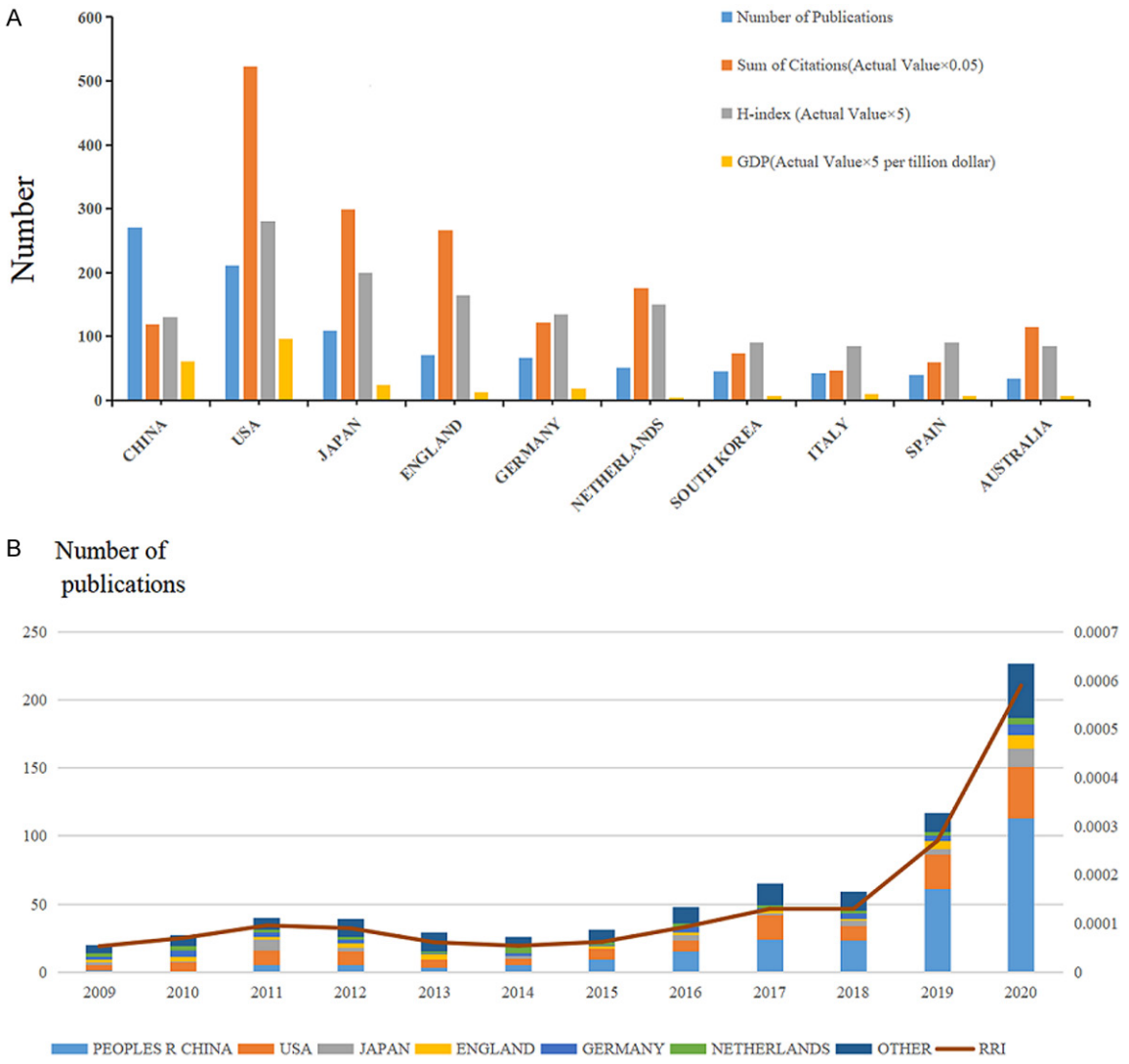


Figure 2. Contributions of different countries/regions to the research field regarding osteoimmunology on OA. A. The number of publications, citation frequency (×0.05), H-index (×5) and GDP (×5, per trillion dollar) in the top 10 countries or regions; B. The number of publications worldwide and the time course of relative research interest of osteoimmunology on OA.

Citations and H-index analysis

According to the Journal Citation Report obtained from the WoS database, all osteoimmunology articles on OA have been cited 35,675 times since 1975 (33,351 times without self-citations), with an average citation frequency of 35.57 times per paper. US citations accounted for 28.3% of the total, 10,130 times (9856 times without self-citations), with an H-index of 55. The number of citations from Japan was 5,684 times (5,640 times without self-citations) with an H-index of 38, and thus Japan ranked second among all involved countries and districts. While China ranked first in the number of publications, it ranked sixth with respect to citation frequency and H-index, even though it had 2368 citations (**Figure 2A**).

Journals with research publications on osteoimmunology of OA

Almost one-third of the papers in this scope were published in 10 journals (313, 31.11%). The number of papers published on *Osteoarthritis and Cartilage* (IF=4.793) was the highest with 53 records. *Arthritis Research Therapy* (IF=4.148) ranked second with 52 publica-

