Knowledge mapping of cell therapy in rheumatoid arthritis disease: a bibliometric analysis (2003-2022)

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Research Article

Keywords: Bibliometrics, cell therapy, rheumatoid arthritis, CiteSpace, VOSviewer

Posted Date: May 25th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2971839/v1

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Abstract

Background:

Rheumatoid arthritis (RA) is a chronic autoimmune joint disease characterized by persistent synovitis and systemic inflammation of the joints. Cell therapy, a cellular drug delivery therapy based on the control of immune dysregulation, inflammatory cytokine production, and overall systemic inflammation, is expected to reverse the process of joint destruction when applied to RA. Based on this, the field of cell therapy applied to RA treatment has been gaining attention in recent years and many results have been achieved. Bibliometric analysis can provide insight into the development of a field. This study aims to provide an overview of the knowledge structure and research hotspots of cell therapy in RA through bibliometrics.

Method:

The Web of Science Core Collection (WoSCC) database was used to search the literature on cellular therapies related to RA between 2003 and 2022. VOSviewers, CiteSpace, and the R package "bibliometrics" were used to perform the bibliometric analysis.

Results:

This article includes 8822 articles from 107 countries, mainly from China and the United States. Fluctuating growth in the number of articles published on cell therapy applied to RA. The University of Amsterdam, Harvard University, Karolinska Institutet, and Stanford University are the main research institutions. The journal Arthritis research & therapy is the most popular journal in the field, and the journal Annals of rheumatic diseases is the most frequently cited. 41982 authors have published in this field, including more collaborative publications; Tak, paul p, Emery, paul, Doemer, Thomas, Isaacs, john d, Tanaka, and Yoshida have published several papers, while Arnett Fc is the author of most frequently cited paper. The University of Amsterdam has been extensively involved in the publication of papers on this topic. Swedish and Korean scientists have published fewer relevant papers as corresponding authors, but have been extensively involved in the investigation of this topic. Studying the mechanisms of various factors (e.g. immune cells, immune molecules, cytokines, and inflammatory responses) in the occurrence and development of RA and studying the therapeutic strategies of cellular therapies for the future precision treatment of RA are the two main topics in this research area. "T cells", "bone marrow (BM) transplantation", "mesenchymal cells", and "monoclonal antibodies" are the emerging research top keywords of the hot spots.

Conclusion:

This article is the first bibliometric study that comprehensively summarizes the research trends and their developments in the application of cell therapy to the treatment of RA. The content includes recent research results and hot directions in the field, providing reference information for scholars studying cell therapy and RA.

1. Introduction

RA is one of the most common chronic autoimmune joint diseases, characterized by persistent synovitis and systemic inflammation of the joints and associated with autoantibodies targeting various molecules, including modified autoepitopes. Its etiology and pathogenesis are complex and can involve a combination of genetic, infectious, environmental, and other factors. Autoimmune reactions leading to impaired function and repair of the innate and adaptive immune systems underlie the onset and development of RA.

At present, RA is not completely curable, and its treatment mainly relies on non-steroidal anti-inflammatory drugs, traditional disease-modifying anti-rheumatic drugs (DMARDs), glucocorticoids, botanical preparations and other drug treatments, which can improve patients' disease symptoms to some extent, but there are various adverse effects and toxic side effects with long-term use. The advent of biologics has slowed disease progression in RA patients, but their use is limited by their high price, lack of organ-targeting specificity, and the development of drug resistance in some patients.

Therefore, finding safer and more efficient therapies by identifying key cells or cell subpopulations and cytokines are crucial for RA patients, and cell therapy has a promising future in the treatment of RA.

Cell therapy includes targeted cell therapy and cell transplantation therapy. Targeted cell therapy is a treatment modality that targets an already defined disease-causing site, which can be either a disease-causing cell or a cytokine. By designing the appropriate therapeutic drug
so that it enters the body and specifically selects the disease-causing site and binds, it causes specific death of the disease-causing cells without affecting the surrounding normal tissue cells. When applied to RA treatment, it can target T cells, B cells, cytokines, and synovial fibroblast-like synoviocytes (FLS). Cell transplantation is the use of certain cells with specific functions, which are treated with bioengineering methods, in vitro expansion, or special culture to make them more therapeutic, and then returned to the body to treat diseases. Most cell therapies use cells with potential immunomodulatory properties and regenerative potential. Cell transplantation therapies such as hematopoietic stem cells, mesenchymal stem cells (MSCs), and induced versatile stem cell (iPSCs) transplantation have had a profound impact on the treatment of RA.

The term bibliometrics was first coined by Pritchard in 1969 and uses quantitative methods to describe, evaluate and monitor published research. We use bibliometric methods to describe the progress of cell therapy in the treatment of RA to provide information on the application of cell therapy in the treatment of RA without subjective bias and to provide new ideas for clinical practitioners.

2. Method
2.1 Search Strategy
We conducted a literature search in the Web of Science Core Collection (WoSCC) database (https://www.webofscience.com/wos/woscc/basic-search) on August 21, 2022. The search formula was ((TS = (cell therapy)) AND TS = (rheumatoid arthritis)) AND LA = (English), spanning from January 2003 to August 2022, with a search period ending on August 21, 2022, with article type limited to articles or reviews and language limited to English (Fig. 1). The search results are then recorded in "plain text" format as “full record and references cited”. All searches and data downloads were completed on August 21, 2022, to minimize errors caused by frequent database updates.

2.2 Data Analysis
VOSviewer (version 1.6.18) is a freely available computer program developed for building and viewing bibliometric maps, with the function of displaying large bibliometric maps in an easily interpretable manner. VOSviewer software offers three types of visualization maps: network, overlay, and density visualization. In our study, VOSviewer software accomplished the following analyses: analysis of RA-related journals and co-cited journals in cell therapy, analysis of countries and institutions, analysis of authors, analysis of co-cited references, and analysis of keyword co-occurrence.

CiteSpace (version 6.1.R1) is a Java application for analyzing and visualizing co-citation networks. It is a system used by scientists, science policy researchers, and graduate students to detect and visualize trends and fundamental changes in scientific disciplines over time. Understanding the dynamics of how transient articles change the knowledge landscape in science is of great practical importance to scientists across disciplines. The main goal of CiteSpace is to facilitate the analysis of emerging trends in the knowledge field, providing an experimental platform for researching new ideas and comparing existing methods. CiteSpace makes it easier for analysts to conduct quantitative and qualitative research in scientific subject areas. CiteSpace software accomplished the following analyses in the study: biplot coverage of journals in cell therapy studies in RA, reference analysis, keyword co-occurrence analysis, etc.

The application of the R package "bibliometrics" (version 3.2.1) (https://www.bibliometrix.org) makes it easy to work with large databases and provides a wide range of highly scalable statistical and graphical techniques. The R package is powerful enough to perform analyses and create new functions automatically or manually, often with contributions from distinguished statisticians; the tools used for programming in R are flexible enough to be quickly upgraded and integrated with other statistical R packages, so it is often used in the ever-changing science of bibliometrics. In this article, the R package is mainly involved in the completion of publications and cell therapy in RA subject analysis, country analysis, and corresponding author analysis.

In addition, a quantitative analysis of publications was performed using Microsoft Office Excel 2019.

3. Results
3.1 Quantitative analysis of the publications
According to our search strategy, there were 8822 publications on cellular therapies for RA in the past 20 years, including 5987 "articles" and 2835 "reviews". The 8822 papers used in this study were from 41982 authors at 7556 institutions in 107 countries, published in 1678 journals, and cited 304556 citations from 18124 journals. In terms of the number of articles issued each year, the overall fluctuations
throughout the period were relatively flat (Figure 2). From 2003 to 2009, the number of publications on cell therapy applied to RA showed a fluctuating upward trend, with an average of 317 publications per year; from 2010 to 2013, the number of publications on cell therapy applied to RA was stable; from 2014 to 2021, the number of related papers published showed a fluctuating upward trend. It is evident that many scholars are continuing to focus on the application of cell therapy to RA, and with this trend, the number of articles published in this field is likely to rise in 2022 and continue to rise in the coming years.

3.2 Journals and co-cited academic journals

We found 8822 articles related to RA in cell therapy published in 1678 academic journals (Table 1). Arthritis research & therapy (292, 3.31%), an international, open-access, peer-reviewed journal established in 1999, has the highest number of outputs and tends to publish original articles in the field of arthritis research and its treatment. This journal focuses on several factors associated with rheumatic autoimmune diseases, with an emphasis on the immune processes of inflammation, injury, and repair. The journal Arthritis research & therapy is like a little starlight in the sky on the subject of cell therapy for RA. As more and more scholars join, the journal's influence gradually deepens, and the field continues to develop, a little starlight can eventually become a sea of stars. This was followed by Arthritis research & therapy (240, 2.72%), Frontiers in immunology (212, 2.40%), Frontiers in Physiology (25, 2.41%), and Annals of the rheumatic diseases (193, 2.19%). The top five impact factors among the 32 journals in rheumatology are Lancet, Nature, Annals of the rheumatic diseases, Arthritis research & therapy, and Osteoarthritis and Cartilage. Among the top 15 journals, Annals of the rheumatic disease has the highest impact factor (IF: 27.973), the official journal of the European League Against Rheumatic Diseases, dedicated to promoting the highest level of scientific communication and education, and the third highest impact factor among 32 journals in the field of rheumatology. This was followed by Autoimmunity reviews with an IF of 17.39.

