**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 need 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-
A bibliometrics analysis

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 Arthritis, Degenerative OR Degenerative Arthritis OR Degenerative Arthritis OR Arthritis OR Arthroses OR Osteoarthritis 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].

Figure 1. Flow diagram of the inclusion process. The detailed process of screening and enrollment.
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 ($\times 0.05$), H-index ($\times 5$) and GDP ($\times 5$, 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.
A bibliometrics analysis

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).

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

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.
A bibliometrics analysis

Table 1. The top 10 journals on osteoimmunology in OA

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

SCR, standard competition ranking; IF, impact factor. *Equal journals have the same rank, and then a gap is left in the ranks.

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

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

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
A bibliometrics analysis

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.
A bibliometrics analysis

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

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

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

<table>
<thead>
<tr>
<th>Title</th>
<th>Corresponding authors</th>
<th>Journal</th>
<th>Publication Year</th>
<th>Total Citations</th>
<th>Corresponding author's country</th>
</tr>
</thead>
<tbody>
<tr>
<td>The role of cytokines in osteoarthritis pathophysiology</td>
<td>Fernandes, JC</td>
<td>BIORHEOLOGY</td>
<td>2002</td>
<td>726</td>
<td>Canada</td>
</tr>
<tr>
<td>Synovial tissue inflammation in early and late osteoarthritis</td>
<td>Bresnihan, B</td>
<td>ANNALS OF THE RHEUMATIC DISEASES</td>
<td>2005</td>
<td>561</td>
<td>Ireland</td>
</tr>
<tr>
<td>The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis</td>
<td>Berenbaum, F</td>
<td>NATURE REVIEWS RHEUMATOLOGY</td>
<td>2010</td>
<td>558</td>
<td>France</td>
</tr>
<tr>
<td>The Role of Inflammatory and Anti-Inflammatory Cytokines in the Pathogenesis of Osteoarthritis</td>
<td>Szukiewicz, D</td>
<td>MEDIATORS OF INFLAMMATION</td>
<td>2014</td>
<td>513</td>
<td>Poland</td>
</tr>
<tr>
<td>The role of synovitis in osteoarthritis pathogenesis</td>
<td>Scanzello, CR</td>
<td>BONE</td>
<td>2012</td>
<td>468</td>
<td>USA</td>
</tr>
<tr>
<td>NF-kappa B as a potential therapeutic target in osteoarthritis and rheumatoid arthritis</td>
<td>Roman-Blas, JA</td>
<td>OSTEOARTHRITIS AND CARTILAGE</td>
<td>2006</td>
<td>426</td>
<td>USA</td>
</tr>
<tr>
<td>Osteoarthritis, angiogenesis and inflammation</td>
<td>Walsh, DA</td>
<td>RHEUMATOLOGY</td>
<td>2005</td>
<td>360</td>
<td>England</td>
</tr>
<tr>
<td>Role of Th17 Cells in Human Autoimmune Arthritis</td>
<td>Schulze-Koops, H</td>
<td>ARTHRITIS AND RHEUMATISM</td>
<td>1994</td>
<td>296</td>
<td>Germany</td>
</tr>
<tr>
<td>Synovial inflammation, immune cells and their cytokines in osteoarthritis a review</td>
<td>de Lange-Brokaar, BJ E</td>
<td>OSTEOARTHRITIS AND CARTILAGE</td>
<td>2012</td>
<td>271</td>
<td>Netherlands</td>
</tr>
<tr>
<td>The role of synovial macrophages and macrophage-produced cytokines in driving aggreganases, matrix metalloproteinases, and other destructive and inflammatory responses in osteoarthritis</td>
<td>Bondeson, J</td>
<td>ARTHRITIS RESEARCH &amp; THERAPY</td>
<td>2006</td>
<td>269</td>
<td>Wales</td>
</tr>
</tbody>
</table>

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-
A bibliometrics analysis

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 strength endured 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 bibliometrics analysis

Top 16 Keywords with the Strongest Citation Bursts

<table>
<thead>
<tr>
<th>Keywords</th>
<th>Year</th>
<th>Strength</th>
<th>Begin</th>
<th>End</th>
<th>1991 - 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>peripheral blood</td>
<td>1991</td>
<td>8.5812</td>
<td>1991</td>
<td>2011</td>
<td></td>
</tr>
<tr>
<td>antibody</td>
<td>1991</td>
<td>5.1457</td>
<td>1995</td>
<td>2004</td>
<td></td>
</tr>
</tbody>
</table>
A bibliometrics analysis

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 metalloprotease (MMP) and tissue inhibitors of metalloprotease (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 CIA 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 inra-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
A bibliometrics analysis

role in the production of degradation media-
tors. In normal conditions, synovial macro-
phages exist in a resting state. Macrophages
can be categorized into two types based on
their activation: classically activated macro-
phages (M1) and alternatively activated macro-
phages (M2) when the macrophages are acti-
vated [51]. Studies have shown that M1 macro-
phages are mainly involved in the inflammatory
response, whereas M2 macrophages inhibit
the inflammatory response [52, 53]. Osteoar-
thritis severity is associated with the imbalance
of M1/M2 macrophages. Multiple studies indi-
cate that macrophage polarization can attenu-
ate 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
deprecated 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 pathogen-
esis 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 pro-
mote the development of OA [57]. By binding to
the RANK ligand (RANKL), TNF-α initiates a
bone-degrading pathway and initiates osteo-
clast 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 disci-
plines, such as chemistry and materials engi-
neering, has also accelerated molecular re-
search. Although the role of the immune sys-
tem 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 analy-
sis might not reflect the latest publishing
conditions. It is well known that major data-
bases, 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 lan-
guages 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 linguis-
tic 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 exam-
ple, some recently published high-quality
papers may not receive attention because of
low citation rates. Thus, it is important to moni-
tor the latest published papers and other non-
English publications in daily research.

Conclusions

This study reveals the current status and glo-
bal 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, technologi-
cal progress is deepened, and clinical medi-
cine is integrated into the process, it is reason-
able to believe that osteoimmunology will pro-
vide more effective and safer new therapies for
OA patients in the near future.

Disclosure of conflict of interest

None.

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A bibliometrics analysis

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A bibliometrics analysis