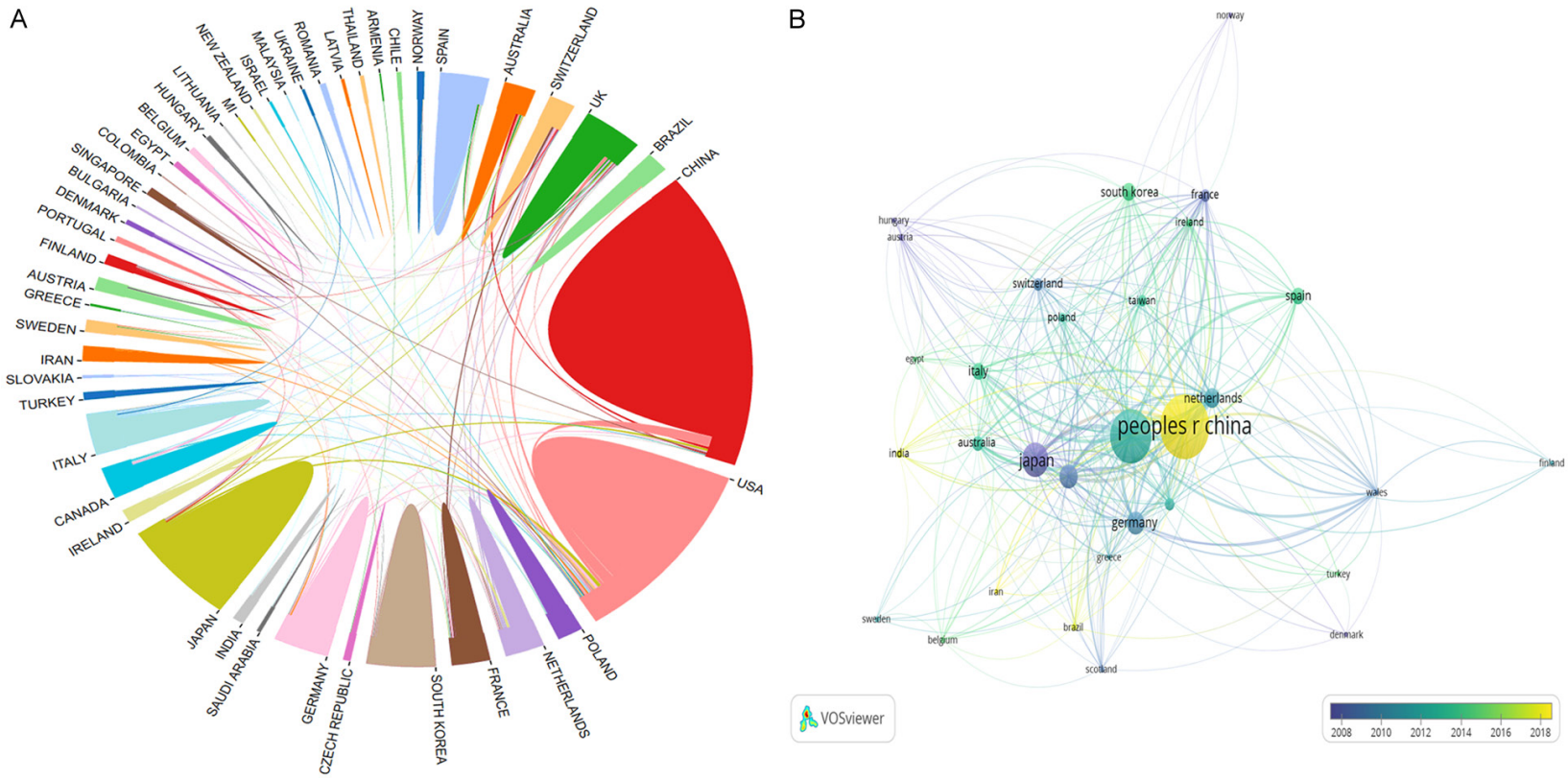


Figure 3. The cooperation network of countries/regions in osteoimmunology on OA. The cooperative relations between countries/regions can be visualized. A. The cooperation relations between countries and regions. B. The network of cooperative relations between nations/regions.

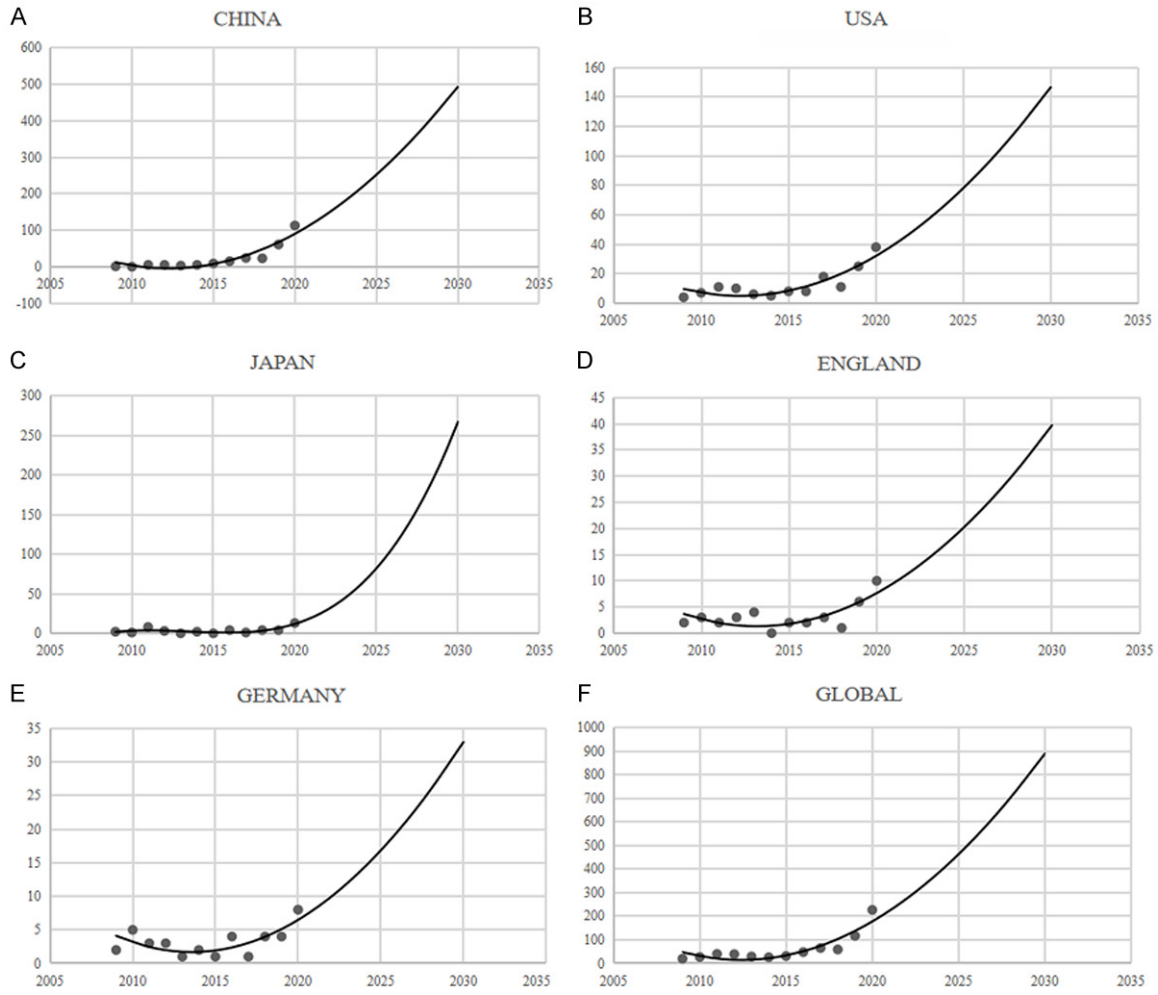


Figure 4. The model fitting curves of growth trends of publications associated with osteoimmunology on OA. A. China; B. USA; C. Japan; D. England; E. Germany; F. Global.