The purpose of the co-citation analysis is to capture the high-frequency cited papers in the field and the journals that publish them, intending to measure the degree of relationship between articles. The size of a journal's impact depends on its co-citation frequency, reflecting the journal's influence in a particular field of study. Of the 18,124 co-cited journals, six have been cited more than 1,000 times.

As shown in Table 1, Annals of the rheumatic diseases (22518) was the most frequently cited journal, followed by Arthritis rheum-us (21342) and Journal of immunology (21240). Among the top 15 journals, Lancet has the highest IF (202.731), and it is not only the world's leading independent general medical journal, but it also has the highest impact factor among 32 journals in the field of rheumatology, making it the leading journal in this field of research. It aims to publish articles of the highest standard through rigorous editing and peer review to ensure the scientific value and clinical relevance of diverse content, thereby enriching physicians’ clinical insights and raising their awareness of current issues in global medical practice to meet the needs of clinical practice. The second is the New england journal of medicine, with an IF of 176.079 New england journal of medicine, the world's longest continuously published medical journal, is a refereed medical journal and general medical journal founded by the Massachusetts Medical Society in 1811, often ranked as the world's highest impact factor journal in the field of medicine, with a very rigorous review process, mainly providing important, unpublished research results, clinical findings, and ideas. The journal focuses on the practical nature of the articles and publishes articles with mostly clinical practice recommendations. These two journals are like lighthouses for the subject. Inevitably, there are various problems and setbacks in academic research, and they are the inextinguishable beacons opposite scholars when they are sailing in the rain, always guiding the scholars on their way forward.

According to the 2022 Journal Citation Report, all the cited journals were distributed in the Q1 region of the top 15 journals except Journal of immunology, Journal of rheumatology, Journal of biological chemistry which were distributed in the Q2 region, and Arthritis rheum-us journal which was not included in the JCR. Annals of the rheumatic diseases is one of the top 15 journals with a high impact factor and is the most frequently cited journal among the co-cited journals, which shows that this journal has a far-reaching impact on the subject of research. The 1,678 academic journals and 18,124 co-cited journals are the footsteps of a quartet chasing the sun, the wings of an eagle not resting when the wind is raging, and each of them is like a small green leaf that decorates the whole spring.

We screened 40 journals based on the minimum number of relevant publications equal to 30, and the journal network was mapped by VOSviewer for journal mapping (Fig. 3A). Figure 3A shows the relationship between the individual journals. The co-citation mapping of journals was performed by VOSviewer, setting the threshold of the minimum number of journal co-citations to 2006, leaving 40 journals for co-citation analysis of cited journals, and the final co-citation relationship mapping was presented in Fig. 3B.
Table 1
Top 10 journals and co-citations of cell therapy in RA

<table>
<thead>
<tr>
<th>No.</th>
<th>Journal</th>
<th>Count(%)</th>
<th>IF(2022)</th>
<th>JCR</th>
<th>Co-cited journal</th>
<th>Citations</th>
<th>IF(2022)</th>
<th>JCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Arthritis research &amp; therapy</td>
<td>292(3.31%)</td>
<td>5.606</td>
<td>Q1</td>
<td>Annals of the rheumatic diseases</td>
<td>22518</td>
<td>27.973</td>
<td>Q1</td>
</tr>
<tr>
<td>2</td>
<td>Arthritis rheum-us</td>
<td>240(2.72%)</td>
<td>0.000</td>
<td>Not included</td>
<td>Arthritis rheum-us</td>
<td>21342</td>
<td>7.764(2015)</td>
<td>Not included</td>
</tr>
<tr>
<td>3</td>
<td>Frontiers in immunology</td>
<td>212(2.40%)</td>
<td>8.786</td>
<td>Q1</td>
<td>Journal of immunology</td>
<td>21240</td>
<td>5.426</td>
<td>Q2</td>
</tr>
<tr>
<td>4</td>
<td>Annals of the rheumatic diseases</td>
<td>193(2.19%)</td>
<td>27.973</td>
<td>Q1</td>
<td>Arthritis &amp; Rheumatology</td>
<td>15046</td>
<td>5.606</td>
<td>Q1</td>
</tr>
<tr>
<td>5</td>
<td>Rheumatology</td>
<td>177(2.01%)</td>
<td>7.046</td>
<td>Q1</td>
<td>New england journal of medicine</td>
<td>11050</td>
<td>176.079</td>
<td>Q1</td>
</tr>
<tr>
<td>6</td>
<td>Autoimmunity reviews</td>
<td>131(1.48%)</td>
<td>17.390</td>
<td>Q1</td>
<td>Blood</td>
<td>10747</td>
<td>25.476</td>
<td>Q1</td>
</tr>
<tr>
<td>7</td>
<td>Clinical and experimental rheumatology</td>
<td>130(1.47%)</td>
<td>4.862</td>
<td>Q2</td>
<td>Journal of rheumatology</td>
<td>9727</td>
<td>5.346</td>
<td>Q2</td>
</tr>
<tr>
<td>8</td>
<td>Plos one</td>
<td>127(1.44%)</td>
<td>3.752</td>
<td>Q2</td>
<td>Journal of Experimental Medicine</td>
<td>9541</td>
<td>17.579</td>
<td>Q1</td>
</tr>
<tr>
<td>9</td>
<td>Journal of rheumatology</td>
<td>119(1.35%)</td>
<td>5.346</td>
<td>Q2</td>
<td>Arthritis research &amp; therapy</td>
<td>9498</td>
<td>5.606</td>
<td>Q1</td>
</tr>
<tr>
<td>10</td>
<td>Journal of immunology</td>
<td>107(1.21%)</td>
<td>5.426</td>
<td>Q2</td>
<td>Proceedings of the National Academy of Sciences of the United States of America</td>
<td>8800</td>
<td>12.779</td>
<td>Q1</td>
</tr>
<tr>
<td>11</td>
<td>Rheumatology international</td>
<td>93(1.05%)</td>
<td>3.580</td>
<td>Q3</td>
<td>Rheumatology</td>
<td>8619</td>
<td>7.046</td>
<td>Q1</td>
</tr>
<tr>
<td>12</td>
<td>Clinical and experimental immunology</td>
<td>90(1.02%)</td>
<td>5.732</td>
<td>Q2</td>
<td>Nature</td>
<td>7200</td>
<td>69.054</td>
<td>Q1</td>
</tr>
<tr>
<td>13</td>
<td>Clinical rheumatology</td>
<td>90(1.02%)</td>
<td>3.650</td>
<td>Q3</td>
<td>Journal of clinical investigation</td>
<td>7174</td>
<td>19.456</td>
<td>Q1</td>
</tr>
<tr>
<td>14</td>
<td>International journal of molecular sciences</td>
<td>90(1.02%)</td>
<td>6.208</td>
<td>Q1</td>
<td>Lancet</td>
<td>6717</td>
<td>202.731</td>
<td>Q1</td>
</tr>
<tr>
<td>15</td>
<td>International immunopharmacology</td>
<td>88(1.00%)</td>
<td>5.714</td>
<td>Q1</td>
<td>Journal of biological chemistry</td>
<td>6206</td>
<td>5.486</td>
<td>Q2</td>
</tr>
</tbody>
</table>

IF, Impact Factor; JCR, Journal Citation Reports

Figure 4 shows the double map overlay of journals, which shows the citation relationship between journals and co-cited journals. The clustering of cited journals is shown on the left, and the cited clustered journals are shown on the right. The orange and green paths are the two main citation paths. The orange path represents studies published in Molecular/Biology/Immunology journals that are primarily cited in Molecular/Biology/Genetics and Health/Nursing/Medicine journals; the green path represents studies published in green pathway represents studies published in Medicine/Medical/Clinical journals that are primarily cited in Molecular/Biology/Genetics and Health/Nursing/Medicine journals.

### 3.3 Geography and author distribution

To understand which countries contribute most to research in the field of cell therapy RA, this paper analyzes the volume of publications from 107 countries. The results are visualized by VOSviewer for countries with more than or equal to 88 posts and are shown in Fig. 5. The larger the circle node in the figure, the more the number of articles issued; the node connecting line represents the association strength, the thicker the line indicates the more the number of articles issued by two countries in cooperation; the node color represents different clusters. As can be seen from the figure, the distribution of publications in this field is very uneven in terms of countries, and the top effect is very significant, with most of the papers being authored by scholars from a few countries.
In addition to the number of papers published, the number of citations of a country’s published papers reflects its contribution to the field. Table 2 shows the top 10 countries in terms of papers published and the number of citations to their articles. The United States published the most papers and was cited more frequently, with upwards of 14,000 citations. The second most published country is China, with 5,000 citations. The most cited papers were in the UK, with 891 papers cited 62,807 times, and the average number of citations per paper can be as high as 70. In contrast, although a certain number of papers have been published by Chinese scholars on this topic, Chinese articles in the field have not received many citations. Although the ranking order in Fig. 3 and Table 2 do not precisely match, the countries/regions in Table 2 all appear in Fig. 3. This means that the countries most involved in this topic are also the main drivers of this topic.

These articles come from 107 countries and 7,556 institutions. As shown in Table 2, the most important number of publications came from the United States (2615, 30.05%) and China (1217, 13.80%), followed by England (891, 10.10%), Japan (701, 7.95%) and Germany (681, 7.12%). These two highest-ranked countries accounted for almost half of the total number of articles (43.85%). Several countries and institutions, such as the United States (0.21), Germany (0.12), Stanford University (0.12), and Karolinska Institutet (0.11), have a high centrality, representing them as more representative of this research theme.

Figure 6 shows the top 20 countries with the most published articles (corresponding authors’ countries). The United States produced the most results within this field, participating in the writing of 2,058 papers. China is second only to the United States in terms of the number of papers published, with 1107 papers. All countries participated in international collaborative research to a greater or lesser extent, with 416, 167, and 211 papers from the United States, China, and the United Kingdom, respectively, being joint publications from multiple countries. The 20 countries in Fig. 6 have formed a network of international cooperation, a phenomenon that shows that although international cooperation is infrequent in each country, there is a sense of international cooperation.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Country</th>
<th>Count(%)</th>
<th>Centrality</th>
<th>Total Citations</th>
<th>Institution</th>
<th>Count(%)</th>
<th>Centrality</th>
<th>Total Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>USA</td>
<td>2615(30.05%)</td>
<td>0.21</td>
<td>14167</td>
<td>Univ Amsterdam(Netherlands)</td>
<td>131(1.48%)</td>
<td>0.07</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>CHINA</td>
<td>1217(13.80%)</td>
<td>0.02</td>
<td>5085</td>
<td>Harvard Univ(USA)</td>
<td>115(1.30%)</td>
<td>0.09</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>ENGLAND</td>
<td>891(10.10%)</td>
<td>0.2</td>
<td>10393</td>
<td>Karolinska Inst(Sweden)</td>
<td>102(1.16%)</td>
<td>0.11</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>JAPAN</td>
<td>701(7.95%)</td>
<td>0.08</td>
<td>2647</td>
<td>Stanford Univ(USA)</td>
<td>100(1.13)</td>
<td>0.12</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>GERMANY</td>
<td>681(7.12%)</td>
<td>0.12</td>
<td>5521</td>
<td>Univ Leeds(UK)</td>
<td>91(1.03)</td>
<td>0.05</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>ITALY</td>
<td>645(7.31%)</td>
<td>0.07</td>
<td>4667</td>
<td>Univ Calif San Diego(USA)</td>
<td>86(0.97%)</td>
<td>0.05</td>
<td>29</td>
</tr>
<tr>
<td>7</td>
<td>NETHERLANDS</td>
<td>506(5.74%)</td>
<td>0.04</td>
<td>5640</td>
<td>Mayo Clin(USA)</td>
<td>84(0.95%)</td>
<td>0.04</td>
<td>27</td>
</tr>
<tr>
<td>8</td>
<td>FRANCE</td>
<td>458(5.20%)</td>
<td>0.07</td>
<td>4963</td>
<td>Johns Hopkins Univ(USA)</td>
<td>64(0.72%)</td>
<td>0.05</td>
<td>28</td>
</tr>
<tr>
<td>9</td>
<td>SPAIN</td>
<td>312(3.53%)</td>
<td>0.08</td>
<td>2612</td>
<td>Brigham &amp; Womens Hosp(USA)</td>
<td>62(0.70%)</td>
<td>0.07</td>
<td>45</td>
</tr>
<tr>
<td>10</td>
<td>SWEDEN</td>
<td>231(2.62%)</td>
<td>0.04</td>
<td>2481</td>
<td>Inserm(France)</td>
<td>54(0.61%)</td>
<td>0.06</td>
<td>5</td>
</tr>
</tbody>
</table>

An analysis of the authors of the literature reveals the representative scholars and core research teams in the research area. Table 3 shows the highly productive authors with more than or equal to 25 publications in this field. Among the highly productive authors, the most prolific posters are Tak, and Paul Peter. A total of 46 publications from 2003 to August 2022, which received 2862 citations, with an average of about 62 citations per article; In second place is Emery, Paul, with 45 articles, 4,497 citations, and about 99 citations per article. Tak, Paul Peter belongs to the Department of Rheumatology and Clinical Immunology at the Amsterdam Rheumatology and Immunology Center in the Netherlands and has studied cell therapy in the treatment of RA.
Table 3
Most important authors in the cell therapy and RA big data research field

<table>
<thead>
<tr>
<th>Rank</th>
<th>Author</th>
<th>Publications</th>
<th>Citations</th>
<th>Average Citation/Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tak, paul p</td>
<td>46</td>
<td>2862</td>
<td>62.22</td>
</tr>
<tr>
<td>2</td>
<td>Emery, paul</td>
<td>45</td>
<td>4497</td>
<td>99.94</td>
</tr>
<tr>
<td>3</td>
<td>Doemer, thomas</td>
<td>35</td>
<td>2429</td>
<td>69.40</td>
</tr>
<tr>
<td>4</td>
<td>Isaacs, john d,</td>
<td>28</td>
<td>1846</td>
<td>65.92</td>
</tr>
<tr>
<td>5</td>
<td>Tanaka, yoshiya</td>
<td>25</td>
<td>784</td>
<td>31.36</td>
</tr>
</tbody>
</table>

Figure 7 shows the nine affiliations with the highest number of publications on cellular therapies applied to RA. The University of Amsterdam is involved in 186 publications on this topic and has a clear advantage in terms of the total number. Harvard University came in second with 152 articles. Stanford University, the University of Rochester, and the University of Pennsylvania were all involved in the publication of at least 126 papers. The affiliations in Fig. 7 include the United States, the Netherlands, Sweden, the United Kingdom, and South Korea. Except for Sweden and South Korea, these affiliations are the top-ranked countries in Fig. 5. This means that Swedish and Korean scientists have been extensively involved in the investigation of this topic, even though they have published few papers as corresponding authors.

3.4. Literature analysis

3.4.1 Co-cited references

In 1988, Arnett Fc et al. published the most co-cited study that proposed new classification criteria for RA in both traditional and tree-like formats, which laid the foundation for therapeutic research in RA. Four of these 10 total cited papers were published in the New england journal of medicine.

Over the past two decades, there are 304,556 co-cited references on research on cell therapy in RA. Of the top 10 co-cited references (Table 3), all references were co-cited at least 147 times, and one reference was co-cited more than 625 times. We selected references with co-citations greater than or equal to 147 to construct the co-citation network graph (Fig. 6). According to Fig. 6, "Arnett Fc, 1988, Arthritis Rheum" shows active co-citation relationships with "Edwards Jcw, 2004, New Engl J Med", "Mcinnes Ib, 2011, New Engl J Med" and "Firestein Gs, 2003, Nature", among others.

Table 4
Top 10 co-cited references for cell therapy in RA studies

<table>
<thead>
<tr>
<th>Rank</th>
<th>Co-cited reference</th>
<th>Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Arnett Fc, 1988, Arthritis Rheum, V31, P315</td>
<td>629</td>
</tr>
<tr>
<td>5</td>
<td>Cohen Sb, 2006, Arthritis Rheum-us, V54, P2793</td>
<td>322</td>
</tr>
<tr>
<td>6</td>
<td>Lipsky Pe, 2000, New Engl J Med, V343, P1594</td>
<td>267</td>
</tr>
<tr>
<td>8</td>
<td>Bongartz t, 2006, Jama-j Am Med Assoc, V295, P2275</td>
<td>251</td>
</tr>
</tbody>
</table>