tions. The journal with the highest IF, the British Journal *Annals of the Rheumatic Diseases* (IF=16.102), published 27 papers on osteoimmunology on OA and ranked fourth on publications. The top 10 journals with most publications on osteoimmunology on OA are listed in **Table 1**.

Institutions with research publications on osteoimmunology of OA

With 22 papers each, the University of California system in the United States and the Shandong University in China published the most papers worldwide, equaling 2.19% of all publications. There were 9 USA institutions on the top 20 list, followed by four Chinese institutions, two France institutions, two British institutions, one Japanese institution, one Netherlands institution and one Korean institution (**Table 2**).

We also got the information about the published time of all articles in different kinds of institutions (**Figure 5A**). According to the color scheme, greens indicate early publications in the research stage, while reds reflect more recent publications. According to this figure, Shandong University has been publishing numerous articles in recent years, with the highest number of publications among all institutions. In **Figure 5B** and **5C**, the size of the ball represents the number of publications of the institutions, so Shandong University, Wenzhou Medical University and Duke University are the top three institutions of publications.

Authors with research publications on osteoimmunology of OA

In this research area, 106 papers were published by the top 10 authors, accounting for 10.5% of total publications. TAK PP from the

Table 1. The top 10 journals on osteoimmunology in OA

SCR[a]	Journal	Contribution (%)	H-index	IF[b]
1st	OSTEOARTHRITIS AND CARTILAGE	53 (5.279)	24	4.793
2nd	ARTHRITIS RESEARCH THERAPY	52 (5.179)	25	4.148
3rd	ARTHRITIS AND RHEUMATISM	48 (4.718)	37	7.75
4th	ANNALS OF THE RHEUMATIC DISEASES	38 (3.785)	27	16.102
5th	JOURNAL OF RHEUMATOLOGY	34 (3.386)	21	3.35
6th	JOURNAL OF IMMUNOLOGY	20 (1.992)	20	4.886
7th	INTERNATIONAL IMMUNOPHARMACOLOGY	19 (1.892)	7	3.943
8th	ARTHRITIS RHEUMATOLOGY	17 (1.693)	10	9.586
9th	CLINICAL AND EXPERIMENTAL RHEUMATOLOGY	16 (1.594)	9	3.319
9th	JOURNAL OF ORTHOPAEDIC RESEARCH	16 (1.594)	11	2.728

SCR, standard competition ranking; IF, impact factor. [a]Equal journals have the same rank, and then a gap is left in the ranks. [b]The impact factor was reported according to journal citation reports (JCR) 2020.

Table 2. The top 20 institutes with the most publications on osteoimmunology in OA

Rank	Institution	Contribution (%)	Country
1st	SHANDONG UNIVERSITY	2.191	China
1st	UNIVERSITY OF CALIFORNIA SYSTEM	2.191	USA
3rd	UNIVERSITY OF LONDON	1.992	England
4th	US DEPARTMENT OF VETERANS AFFAIRS	1.892	USA
4th	VETERANS HEALTH ADMINISTRATION VHA	1.892	USA
6th	DUKE UNIVERSITY	1.693	USA
6th	NORTHWESTERN UNIVERSITY	1.693	USA
6th	WENZHOU MEDICAL UNIVERSITY	1.693	China
9th	CATHOLIC UNIVERSITY OF KOREA	1.594	Korea
10th	SHANDONG FIRST MEDICAL UNIVERSITY SHANDONG ACADEMY OF MEDICAL SCIENCES	1.494	China
10th	UNIVERSITY OF AMSTERDAM	1.494	Netherlands
10th	UNIVERSITY OF MICHIGAN	1.494	USA
10th	UNIVERSITY OF MICHIGAN SYSTEM	1.494	USA
14th	ACADEMIC MEDICAL CENTER AMSTERDAM	1.394	USA
14th	ASSISTANCE PUBLIQUE HOPITAUX PARIS APHP	1.394	France
14th	OSAKA UNIVERSITY	1.394	Japan
17th	HARVARD UNIVERSITY	1.295	USA
17th	INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE INSERM	1.295	France
17th	SUN YAT SEN UNIVERSITY	1.295	China
17th	UNIVERSITY OF NOTTINGHAM	1.295	England

University of Amsterdam had published 15 papers related to osteoimmunology on OA, ranking the first in the number of publications. KOCH AE had published 14 papers in total and ranked second among all authors. As shown in **Table 3**, among the top 10 authors with most publications on osteoimmunology on OA, there were three from the USA, two from Japan, two from South Korea, one from China, and one from France and one from the Netherlands. Notably, the citation frequency of all three authors from the USA all exceed 1,000 times (**Table 3**).