3.4.2 Burst citation of literature
Burst-cited references are those that are frequently cited by scholars in a particular field over some time. In our study, CiteSpace identified 15 references with strong citation bursts (Fig. 9). As shown in Fig. 9, the blue line is the timeline, and the blue timeline shows a red segment representing a strong citation burst, which can also indicate the start year, end year, and duration of the reference of the strong citation burst. Burst citation references appeared as early as 2003 and as late as 2019. The reference with the strongest citation burst (intensity = 84.77) was titled 'Observations on the efficacy of rituximab b-cell targeted therapy for RA' by Edwards, J. C. et al. The years of the citation burst were 2005 to 2009. The study conducted by Edwards, J. C. et al. provides clear evidence that a single short course of rituximab is clinically significant in patients with active RA and has attracted the most scholarly citations. The second strongest citation burst (intensity = 58.8) was for a reference titled 'Pathogenesis of RA' published in the New England Journal of Medicine by McInnes, I. B et al. The citation burst years was 2012 to 2016. This reference, with an impact factor of 176.079 and 2232 citations to date, summarizes the key mechanistic issues of RA, as shown in Table 5. Overall, the burst intensity of these 15 references ranged from 30.41 to 84.77, with an endurance intensity of 2 to 5 years. Table 5 summarizes the main studies of the 15 references in the order of the literature in Fig. 9.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Strength</th>
<th>Main research content</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>Effect of infliximab and methotrexate therapy on joint and clinical benefits in patients with RA</td>
</tr>
<tr>
<td>2</td>
<td>32.47</td>
<td>Efficacy of fusion protein-cytotoxic T-lymphocyte-associated antigen 4-IgG1 in the treatment of RA patients</td>
</tr>
<tr>
<td>3</td>
<td>84.77</td>
<td>Proven selective depletion of b cells with rituximab leads to sustained clinical improvement in RA patients</td>
</tr>
<tr>
<td>4</td>
<td>58.13</td>
<td>To determine the efficacy and safety of rituximab in combination with methotrexate (MTX) in patients with active RA who are not responding to anti-tumor necrosis factor (anti-TNF) therapy and to investigate the pharmacokinetics and pharmacodynamics of rituximab in this population</td>
</tr>
<tr>
<td>5</td>
<td>41.77</td>
<td>Study the efficacy and safety of different doses of rituximab plus MTX (with or without glucocorticoids) in patients with active RA who are resistant to DMARDs, including biologics</td>
</tr>
<tr>
<td>6</td>
<td>41.44</td>
<td>The extent to which anti-TNF antibody therapy may increase the risk of serious infections and malignancies in patients with RA by conducting a meta-analysis to derive estimates of sparse harmful events that occurred in randomized trials of anti-TNF therapy</td>
</tr>
<tr>
<td>7</td>
<td>58.8</td>
<td>To study the pathogenesis of RA, such as how it leads to joint localization, the causes of persistent synovial inflammation, what drives local destruction leading to joint dysfunction, and the mechanisms by which RA causes systemic disease</td>
</tr>
<tr>
<td>8</td>
<td>30.41</td>
<td>Pathophysiology, epidemiology, classification and diagnosis, clinical assessment, care, management, difficulties and prospects of RA</td>
</tr>
<tr>
<td>9</td>
<td>34.12</td>
<td>To improve the prognosis of patients with RA, the 2010 European League Against Rheumatism (EULAR) recommendations on the use of synthetic and biologic sDMARDs and bDMARDs, respectively for the treatment of RA have been updated</td>
</tr>
<tr>
<td>10</td>
<td>42.77</td>
<td>To obtain optimal results with synthetic and biological disease-mitigating antirheumatic drugs for RA, the recommendations of the European League Against Rheumatism (EULAR) were updated in 2016</td>
</tr>
<tr>
<td>11</td>
<td>33.98</td>
<td>Immunopathogenesis of RA, expressing a bold vision for the future of RA therapeutics</td>
</tr>
<tr>
<td>12</td>
<td>33.51</td>
<td>Etiological insights from the treatment of RA: studies of the mode of action of specific immune-targeted drugs reveal which immune pathways drive joint inflammation and associated comorbidities</td>
</tr>
<tr>
<td>13</td>
<td>39.32</td>
<td>RA epidemiology, pathophysiology, diagnosis, and treatment</td>
</tr>
<tr>
<td>14</td>
<td>34.42</td>
<td>Up-to-date insights into RA genetics and etiology, pathophysiology, epidemiology, assessment, therapeutic agents, and treatment strategies to address the unmet needs of patients</td>
</tr>
<tr>
<td>15</td>
<td>31.73</td>
<td>RA-related disability can be prevented with sequential drug therapy, such as early treatment with methotrexate plus glucocorticoids, followed by other DMARDs (e.g. TNF, IL-6, etc.)</td>
</tr>
</tbody>
</table>

3.5. Keyword/Terms Analysis
Keywords condense the core and essence of a paper, and keyword co-occurrence analysis is not only the most effective way to discover the research hotspots in a scientific field but also the most effective way to understand the direction of investigation of issues of concern in a topic. We used VOSviewer to plot the keyword co-occurrence network view for 8822 documents and selected 50 key keywords with a frequency greater than or equal to 201 for visualization, and the results are shown in Fig. 6(A). The larger the circle node in the graph, the more the keyword appears, and the more it represents the hotspot of the field; the node connecting line represents the association strength, and the thicker the line indicates that the two appear together in the same literature more often; the node color represents different clusters (research topics). The statistical analysis of the words in different parts of the paper gives a concept of the different research directions of the topic. Table 6 lists the top 15 keywords in this topic and, not surprisingly, RA was the most common keyword with 6,215 occurrences; treatment followed closely behind with 1,604 occurrences.

CiteSpace clustering analysis can further understand the different investigation directions of the topic. To show more details and verify the information in the keyword clustering, we conducted a Citespace analysis based on Vosviewer. Figure 8 shows the 20 clusters formed by CiteSpace after clustering the keywords. CiteSpace provides two metrics, module value (Q value for short) and average profile value (silhouette, S value for short), based on the clarity of network structure and clustering, which can be used as a basis for us to judge the effectiveness of mapping. Q = 0.7919 (> 0.3) in Fig. 8 implies that the delineated clustering structure is significant and S = 0.9218 (> 0.7) implies that the clustering is convincingly efficient. Overall, there are areas of overlap between many of the clusters, indicating that their content has more similarities to each other. Table 7 shows a detailed description of the clusters and their IDs, sizes (number of papers), profile values, and corresponding keywords.

<table>
<thead>
<tr>
<th>NO.</th>
<th>Count</th>
<th>Keyword</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6215</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>2</td>
<td>1604</td>
<td>Therapy</td>
</tr>
<tr>
<td>3</td>
<td>1108</td>
<td>Expression</td>
</tr>
<tr>
<td>4</td>
<td>985</td>
<td>Double-blind</td>
</tr>
<tr>
<td>5</td>
<td>957</td>
<td>T cell</td>
</tr>
<tr>
<td>6</td>
<td>947</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>7</td>
<td>773</td>
<td>B cell</td>
</tr>
<tr>
<td>8</td>
<td>770</td>
<td>Disease</td>
</tr>
<tr>
<td>9</td>
<td>738</td>
<td>Collagen-induced arthritis</td>
</tr>
<tr>
<td>10</td>
<td>689</td>
<td>Tumor necrosis factor</td>
</tr>
<tr>
<td>11</td>
<td>588</td>
<td>Autoimmune disease</td>
</tr>
<tr>
<td>12</td>
<td>562</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>13</td>
<td>561</td>
<td>Inflammation</td>
</tr>
<tr>
<td>14</td>
<td>547</td>
<td>Regulatory t cell</td>
</tr>
<tr>
<td>15</td>
<td>509</td>
<td>Necrosis factor alpha</td>
</tr>
</tbody>
</table>
Table 7
Clusters of cell therapy in RA regarding the keyword co-occurrence of each cluster

<table>
<thead>
<tr>
<th>Cluster-ID</th>
<th>Size</th>
<th>Silhouette</th>
<th>Mean(Year)</th>
<th>Keywords</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>65</td>
<td>0.882</td>
<td>2009</td>
<td>Double-blind; Inadequate response; Placebo; Trial; Abatacept</td>
</tr>
<tr>
<td>1</td>
<td>46</td>
<td>0.957</td>
<td>2009</td>
<td>Bone marrow transplantation; Natural killer cell; Juvenile idiopathic arthritis; Interleukin 1 receptor antagonist</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>0.903</td>
<td>2009</td>
<td>Nf kappa b; risk; Inflammation; Combination therapy; Cancer</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>0.944</td>
<td>2010</td>
<td>Efficacy; Rituximab; Safety; Inflammation; Non Hodgensks lymphoma</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>0.934</td>
<td>2008</td>
<td>Synovial tissue; Endothelial growth factor; Angiogenesis; Chronic lymphocytic leukemia; Vegf</td>
</tr>
<tr>
<td>5</td>
<td>38</td>
<td>0.887</td>
<td>2010</td>
<td>Mesenchymal stem cell; Osteoarthritis; ; Cell therapy</td>
</tr>
<tr>
<td>6</td>
<td>37</td>
<td>0.969</td>
<td>2010</td>
<td>Collagen-induced arthritis; Macrophages Neutrophil; Response; Improvement</td>
</tr>
<tr>
<td>7</td>
<td>37</td>
<td>0.905</td>
<td>2008</td>
<td>Regulatory t cell; Tgf beta; Tnf alpha therapy; Immune tolerance</td>
</tr>
<tr>
<td>8</td>
<td>35</td>
<td>0.975</td>
<td>2008</td>
<td>Tumor necrosis factor; Rheumatoid arthritis; Therapy; T cell</td>
</tr>
<tr>
<td>9</td>
<td>34</td>
<td>0.886</td>
<td>2010</td>
<td>Gene therapy; Versus host disease; American college; Bone marrow; Marrow stromal cell</td>
</tr>
<tr>
<td>10</td>
<td>34</td>
<td>0.906</td>
<td>2007</td>
<td>Dendritic cell; B cell depletion; Cd4(+) t cell; B lymphocyte</td>
</tr>
<tr>
<td>11</td>
<td>34</td>
<td>0.885</td>
<td>2010</td>
<td>Cell; Synovial fibroblast; Activation; Apoptosis; Lymphocyte</td>
</tr>
<tr>
<td>12</td>
<td>34</td>
<td>0.857</td>
<td>2008</td>
<td>Sjogren’s syndrome; Peripheral blood; Primary Sjogren’s syndrome; Depletion therapy; Epstein-Barr virus</td>
</tr>
<tr>
<td>13</td>
<td>33</td>
<td>0.969</td>
<td>2008</td>
<td>Extracellular vesicles; Patient; Bone resorption ; Interleukin 15; Antibody therapy</td>
</tr>
<tr>
<td>14</td>
<td>33</td>
<td>0.974</td>
<td>2013</td>
<td>Modifying antirheumatic drug; Interstitial lung disease; Systemic sclerosis; Rheumatoid Arthritis; Photothermal therapy</td>
</tr>
<tr>
<td>15</td>
<td>32</td>
<td>0.868</td>
<td>2009</td>
<td>Inflammatory bowel disease; Crohn’s disease; Multiple sclerosis; T cell lymphoma; Ulcerative colitis</td>
</tr>
<tr>
<td>16</td>
<td>31</td>
<td>0.943</td>
<td>2007</td>
<td>Expression; Protein; Synovial fluid ; Tissue; Serum</td>
</tr>
<tr>
<td>17</td>
<td>31</td>
<td>0.892</td>
<td>2011</td>
<td>Psoriatic arthritis; Giant cell arteritis; Nivolumab; Blockade; Giant cell arteritis</td>
</tr>
<tr>
<td>18</td>
<td>31</td>
<td>0.891</td>
<td>2007</td>
<td>Disease activity; Growth factor; In vivo ; Classification; Immune system</td>
</tr>
<tr>
<td>19</td>
<td>30</td>
<td>0.938</td>
<td>2008</td>
<td>Autoimmune disease; Systemic lupus Erythematosus; Autoimmune diseases; Monoclonal antibody; Periodontal disease</td>
</tr>
</tbody>
</table>

4. Discussion

4.1 General Information

From 2003 to 2009, the number of publications on cell therapy in RA showed a fluctuating upward trend with an average of 317 publications per year; from 2010 to 2013, the number of publications on cell therapy in RA was more stable; from 2014 to 2021, the number of related papers published showed a fluctuating upward trend and may still keep rising in the coming years, which indicates that the research on cell therapy in RA has been gaining the attention of scholars and more scholars may join in the future.

Most of the research on RA in cell therapy is published in Arthritis research & therapy (IF = 5.606, Q1), indicating that it is currently the most popular journal in this research area. Among the journals, the journal with the highest impact factor was Annals of the rheumatic diseases (IF = 27.973, Q1), followed by Autoimmunity reviews (IF = 17.390, Q1). Regarding the co-cited journals, we can find that most of them are high-impact Q1 journals. Among them, the longest continuously published medical journal in the world, New england journal of medicine, has an impact factor of 176.079 and is included in Q1. Four of the top 10 total cited papers in the co-cited references were published in the New england journal of medicine. Several papers on related topics have been published in the above-mentioned high-quality international comprehensive journals, supporting research in cell therapy for the treatment of RA. More importantly, current research on cell therapy in RA...
is mainly published in molecular, biological, genetic, immunological, pharmacological, medical, and clinical-related journals, indicating that the current research is more extensive and in the stage of gradual basic to clinical development.

The United States and China are the leading countries researching cellular therapies in RA, with the United States leading the way, followed by China with 1217 publications in the relevant literature. Approximately 60% of the top 10 research institutions are located in the United States, followed by the Netherlands (n = 1, 10%), Sweden (n = 1, 10%), the United Kingdom (n = 1, 10%), and France (n = 1, 10%). We note the close cooperation that exists between the United States and five countries - China, England, Germany, Italy, and Japan. In addition, China is also actively cooperating with the United States, Japan, Australia, South Korea, India, Iran, and Canada. All countries are not only involved, but domestic cooperation is more or less involved in international cooperation, but the percentage of international cooperation carried out by each country is small, and in the long run, this situation will hinder the development of the research field. Therefore, we strongly recommend extensive collaboration and communication among national research institutions to promote the development of cell therapy in RA.

Co-cited references are references that are cited together by multiple other publications so that co-cited references can be considered as the research base of the field 7. In this bibliometric study, we selected the top 10 co-cited references with the highest number of co-citations to determine the research progress of cellular therapies in RA. In 1988, Arnett Fc et al. published the most co-cited study that proposed new classification criteria for RA in both traditional and tree-like formats, which laid the foundation for therapeutic research in RA 10. From Table 3, we can find that 4 of the top 10 total cited papers were published in the New england journal of medicine.

### 4.2 Hotspots and Frontiers

Keywords help us to quickly capture the hot distribution of cell therapy in the RA research field, and keyword analysis identifies the most popular topics covered by the bibliometric analysis 29. In addition to the keywords RA, treatment, double-blind, and SLE, Table 3 mainly includes the following keywords: T cells, tumor necrosis factor, collagenous arthritis, monoclonal antibody, inflammation, and tumor necrosis factor-alpha. Based on the keyword clustering analysis (Fig. 10) and the keyword table (Tables 6 and 7), we conclude that the research on cell therapy in RA is mainly focused on the following areas:

#### 4.2.1 Influencing factors/pathogenesis of RA

Innate immune system factors are associated with the pathogenesis of RA. Important representatives of the natural immune system cells are mononuclear phagocytes (monocytes, macrophages, and dendritic cells), granulocytes (neutrophils, basophils, and eosinophils), mast cells, and NK cells; soluble factors, such as the complement system, defensins, lysozyme, and cytokines, facilitate communication between immune cells or immune cells and organs or tissues. The interaction between the innate and adaptive immune systems is important, so it is difficult to draw a line between the two 30. The main site of inflammation in RA is in the synovial membrane, where the cells present are usually called synovial cells and consist of various cells that secrete synovial fluid, such as macrophages, fibroblasts, and dendritic cells. During RA joint inflammation, various immune system inflammatory cells are recruited to the synovium, including T cells, B cells, monocytes, dendritic cells, mast cells, neutrophils, NK cells, and fibroblasts 31.

### 4.2.1.1 Innate immune system

Macrophages in cluster 6 of Table 7 play a central role in triggering and driving the pathogenesis of RA. The pathogenic role of monocytes and macrophages in RA is mainly due to the production of pro-inflammatory cytokines, chemokines, growth factors, and free radicals and the release of matrix metalloproteinases leading to joint inflammation and destruction 32. Circulating monocytes infiltrate from the blood into inflamed RA joints, where they differentiate into macrophages. They can be polarized into M1 macrophages, classically activated cells that produce pro-inflammatory cytokines that mediate resistance to pathogens and tissue destruction, or into M2 macrophages, alternatively activated cells that produce anti-inflammatory cytokines that promote tissue repair, have anti-inflammatory properties, and can initiate tissue repair 33,34. TNF, IL-1, IL-6, and IL-18 secreted by M1 macrophages, in combination with local hypoxic conditions, activate RA macrophages and synovial tissue fibroblasts to secrete growth factors such as vascular endothelial growth factor (VEGF) and/or basic fibroblast growth factor, key regulators of angiogenesis 35. VEGF promotes angiogenesis through the activation of receptor tyrosine kinases 35,36. In RA, excessive pro-angiogenic factors counteract the effects of angiogenesis inhibitors to support elevated transendothelial leukocyte infiltration, which promotes synovial inflammation as well as bone and cartilage destruction. Conversely, inhibition of joint neovascularization alleviates synovitis and vascular endothelial formation 37.

The phenotypic and functional plasticity of dendritic cells in cluster 10 of Table 7 highlights the complex and dichotomous role they may play in the pathogenesis of RA 32. Dendritic cells are not only immunogenic, activating and regulating adaptive immunity, but also...
tolerogenic, and tolerance plays a negative regulatory role in the pathogenesis of RA.\textsuperscript{38} Dendritic cells are involved in regulating the activation of the adaptive immune system and the destruction of self-tolerance on the one hand, and mediating organ damage caused by clinical symptoms of specific autoimmune diseases through the production of pro-inflammatory cytokines (TNF, IF-1, IL-2, IL-6) that amplify local inflammation and further activate other nearby immune or parenchymal cells, matrix degradation and production of protein hydrolases or reactive oxygen species that directly cause tissue damage.\textsuperscript{30} Accumulation of danger signals in inflamed tissues stimulates and drives dendritic cells to immunogenic or tolerogenic features. The release of cytokines that trigger inappropriate autoantigen presentation leads to dysregulation of auto-reactive T and B lymphocytes, resulting in the pathophysiology of autoimmune disease.\textsuperscript{30}

The pathogenic role of neutrophils involved in cluster 6 of Table 7 triggers positive regulatory feedback through the secretion of immune mediators, including IL-1, IL-6, IL-12, TGF-b, and TNF, which lead to acute and persistent inflammation\textsuperscript{39}; and through activated RA neutrophils, especially infiltrating neutrophils, which allow for a delay in the apoptotic process, thereby increasing the inflammatory state and promoting tissue damage.\textsuperscript{39} Promotes inflammatory cytokine production through myeloperoxidase, an intracellular component of neutrophils, which is the most abundant cytotoxic enzyme found in the asplenophilic granules of neutrophils and is involved in T cell activation and pathogen elimination.\textsuperscript{40}