Articles with research publications on osteoimmunology of OA

The most cited article in osteoimmunology on OA is about *the role of cytokines in osteoarthritis pathophysiology*. This article focuses on the

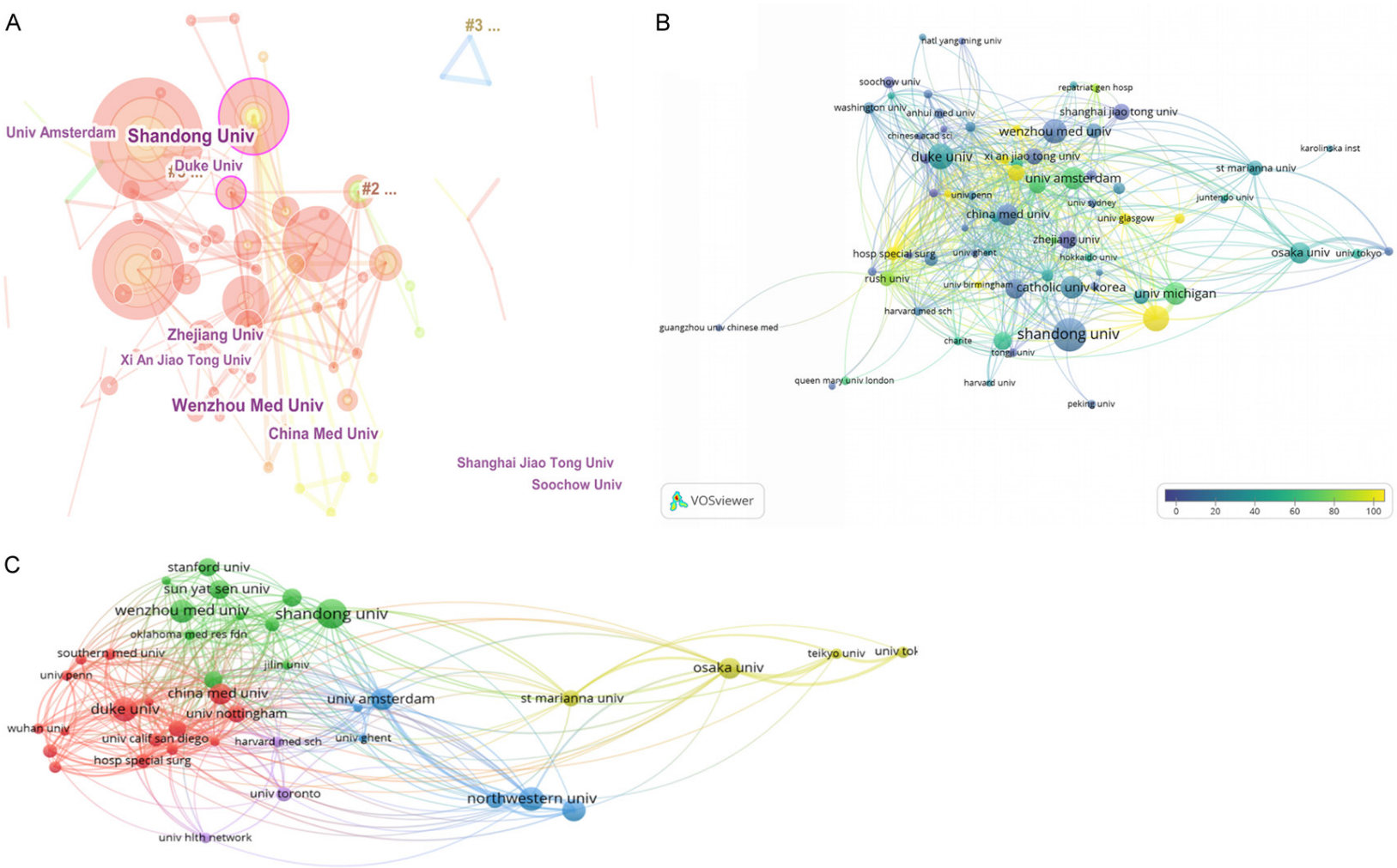


Figure 5. The distribution and association of institutions engaged in research of osteoimmunology on OA. A. The network of institutions by Citespace; B, C. The network of institutions by VOSviewer.

Table 3. The top 10 authors with the most publications in the field of osteoimmunology in OA

Author	Country	Affiliation	No. of Publications	No. of Citations
TAK PP	Netherlands	University of Amsterdam	15	1020
KOCH AE	USA	Eli Lilly	14	1724
KRAUS VB	USA	Duke University	11	345
OCHI T	JAPAN	Japan High Sch Baseball Federat	11	430
HAINES GK	USA	Icahn School of Medicine at Mount Sinai	10	1492
BERENBAUM F	FRANCE	Sorbonne University	9	918
LEE SH	SOUTH KOREA	Sun Moon University	9	211
LIU Y	China	Shandong University	9	29
PARK SH	SOUTH KOREA	Catholic University of Korea	9	296
TOMITA T	JAPAN	Osaka University	9	323

Table 4. Top 10 most-cited papers related to osteoimmunology on OA

Title	Corresponding authors	Journal	Publication Year	Total Citations	Corresponding author's country
The roe of cytokines in osteoarthritis pathophysiology	Fernandes, JC	BIORHEOLOGY	2002	726	Canada
Synovial tissue inflammation in early and late osteoarthritis	Bresnihan, B	ANNALS OF THE RHEUMATIC DISEASES	2005	561	Ireland
The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis	Berenbaum, F	NATURE REVIEWS RHEUMATOLOGY	2010	558	France
The Role of Inflammatory and Anti-Inflammatory Cytokines in the Pathogenesis of Osteoarthritis	Szukiewicz, D	MEDIATORS OF INFLAMMATION	2014	513	Poland
The role of synovitis in osteoarthritis pathogenesis	Scanzello, CR	BONE	2012	468	USA.
NF-kappa B as a potential therapeutic target in osteoarthritis and rheumatoid arthritis	Roman-Blas, JA	OSTEOARTHRITIS AND CARTILAGE	2006	426	USA
Osteoarthritis, angiogenesis and inflammation	Walsh, DA	RHEUMATOLOGY	2005	360	England
Role of Thl7 Cells in Human Autoimmune Arthritis	Schulzc-Koops, H	ARTHRITIS AND RHEUMATISM	1994	296	Germany
Synovial inflammation, immune cells and their cytokines in osteoarthritis a review	de Lange-Brokaar, BJE	OSTEOARTHRITIS AND CARTILAGE	2012	271	Netherlands
The role of synovial macrophages and macrophage-produced cytokines in driving aggrecanases, matrix metalloproteinases, and other destructive and inflammatory responses in osteoarthritis	Bondeson, J	ARTHRIITS RESEARCH & THERAPY	2006	269	Wales

role of cytokine networks in the physiopathology of osteoarthritis. Since its publication in 2002, it has been cited 726 times. The second most cited article was written in 2005 by Bresnihan, B, *Synovial tissue inflammation in early and late osteoarthritis*, which was cited 561 times. Notably, four of the top ten most-cited articles were about synovitis, which partly explains the importance of the synovitis study (**Table 4**).