The pathogenic mechanism of NK cells in cluster 1 of Table 7 for RA is unclear and two main mechanisms are widely accepted, on the one hand, possibly through cytokine secretion to communicate with other immune cells or by lysing auto-reactive immune cells that cause autoimmune disease to act as protective participants. Activated NK cells may infiltrate the inflamed synovial membrane of RA patients, and NK cells obtained from the synovial fluid of RA patients and co-cultured with monocytes may induce monocytes to differentiate into osteoblasts.\textsuperscript{41} On the other hand, NK cells may produce inflammatory cytokines through cytotoxic effects or have direct pathogenic functions in autoimmunity.\textsuperscript{42} TNF-α, as a transducing cytokine in RA, is the most studied cytokine in the analysis of NK cell function in RA pathophysiology and has been shown to regulate NK cell differentiation and induce their maturation.\textsuperscript{43}

### 4.2.1.2 Adaptive immune system

The immunogenetics of RA suggests that abnormal pathways of T-cell activation play a key role in disease initiation and/or perpetuation. During T cell activation, in addition to co-stimulatory molecules (e.g. CD80/CD86) expressed on the surface of professional antigen-presenting cells, CD4 T cells are engaged by antigenic peptide fragments in complex with human leukocyte antigen (HLA) class II molecules. The strongest evidence supporting the role of CD4 T cells in disease pathogenesis is the association between RA and HLA-DRB1; however, the functional role of this association has not been determined.\textsuperscript{44} Activated T cells are known to promote bone damage in RA joints by producing osteoclast-producing cytokines such as IL-17\textsuperscript{45} and RANKL (receptor activator of nuclear factor-κ B ligand).\textsuperscript{46} They can promote bone damage in RA joints. Regulatory T cells (Treg) play a crucial role in maintaining tolerance to autoantigens by actively suppressing the proliferation of self-reactive T cells and the production of pro-inflammatory cytokines to prevent disease.\textsuperscript{47} In addition, in RA, dysregulation of self-tolerance leads to the production of auto-reactive lymphocytes that target tissue-specific autoantigens in the joint.\textsuperscript{48} Mediating T cells can re-induce self-tolerance before severe tissue damage. However, the number and function of Tregs are significantly deficient in RA patients compared to healthy individuals.\textsuperscript{49} The link between Tregs deficiency and autoimmune mechanisms in RA patients lays the foundation for the use of Tregs therapy for RA.\textsuperscript{50} Although IFN-γ levels are not high in the synovium of RA patients, this cytokine is thought to play a key role in the pathogenesis of RA. It can produce both IFN-γ Th 1 cells and IL-17 helper T (Th 17) cells.\textsuperscript{51-52} Th 17 cells can be divided into two types, "pathogenic" Th 17 cells and "non-pathogenic" Th 17 cells, depending on the cytokine milieu present during differentiation. Typically, "pathogenic" Th 17 cells produce pro-inflammatory cytokines, including IL-17 A, IL-17 F, and IL-22. Therefore it is considered a positive regulator of the immune response. In contrast, "non-pathogenic" Th 17 cells can secrete immunosuppressive factors, such as IL-10, to negatively regulate the immune response. In RA, pathogenic Th 17 cells play a very important role.\textsuperscript{53}

T cells (helper T cells (Th)1, Th 17, Treg, and Th 22) can initiate a series of cascade reactions (rolling, arresting, spreading, creeping, and migrating) that eventually extravasate from the blood vessels to the inflamed joint.\textsuperscript{51} Recent studies have shown that differentiated CD 4 T cell subpopulations exhibit a high degree of plasticity. That is, FoxP 3 Treg and Th 1 and Th 17 effector T cells exhibit high levels of plasticity, allowing functional adaptation to various physiological conditions during the immune response via IL-1, IL-6, IL-12, IL-17, and IFN-γ. Thus, the plasticity of CD-4 T cells may have evolved to remain resilient and stable, allowing the immune system to respond most flexibly to pathogens and environmental changes. However, this flexibility also includes a potential threat to the host. This is because dysregulation of this system increases the risk of autoimmune development. Thus, factors regulating Treg and Th 17 plasticity could be targets for immunotherapy targeting immune system manipulation in the context of autoimmune diseases.\textsuperscript{54}
During RA pathogenesis, B cells can promote the activation, proliferation, and differentiation of other cells in the synovium such as T cells, monocytes, and osteoblasts by providing cytokines, autoantibodies, and other mediators. B-cell-derived IL-6 promotes its proliferation and its role in T helper cell differentiation and subsequent cytokine production by various T cell subsets, and also acts on cytokine production through a range of different key molecules. B cells in the peripheral blood of RA patients secrete a variety of different cytokines involved in bone destruction, including TNF-a, IL-1b, and IL-6. They can promote bone resorption mediated in RA directly by activating osteoclasts or indirectly by inducing M-CSF and RANKL production by FLS-like cells, T cells, or BM stromal cells. In the presence of IL-1b, TNF-a increases the expression of B-cell RANKL, thereby promoting osteoclast formation. In vitro experiments showed that RANKL secreted by B cells could promote the differentiation of monocytes into osteoclasts, leading to bone damage in RA.

Regulatory B cells (Bregs) are immunosuppressive cells that help maintain immune tolerance by suppressing RA through the production of interleukin (IL)-10, IL-35 and transforming growth factor beta 1, by suppressing cytotoxic CD8 + T cells that impair effective tumor clearance, and by suppressing the expansion of pathogenic T cells and other pro-inflammatory lymphocytes and promoting Treg differentiation. Bregs are induced by interleukin-1β and interleukin-6 production driven by the gut microbiota, and in response to inflammatory signals induced by the gut flora and arthritis, Bregs numbers increase and suppress excessive inflammation; mice depleted of endogenous bacteria after administration of broad-spectrum antibiotics do not develop arthritis or Bregs, suggesting a complex relationship between microbiota, inflammation, and Bregs differentiation.

**4.2.1.3 Synovial fibroblast**

FLS in cluster 11 of Table 7 are highly specialized mesenchymal cells found in the synovial membrane of articulated joints, and FLS can control the composition of the extracellular matrix and synovial fluid, thereby lubricating and nourishing the cartilage surface. FLS in RA have unique aggressive behavior and play an active role in disease pathogenesis and progression. The destruction of cartilage and non-bone supporting structures in RA can be attributed mainly to FLS-mediated effects. FLS in RA exhibits a "pro-inflammatory" and "aggressive" phenotype, characterized by the expression of several disease-associated cytokines, chemokines, and extracellular matrix remodeling factors, leading to inflammation and joint destruction. FLS produces not only extracellular matrix and joint lubricants but also pathogenic mediators such as cytokines and proteases, which contribute to disease onset and persistence. During joint destruction in RA, the pathogenic role of FLS is through the production of inflammatory cytokines, pro-angiogenic factors, and matrix-degrading enzymes actively promoting inflammation, angiogenesis, and matrix degradation that can regulate tissue homeostasis, modulate the inflammatory response and mediate tissue damage, while significant FLS proliferation and infiltration of tissues into adjacent tissues occur in RA with disease progression.

In summary, a growing body of data suggests that the pathogenesis of RA is diverse and involves the complex action of multiple immune cells. However, there are still many issues to be resolved. By gaining a deeper understanding of the complex mechanisms of disease, new therapies can be developed that precisely target disease-causing molecules.

**4.2.2 Treatment strategies for RA**

RA is the most common chronic autoimmune joint disease characterized by persistent synovitis of the joints and systemic inflammation. Current treatment of RA relies on a variety of medications that can improve disease symptoms, but long-term use of medications can lead to adverse reactions and toxic side effects. Over the past 20 years, the development of targeted therapeutic agents has been able to provide sustained relief of patient disease activity, radically inhibit progressive tissue and joint damage, and slow or halt disease progression, but some drugs can increase the incidence of adverse effects. Although targeted therapeutic agents have been used as first-line therapy for the primary treatment of RA in some recent studies, this approach has not yet become routinely recommended.

In recent years, with a better understanding of the immunopathological mechanisms of the disease, cell-based therapies have shown to be effective and promising interventions for RA. Cell-based therapies involve a variety of cells, mainly hematopoietic stem cells (BM transplantation), mesenchymal cells, B cells, T cells, macrophages, dendritic cells, neutrophils, NK cells, etc. Overall immune/drug therapy measures for RA we classify broadly into two categories: targeted cell therapy, cell transplantation therapy, etc. The various treatment modalities tend to be combined and not limited to a single approach, coinciding with the combined treatment in cluster 2 of Table 7. With the continuous updating of guidelines, the treatment goal of RA has been constantly updated from the initial relief of joint swelling and pain to the relief of the disease and stopping the bone destruction of the joint, and then to the deep remission of the patient with no joint swelling and pain, no synovial inflammation, and no progression of bone destruction, not only the clinical remission but also the remission of the structural damage and function of the joint. There is also interest in improving the quality of life of RA patients, and more and more clinical practitioners are focusing on cell therapy as an approach. The following is a brief description of targeted cellular therapies and cell transplantation therapies commonly used in RA in keywords.
4.2.2.1 Targeted cell therapy

4.2.2.1.1 T-cell targeted therapy

T cells were one of the first therapeutic targets explored in the early stages of developing cellular therapies, and Abatacept, which appears in the keyword analysis, is the first biologic agent to treat RA by targeting T cells. Treg targeted therapies, and chimeric antigen receptor T (CAR-T) are associated with T cell-targeted therapies.

Abatacept, a synthetic protein produced by recombinant deoxyribonucleic acid technology, consists of the extracellular structural domain of CTLA-4 (cytotoxic T-lymphocyte antigen-4) and the Fc portion of immunoglobulin-G1 and is a biological agent used for the treatment of RA. Several strategies are being investigated for the treatment of RA including cytokine manipulation, B-cell depletion or suppression, as well as T-cell targeted therapy and co-stimulatory blockade. Double-blind experiments in the keyword are usually used when the subjects are human, which avoids the subjective bias of the subjects or the person conducting the study and makes the results more rigorous. Double-blind trials are also used more often for clinical trials of Abatacept. Abatacept selectively regulates CD28:CD80/86 co-stimulatory signaling necessary for T cell activation (inhibits T cell co-stimulation and activation by binding to CD80 and CD86 on the surface of B cells, leading to downregulation of inflammatory mediators) 67. Thus, Abatacept can inhibit T-cell activation and proliferation, suggesting that Abatacept is an important therapeutic option for selective modulation of T-cell co-stimulation in the RA therapeutic arsenal. Biologic Abatacept is the first drug in the co-stimulatory blockade and has now completed phase III clinical trials showing efficacy and safety in established RA 368,69.

With the in-depth study of the role of Treg cells in RA, Treg-targeted therapy has become a promising avenue for the treatment of RA. Treg therapy has the potential to transform into pathogenic cells, thus triggering the development of autoimmunity 70. Drugs that target signaling pathways that promote Treg survival and function protect Treg numbers and function, and histone deacetylases (HDACs) are epigenetic regulators of T cell-mediated immunity. Studies show that HDAC inhibitors have anti-inflammatory effects and are potential treatments for autoimmune diseases 71. HDAC inhibitors may be beneficial for RA treatment, HDAC inhibitors promote Treg function in vivo and in vitro, and peripheral blood mononuclear cells from RA patients co-cultured with lipopolysaccharide and HDACs inhibitors in vitro induce an increased proportion of Treg cells and increased IL-10 expression 72. Targeting Treg cells faces various challenges due to the heterogeneity and plasticity of Treg and the complexity of the immune system. How Treg cells regulate the immune response under different conditions or in different tissues and how Treg cells interact with different subsets of conventional T cells in RA need further investigation. The lack of specific antigens on the surface of Tregs also makes Tregs difficult to purify, thus increasing the risk of effector T cell contamination.

CAR-T cells are bioengineered redirected T lymphocytes expressing specific receptors in the membrane that recognize target cell-specific antigens without MHC restriction, thereby interacting with target cells 73. The steps to create CAR-T cells begin with isolating T cells from the patient's peripheral blood, inserting the CAR gene into the T cell genome, and then amplifying the manufactured CAR-T cells and injecting them into the patient 74. The main use of CAR-T cells is currently for the treatment of various cancers. Recently, CAR-T cells have also been used in preclinical trials for SLE, and RA, bringing new hope for treatment options for autoimmune diseases 75,76. For CAR-T therapies to be used in the clinic, stability, durability, safety, efficacy, manufacturability, and longevity must be confirmed 50. CAR-T cells are used in animal models of lupus and RA with proven efficacy 77. However, there are some challenges in CAR-T translation: firstly, it is difficult to prepare on a large scale, and capacity expansion is difficult; secondly, the preparation cycle is long and conventional methods need to isolate T cells before expansion; finally, the price is high and patients can hardly afford its cost.

4.2.2.1.2 B-cell targeted therapy

Therapeutic approaches targeting B cells can be summarized as direct clearance usually using monoclonal antibodies (e.g. rituximab), indirect clearance through survival cytokine blockade (e.g. belimumab), co-stimulatory blockade, and other approaches that inhibit B cell activation (e.g. small molecule inhibitors of Bruton tyrosine kinase and Janus kinase). Novel relevant B-cell therapies are also emerging from the efforts of a wide range of investigators.

Rituximab in the keyword analysis is a chimeric mouse-human monoclonal antibody against a CD20 molecule expressed on the surface of human B cells. It is the first monoclonal antibody drug targeting B cells in RA and is a B-cell depletion therapy. Because the CD20 antigen is not expressed by pre-B cells or fully differentiated plasma cells, rituximab does not prevent CD20-positive B cells from regenerating from precursor cells or directly interfere with immunoglobulin production 3. The use of rituximab to remove all B cells outside of pre-B cells and plasma cells is currently the most widely used treatment for RA 78. The first open-label study of rituximab in 2001 described its beneficial effects in cases of refractory RA. One of the types of combination therapy chosen for the treatment of B-cell lymphoma was a B-lymphocyte depletion regimen combining rituximab with corticosteroids and cyclophosphamide 79. An open-label study in 2001 showed that selective
depletion of B cells with rituximab resulted in sustained clinical improvement in patients with RA, and we conducted the first randomized, double-blind, placebo-controlled trial, which concluded that a single course of two infusions of rituximab alone or in combination with cyclophosphamide or continuous methotrexate significantly improved disease symptoms at weeks 24 and 48 in patients with active RA despite treatment with methotrexate. Thus, sustained clinical improvement in RA patients by selective depletion of B cells with rituximab exists. Recent data from CERERRA (European Cooperative Registry for the Evaluation of Rituximab in RA) suggest that repeated treatment with rituximab, especially fixed interval retreatment, leads to further clinical improvement more effectively than on-flare retreatment. Studies have shown that rituximab not only significantly reduces clinical symptoms and inflammation in RA, but also inhibits the progression of structural joint damage by increasing bone formation and reducing bone resorption. In conclusion, the advantages of rituximab are: first, the rapid and effective introduction of B-cell count downregulation; and second, lower price. The disadvantages include: difficulty in complete clearance of B cells; need for repeated administration; easy relapse; and easy to develop drug dependence. Several other second-generation anti-CD 20 drugs are currently humanized to reduce immunogenicity, including Obinutuzumab, Ofatumumab, and Veltuzumab for chronic lymphocytic leukemia, and Ocrelizumab for relapsing or primary progressive multiple sclerosis. Belimumab for SLE specifically binds to soluble B-cell stimulating factors, preventing it from binding to B cells and promoting B-cell apoptosis.

Bruton tyrosine kinase (BTK), a cytoplasmic tyrosine kinase expressed in B cells, is involved in regulating the proliferation and activation process of B cells and plays a key role in B cell receptor signaling as well as in the development and maturation of B cells. It has become an important target for tumor therapy and inflammatory diseases. Small molecule BTK inhibitors have the advantages of oral efficacy and specificity compared with traditional drugs and biologics. BTK inhibitors are a new class of drugs that inhibit B-cell receptor activation, FC-γ receptor signaling, and osteoclast proliferation. Regarding BTK inhibitors in development for the treatment of RA, Ibrutinib, compound CGI-1746, and compound RN-486 are in Preclinical (preclinical), Tirabrutinib is in Phase 1 (Phase 1), and Spebrutinib, Acalabrutinib, compound HM-71224, and compound GDC-0853 have entered Phase 2. Although the results of BTK inhibitors in animal models of RA are favorable, the results of subsequent human clinical trials are somewhat unclear. Ongoing studies and clinical data will validate strategies for developing BTK inhibitors for RA.

Janus kinase (JAK) mediates signaling through the IL-6 receptor and many other transmembrane receptors (cytokine receptors, G protein-coupled receptors, receptor tyrosine kinases), and the JAK family consists of four members: JAK1, JAK2, JAK3, and TYK2. JAK inhibitors are small molecule targeted therapeutic agents that block the action of pro-inflammatory cytokines on B cells. Five JAK inhibitors (tofacitinib, upadacitinib, baricitinib, peficitinib, filgotinib) have been approved for the treatment of RA and offer advantages over conventional biological DMARDs. Baricitinib is an oral, low-molecular-weight compound, reversible and selective JAK1/JAK 2 inhibitor, and mediates signaling of multiple cytokines associated with RA pathogenesis, such as interleukin-6, granulocyte-macrophage colony-stimulating factor and interferon. It is more appropriate for patients who prefer oral therapy and do not have a history of severe renal impairment, recent malignancy, or risk factors for adverse events such as venous thromboembolism, opportunistic infections, and diverticulitis. In clinical trials, baricitinib at doses of 2 mg and 4 mg once daily has shown significant clinical efficacy and an acceptable safety profile, with the most commonly reported serious adverse events being infections. In conclusion, JAK inhibitors can treat RA by inhibiting B-cell activation, proliferation, and differentiation.

Supplementing the diet with certain molecules of microbial origins, such as butyrate, may be a promising approach to treating RA, and researchers at University College London found that supplementing rats with RA with butyrate suppressed arthritis. Butyrate is a molecule that is produced by a complex microbiota from the breakdown of dietary starch. Butyrate supplementation supports the inflammatory suppressive function of regulatory B cells by altering the composition of the microbiota and increasing the production of the serotonin-derived metabolite 5-hydroxy indole-3-acetic acid.