Analysis of co-occurrence of keywords in publications of osteoimmunology on OA

The co-occurrence analysis reflects the correlation strength between keywords by counting the co-occurrence terms of the words in the literature collection, which can determine the research hotspots in this field [24]. So, we analyzed keywords extracted from 1,004 publications with VOSviewer. As shown in **Figure 6A**, 165 keywords (defined as terms that occurred more than 30 times within titles and abstracts in all papers) were identified and classified into four clusters: molecular research, human research, animal research and cell research. Cluster of "molecular research" was characterized by the following keywords: "pathway" (380 times), "mmp" (357 times), "nf kappa b" (181 times), and "inflammatory mediator" (99 times). In the cluster of "human research", pri-

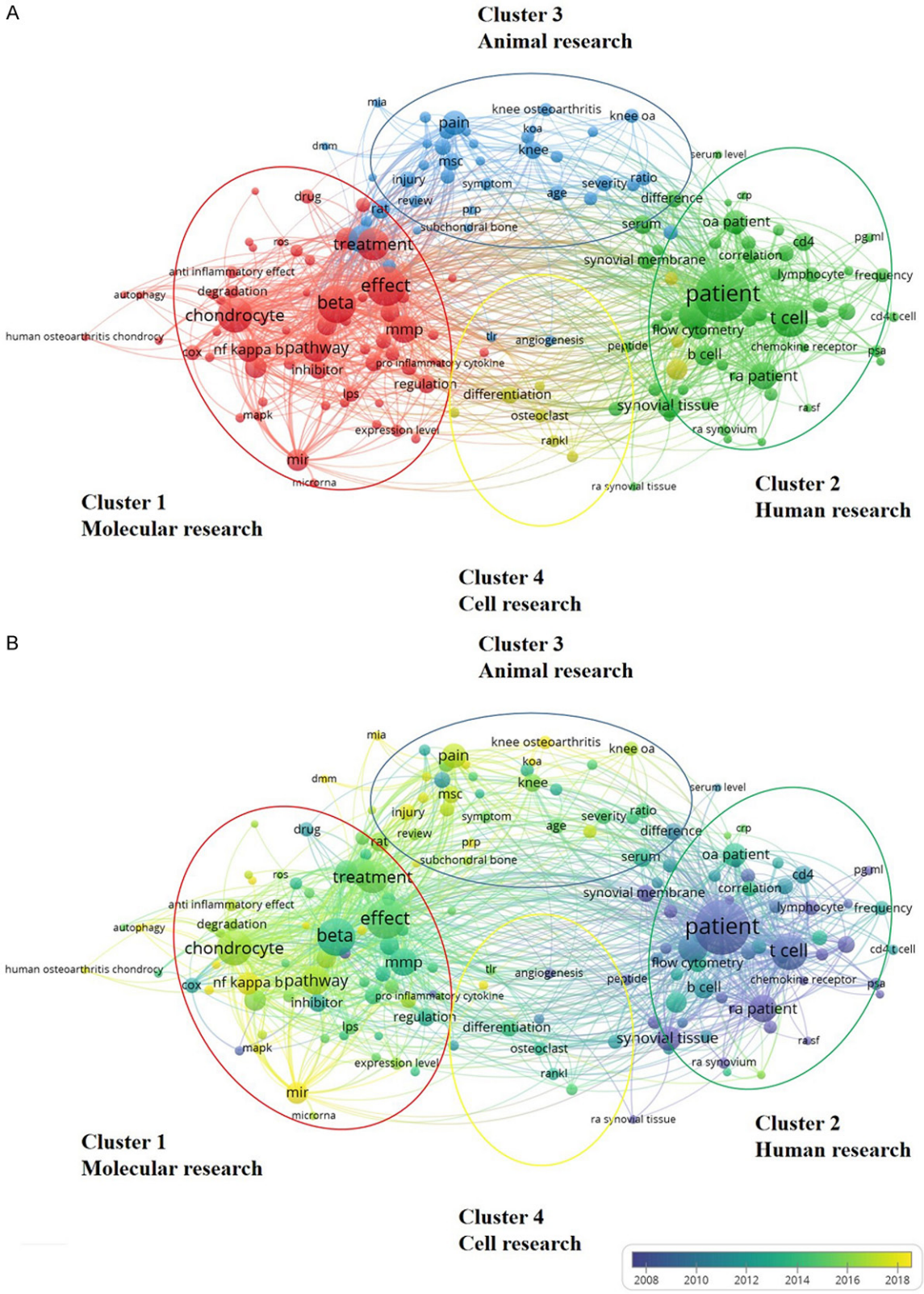


Figure 6. The co-occurrence analysis of all keywords in publications of osteoimmunology on OA. A. Mapping of the keywords in the area of osteoimmunology on OA. The words were divided into 4 clusters in accordance with different colors generated by default, "molecular research" (left in red), "human research" (right in green), and "animal research" (up in blue), "cell research" (below in yellow). Size of the circle represented the frequency of keywords; B. Distribution of keywords was presented under occupation to the average time of application. The blue color repre-

sented early application and yellow color standing for late application. Two keywords were considered co-occurred if the same line in the corpus file. Smaller distance between two keywords individually related higher co-occurrences of the keyword.

mary keywords within publications were "patient" (1379 times), "t cell" (590 times), "synovial tissue" (289 times) as well as "B cell" (201 times). In the cluster of "animal research", relevant keywords were also listed, including "model" (338 times), "synovial tissue" (289 times), "pain" (270 times), "rat" (163 times) and "ratio" (105 times). In the cluster of "cell research", relevant keywords were also listed, including "monocyte" (194 times), "differentiation" (131 times). **Figure 6A** shows details regarding the co-occurrence analysis of all the incorporated keywords.

In **Figure 6B**, VOSviewer colors keywords in accordance with the average time each word appears in the article. In particular, the blue color indicates that the word appears relatively early in the research stage, while the yellow color indicates a more recent entry. For example, in the third cluster, dmm (cluster 3), with an AAY of 2019.5, was the most recently emerging words, which appeared 38 times. In the early stage of research on osteoimmunology of OA, the AAY for mip (cluster 4), which was the major topic in this field, was 2004.7.

More recently, research trends demonstrate that autophagy (cluster 1), with an AAY of 2019.7, maybe a new target. We can also get keyword information from **Figure 7A** below. Tumor necrosis factor is the most prominent keyword, with a strength of 15.1. From 1991 to 2006, it had been strengthened. The next one is the monoclonal antibody, with a strength of 10.5, and the level of research strengthened from 1991 to 1999. The keyword that lasted for a long time was peripheral blood, from 1991 to 2014, with a strength of 8.5. **Figure 7B** mainly describes the clustering situation of different subject terms arranged by time, in which the size of the circle represents the degree of research enthusiasm. As can be seen from **Figure 7B**, the research on cytokines was mainly concentrated in 2016. Since 2016, there has been a great enthusiasm for the study of apoptosis. **Figure 7C** is a visualization of the cross-disciplinary situation in osteoimmunology of OA. As shown in **Figure 7C**, the research on osteoimmunology of OA mainly focused on molecular biology and genes, and also involved some interdisciplinary studies such as material chemistry and physics.

Discussion

Development and status of osteoimmunology on OA

Osteoimmunology was first proposed in 2001, but it had been studied for almost ten years before [25]. Studies have shown that immunity plays a role in osteoarthritis. For instance, rheumatoid arthritis is associated with a different activation pathways than osteoarthritis [26]. Osteoimmunology comprises the integration of the immune and skeletal systems as a new theory to explain the underlying process of osteoarthritis [27, 28]. During the past three decades, 1,004 papers on the immunology of osteoarthritis research had been cited an average of 35.47 times. China contributed the most papers (270), which accounted for 26.9% of all. The H-index represents the quality of publications of a country, the highest H-index and average citation time belonged to the USA (55) and Japan (52.0), respectively (**Figure 1**). Publications on *Osteoarthritis and cartilage* (IF=4.793) consist of the most records (53), and more studies in the field may be published here in the future (**Table 1**). Within the top 10 institutions, four from China and three from the USA simultaneously existed, which suggests that first-class institutions contribute greatly to academic research (**Table 2**). TAK PP is the most published author in this field, so we should keep a close eye on the top authors like TAK PP, who are pioneers in this field (**Table 3**).

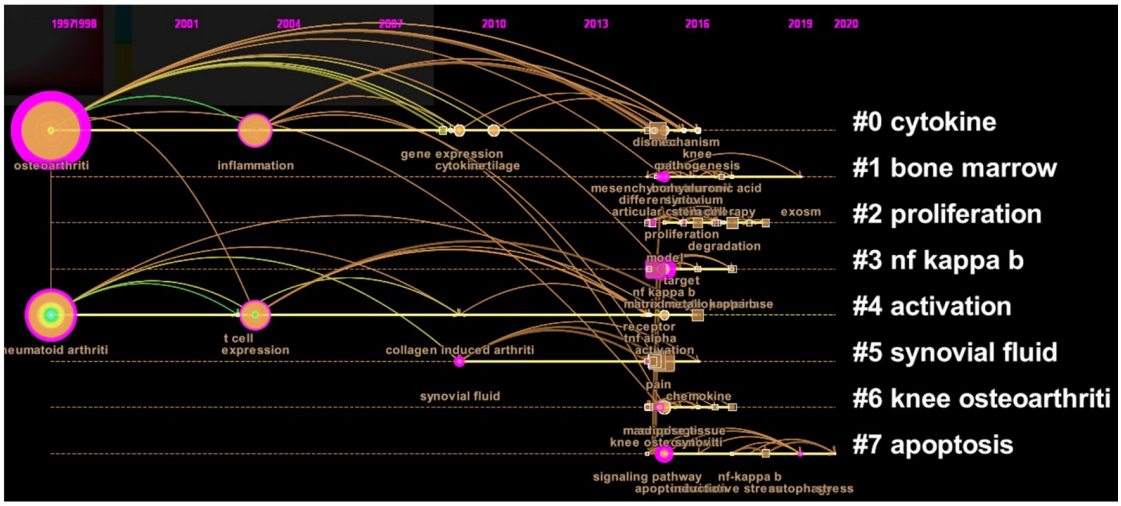
There is a wide variation in the results of publications between countries. To be specific, 58.7% of the total number of applications came from China, the United States and Japan. Also, the number of publications in this field is expected to increase in the future (**Figure 4**). In spite of the highest number of publications, China's H-index and its sum of citations was lower than that of the USA and Japan (**Figure 2A**), possibly due to the dominant role that the USA played in earlier years (**Figure 2B**). Of the

A

Top 16 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	1991 - 2020
human monocyte	1991	5.0752	1991	1998	
induction	1991	5.3121	1991	2009	
factor alpha	1991	4.5279	1991	2005	
lymphocyte	1991	5.1005	1991	2014	
tumor necrosis factor	1991	15.185	1991	2006	
monocyte	1991	3.579	1991	2007	
membrane	1991	5.9523	1991	2008	
interleukin 1	1991	6.3613	1991	2006	
osteo arthriti	1991	4.1276	1991	2002	
peripheral blood	1991	8.5812	1991	2011	
colony stimulating factor	1991	3.7449	1991	2001	
monoclonal antibody	1991	10.503	1991	1999	
fluid	1991	4.6631	1992	2005	
tumor-necrosis-factor-alpha	1991	3.9442	1994	1996	
adhesion molecule	1991	3.7492	1994	1998	
antibody	1991	5.1457	1995	2004	

B



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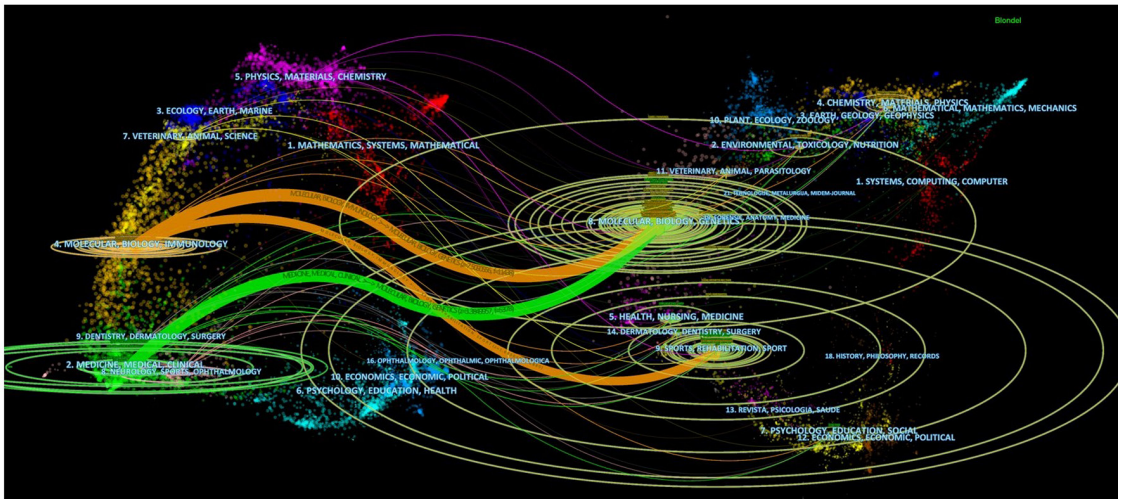

Figure 7. The temporal distribution and clustering of the literature. A. The top 16 keywords with the strongest citation bursts during 2009 to 2020. The red bars represent frequently cited keywords during this time period. The green bars represent infrequently cited keywords; B. The size of the ball reflects the heat of the literature; C. The dual-map overlay of journal, which reflects the clustering of keyword sources.

top 20 published institutions, more than half are based in the United States and China (**Table 2**). We speculate that these phenomena are related to the cooperation between countries (**Figure 3**). For this reason, scientists around the world need to work together. Only in this way can we promote the development and application of osteoimmunology on OA. As for China, Chinese scientists may need to further cooperate with countries other than the United States, which is conducive to the rational distribution of research resources. Meanwhile, Hiroshi Takayanagi from the department of Osteoimmunology of the University of Tokyo has published several influential papers concerning osteoimmunology in *Physiol Rev* (IF= 25.588, 2017) and *Nat Rev Immunol* (IF= 40.358, 2019) [27, 28]. Publication of authoritative masterpiece may explain the proliferation of papers after 2017 (**Figure 2B**). The visible rise of publications from China may be due to their increasing focus on cell biology and immunology. Chinese researchers have found the feasibility of suppressing apoptosis and expression of proinflammatory cytokines in human OA chondrocytes via inhibition of the p38-MAPK signaling pathway [29]. Wang et al. discussed the possibility of using the proinflammatory signaling pathway for the therapeutic target of OA [30]. The focus of Chinese research is consistent with the novel trends in relevant areas as well (**Figure 6**). Additionally, the National Natural Science Foundation of China (NSFC) was able to fund approximately half of the research projects (136/270), which implied that policy support accelerates scientific research to some extent.

The most frequently cited published articles have a relevant academic impact in a particular field. *The Role of cytokines in osteoarthritis pathophysiology* is an influential article about the application of immunotherapy in osteoarthritis, which has been cited 726 times. This article illustrates the role of cytokine networks in the pathology of OA and points out that cytokines such as IL-10 can be a potential target for the treatment of osteoarthritis [31]. Additionally, three of the top ten cited papers study cytokines, which is closely related to the leading frontier of this research. Among these ten articles, three are also related to synovitis, which are respectively about the pathophysiology and clinical manifestations of synovitis, the role of synovitis in clinical symptoms, and the role of synovitis in the pathogenesis of osteoarthritis [32-34]. This shows that the research direction of synovitis has been attracting attention. More importantly, the research indicates that synovial targeted therapy can help alleviate the symptoms of the disease, slowing structural progression, and showing the potential of its future.

Research hotspots and future trends of osteoimmunology on OA

Through statistics on the number of articles published in different research directions in the field of immunotherapy in osteoarthritis, we found that molecular research, human research, animal research and cell research are the four major research directions (**Figure 6**). Combined with the results of co-occurrence analysis of key words and time superposition, the preliminary results show that molecular immunotherapy represented by cytokines is the main development trend in this field (**Figure 7A**, **7C**).

By combining the results of the top research direction with the literature cited in the top 10 citations, this paper found that in the application of using immunotherapy to treat osteoarthritis, the study of cytokines was regarded as the key research content. In the pathogenesis of OA, cytokines contribute to the increased synthesis and release of many proteolytic enzymes that decompose articular cartilage [35]. Julio C pointed out that cytokines could significantly up-regulate the expression of the matrix metalloproteinases (MMP) gene and also inactivate the compensatory synthesis pathway of chondrocytes, which reduces the rate at which the extracellular matrix (ECM) returns to a degraded state [31]. Therefore, exploring the pathogenesis of cytokines in OA is beneficial to the development of immunotherapy in OA. It

has been suggested that cytokine inhibition could be a good strategy for OA treatment. In the field of the application of cytokines to OA, Jan Bondeson et al. found that though the effects of inhibiting each cytokine on its own are less impressive, neutralization of both TNF-α and IL-1β results in significant inhibition of fibroblast-produced cytokines and MMPs [36]. Besides, anti-inflammatory cytokines also have great potential in the immunotherapy of OA. Studies have shown that IL-13 inhibits the proinflammatory effects of TNF [37].

In terms of research hotspots, pathway analysis (cluster 1) is the most popular one. Osteoarthritis signaling comprises several pathways including NF-κB, P38/MAPK, PI3K/AKT/mTOR and SDF-1/CXCR4. There are a wide variety of stimuli that stimulate the classical NF-κB pathway, including RANKL, TNF-α and other inflammatory mediators. In OA, there is an imbalance between matrix metalloproteinase (MMP) and tissue inhibitors of metalloproteinase (TIMP) activity. Furthermore, AGE exposure leads to NF-κB activation, which mediates the upregulation of MMP [38]. Besides, OA chondrocytes also produce TNF-α and IL-1B, both of which are catabolic hormones that signal through NF-κB. Currently, it has been shown that osteoarthritis was effectively treated by inhibiting the NF-κB signaling pathway. Dawei et al. have found that MiR-210 inhibits the NF-κB signaling pathway by targeting DR6 in osteoarthritis [39]. There are studies to support the idea that the PI3K/Akt/mTOR pathway contributes to OA development and progression [40, 41]. In chondrocytes, beta-ecdysterone alleviates osteoarthritis by enhancing autophagy via the PI3K/AKT/mTOR signal pathway [42]. Previous studies showed that targeting the PI3K/Akt/mTOR pathway may be a novel therapeutic method to treat OA. However, simply activating or inhibiting PI3K/AKT/mTOR signaling to protect against OA may be a double-edged sword, since side effects are inevitable. Consequently, it is imperative in the near future to clarify the roles of PI3K/AKT/mTOR in OA during different stages of pathophysiology and to elucidate more specific molecular mechanisms [43]. It is worth noting that among the top 10 cited papers, six of them centered on the pathway, including the cytokines, synovial membrane and nuclear factors in the pathogenesis of OA. This implies that osteoimmunology on OA is based on the study of the pathway.

The word patient from the human cluster (cluster 2) was one of the words that appeared most frequently. Patient is the subject of treatment, different treatment methods should be chosen for different patients, because it will affect the quality of life of patients. This requires that our initial assessment should include a complete history and physical examination to determine the effects of osteoarthritis on function, quality of life, mood, social participation and relationships, occupation, leisure activities, and sleep [44]. Furthermore, the pain management of patients in the treatment process is also a hot topic. At present, in addition to the commonly used first-line analgesics such as paracetamol and NSAID, several new pain treatment methods such as NGF antibody are also being developed [45, 46]. Besides, the effect sizes for the self-management programs were significant for psychological outcomes and overall effect of OA. Therefore, patient education is necessary for better self-management [47].

According to cluster 3 in animal studies, the word model has the highest frequency of occurrence. Animal experiments are an important means to further explore pathogenesis and prevention. More models are used in animal experiments. Common mouse models are related to intramuscular injection drugs, the CIOA model and DMM OA mouse model. Bentley injected 0.3 mL of 4% papain saline solution into the hip joint of rabbits on days 1, 4, and 7, respectively, to establish a stable model of degenerative arthritis [48]. Similarly, in the local intra-articular injection of rapamycin, Gang Xu et al. used the DMM model and found that local intraarticular injection of rapamycin could inhibit the NLRP3 activity of the DMM model in mice and prevent osteoarthritis [46]. Moreover, the DMM model can better reflect the changes of chondral degeneration and subchondral bone with high correlation coefficient [49]. Therefore, DMM has been a new research hotspot in recent years.

In cluster 4, the word monocyte is the most frequent keyword. The synovitis in osteoarthritis is infiltrated by monocytes, which produce inflammatory cytokines such as TNF-α and IL-1β and destructive enzymes such as MMP-1 during the early stages of the disease [32, 50]. Moreover, when monocytes differentiate into macrophages, they will further promote synovial inflammation of OA and play an important

role in the production of degradation mediators. In normal conditions, synovial macrophages exist in a resting state. Macrophages can be categorized into two types based on their activation: classically activated macrophages (M1) and alternatively activated macrophages (M2) when the macrophages are activated [51]. Studies have shown that M1 macrophages are mainly involved in the inflammatory response, whereas M2 macrophages inhibit the inflammatory response [52, 53]. Osteoarthritis severity is associated with the imbalance of M1/M2 macrophages. Multiple studies indicate that macrophage polarization can attenuate the progression of OA, either by causing M2 macrophages or blocking M1 macrophages [21, 54]. Based on these studies, macrophage modulation could play a therapeutic role in OA.

In **Figure 7A**, the word that has received the most attention is lymphocyte, which has declined in popularity in recent years but remained a focus of research. The majority of lymphocytes in the synovial tissue of OA patients are T cells [55]. During the pathogenesis of OA, T cells activation and immune responses play a critical role in bone loss and joint destruction. Furthermore, OA pathology is heavily reliant on T cells, especially Th1, Th9, Th17 and Treg, demonstrating the importance of early widespread T cell activation [56]. The CD4+ T cells can differentiate into effector Th1 cells that secrete IL-2, IL-12, and TNF-α to promote the development of OA [57]. By binding to the RANK ligand (RANKL), TNF-α initiates a bone-degrading pathway and initiates osteoclast maturation [58]. Further study on the role of T cells in osteoarthritis may contribute to provide a new idea for the treatment of arthritis.

Moreover, the intersection of multiple disciplines, such as chemistry and materials engineering, has also accelerated molecular research. Although the role of the immune system in OA is still largely unknown at present, it is obvious that osteoimmunology in OA will have greater potential with the deepening of research on OA.

Limitation

There are some limitations in our study, as we selected only documents published from 1991 to 2020, excluding those published in 2021. Because of this, our bibliometric analysis might not reflect the latest publishing conditions. It is well known that major databases, such as WoS, PubMed, Embase and Cochrane, produce different publications. Therefore, some publications may be missed as a result of bias against the database. In addition, we only include WOS-based English language studies. Publications written in languages other than English, such as Chinese, are excluded. Given a large number of OA patients in these countries, the exclusion of non-English publications may lead to a linguistic bias. As a result of the lack of precision in the search strategy, our search results may be somewhat inadequate. In addition, the results of the bibliometric analysis may be different from the actual research conditions. For example, some recently published high-quality papers may not receive attention because of low citation rates. Thus, it is important to monitor the latest published papers and other non-English publications in daily research.

Conclusions

This study reveals the current status and global trend of osteoimmunology of OA. China leads the world in terms of the total number of articles published, while the United States leads the world in terms of citation frequency. There is a strong possibility that the number of papers will increase in the coming year. It can be predicted that the research on cytokines and pathways will be the next hot topic and will receive increased attention. It is noteworthy that overview macrophages-based therapies have shown promise in treating osteoarthritis. As scientific research is deepened, technological progress is deepened, and clinical medicine is integrated into the process, it is reasonable to believe that osteoimmunology will provide more effective and safer new therapies for OA patients in the near future.

Disclosure of conflict of interest

None.

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