4.2.2.1.3 Targeting cytokines

With a deeper understanding of the structural principles and functional signals of cytokine-receptor interactions, artificial modifications of cytokines by protein engineering and other methods make it increasingly possible for cytokines to become drugs. The keywords regarding the main target cytokines for the treatment of RA are targeting TNF-α and IL-6.

TNF-α, a pro-inflammatory cytokine produced by macrophages and monocytes in response to inflammation, is an important cytokine mediating inflammation in RA, and elevated levels of TNF-α have been observed in the synovial fluid and synovial membranes of RA patients. It's binding to two different receptors (TNFR 1 and TNFR 2) establishes distinct signaling cascades that trigger apoptosis, differentiation, proliferation, and migration of inflammatory cells. Since TNF-α affects the production of metalloproteinases, collagenases, and lysosomal proteases by various cells in the synovium (e.g. synoviocytes, macrophages, chondrocytes and osteoclasts), it...
can induce local inflammation and vascular opacification formation, ultimately leading to further cartilage erosion and bone destruction. The introduction of TNF-α inhibitors has revolutionized RA treatment options \(^{94}\) and has been used clinically to balance high TNF levels \(^{92}\).

There are five TNF inhibitors currently used clinically for the treatment of RA, such as infliximab, etanercept, adalimumab, golimumab, and certolizumab\(^ {95}\). Infliximab is a TNF-α-specific recombinant IgG 1 monoclonal antibody. The therapeutic mechanism is to prevent cytokines from triggering cellular TNF receptor complexes and inhibit progressive joint damage, thereby improving symptoms associated with RA patients. Etanercept is safe and effective in the treatment of RA, and the combination of etanercept + MTX is more effective in reducing disease activity, decreasing total joint score progression, slowing joint destruction, and improving function than monotherapy. ADA is a monoclonal antibody to recombinant immunoglobulin (IgG 1), containing only human peptide sequences, whose therapeutic mechanism is the ability to block TNF-α from binding to its receptor \(^ {96}\). It relieves the signs and symptoms of RA in combination with or without MTX. TNF-α inhibitors significantly improved treatment outcomes in RA, but side effects such as adverse reactions, infections, and injection site reactions still exist. Thankfully most of these side effects are mild or moderate and occur at a low rate. However, there is also a lack of response to anti-TNF alpha therapy in some patients \(^ {95}\). As a result, the growing understanding of the RA pathway has focused attention on other potential targets involved in disease pathogenesis, leading to licenses with different mechanisms of action (e.g.B-cell depletion, T-cell costimulation inhibition, and IL-6 blockade).

IL-6 is a pleiotropic cytokine involved in the regulation of the immune system, a cytokine in the pathogenesis of RA, and a key pro-inflammatory cytokine that acts by promoting the production of acute phase proteins involved in the systemic progression of RA. Bone marrow stromal cells produce IL-6 that induces receptor activators of NF-κB ligand (RANKL), which is important for osteoclast differentiation and activation as well as bone resorption \(^ {97}\). IL-6 has also been reported to control vascular permeability by inducing VEGF production in FLS in RA, enhancing the recruitment of inflammatory cells to the tissue and exacerbating the injury \(^ {98}\). The first IL-6 pathway-targeting drug approved by regulatory agencies for clinical use is Tocilizumab, a humanized IL-6 receptor monoclonal antibody that can be generated by transplanting the complementary decision region of a mouse anti-human IL-6 R antibody into human IgG 1 \(^ {99}\). Tocilizumab binds membrane-bound human IL-6 R and sIL-6 R to the IL-6 binding site and neutralizes IL-6-mediated activity. Other IL-6 inhibitors currently being investigated for the treatment of RA include Sirukumab, Olokizumab, Clazakizumab, and Sarilumab, other biologics that specifically target the IL-6 pathway. Sarilumab has significantly higher affinity compared to Tolimumab, has a longer half-life, allows for less frequent dosing (every two weeks instead of weekly), and holds great promise in the IL-6 blocker class \(^ {100-101}\).

Regarding other targeted cytokines for the treatment of RA, such as daratumumab, which is an anti-CD38 monoclonal antibody. Data from experiments conducted by Suzanne Cole and Alice Walsh et al. showed that daratumumab ablates plasma cells and plasma mother cells in peripheral blood mononuclear cells of RA patients in a dose-dependent manner under ex vivo conditions. However, the efficacy and safety of daratumumab for RA patients still need to be confirmed \(^ {102}\).

In RA, FLS has long been considered an attractive therapeutic target, yet there are no approved therapies that directly target FLS. A study from Harvard Medical School showed that knocking out the gene for Notch3 or blocking NOTCH3 signaling in mice reduced inflammation and prevented joint damage in inflammatory arthritis. NOTCH3, as a Notch signaling pathway receptor highly selectively expressed in FLS, may play an important role in mediating Notch signaling in FLS. NOTCH3 signaling contributes to the differentiation of mural cells and THY1-expressing subintimal fibroblasts, a step that is required for the development of inflammatory arthritis. NOTCH3 may be a key receptor in the differentiation and pathological expansion of FLS in RA and is expected to be a potential therapeutic target for RA \(^ {103}\).

A novel bionic therapeutic strategy for RA is to wrap IFN-γ and rapamycin-induced regulatory phenotypes of FLS-derived cell membranes on nanoparticles called FIRN. The use of FLS cell membranes as a shell for nanoparticles provides a unique targeting ability to RA-inflamed joints due to its isotype targeting ability. The application of the cell membrane as a shell preserves the anti-inflammatory properties of FLS induced by IFN-γ and rapamycin in vitro while avoiding the introduction of the pro-inflammatory properties of IFN-γ on FLS. FIRN has shown good efficacy, stability, and inflammatory joint targeting ability in mouse models of RA. This finding will facilitate the development of new therapeutic strategies for RA \(^ {104}\).

### 4.2.2.2 Cell transplantation therapy

#### 4.3.2.2.1 Hematopoietic stem cell transplantation (HSCT)

HSCT can be divided into peripheral blood HSCT (the most widely used), bone marrow transplantation (BMT), and cord blood transplantation, depending on the source of the transplant. BMT in a homozygous environment offers theoretically greater healing potential. However, the ongoing risks of allogeneic hematopoietic stem cell transplantation and the uncertainty of its curing ability suggest that a safer procedure should be started. This suggests that the potential of BMT to treat severe RA needs further evaluation \(^ {105}\). RA may
progress even after successful BMT in the presence of complete donor lymphopoiesis. The use of allogeneic BMT as the underlying form of
immunotherapy in established RA may not always be effective in halting the development of joint destruction and deformity \(^\text{106}\). Treatment
of RA has shifted from progressive therapy to more aggressive treatment through cytokine mobilization of blood stem and progenitor cells
while the use of high-dose therapies may be seen as a logical extension \(^\text{107}\). Since 1996, HSCT has been used to treat severe RA.
Autologous HSCT is a relatively safe form of salvage therapy in severe drug-resistant RA. Although the procedure is not curative, recurrent or
persistent disease activity can subsequently be controlled in some patients on anti-rheumatic drugs (DMARD) \(^\text{108}\). Clinical evidence
suggests that in patients with severe RA, HSCT is relatively well tolerated and maintains remission in the short term. However, patients need
to receive a cytotoxic regimen before HSCT, which has potential immune complications and a relatively low benefit/risk ratio. Therefore,
HSCT has a limited therapeutic capacity in rare and refractory patients. More importantly, other stem cells have been found to have
immunomodulatory effects without the need for regimen modulation before transplantation. This intense approach may be replaced in the
future by highly effective and low-side-effect cellular therapies \(^\text{3}\).

4.2.2.2.2 Mesenchymal stem cells transplantation

MSC therapy has been used as a cell-based therapy for decades due to its anti-inflammatory, immunomodulatory, and regenerative
properties. Expectations are high, and many ongoing clinical trials are studying the safety and efficacy of MSC for the treatment of arthritic
disease. Most of the studies showing positive clinical results have been in osteoarthritis, and a small number of clinical MSC trials in
patients with RA have also shown some promising results. Thus, establishing MSCs as a promising tool for RA treatment \(^\text{109}\). MSCs can be
derived from different cells: BM, umbilical cord \(^\text{110}\), etc. It was found that long-term MSC cultures could be established from all organs and
tissues studied, regardless of their embryonic origin. The resulting cell population exhibits a prolonged self-renewal capacity and
differentiates along the mesenchymal cell lineage \(^\text{111}\).

BM is the first tissue source used to isolate and expand MSCs for cell-based therapies; therefore, it has been most commonly used as an
animal model for RA. Park et al. were the first human trials to study the outcomes of infusion of human umbilical cord blood mesenchymal
stem cells (hUCB-MSCs) in patients with RA. A single infusion of hUCB-MSCs in RA patients with moderate disease activity was
demonstrated with cell counts up to \(1 \times 10^8\), and no ominous short-term safety signals were observed. In addition, a single infusion of
hUCB-MSCs reduced the mean disease activity of study participants. Data from this trial provide insights and recommendations for future
trials evaluating the safety and clinical efficacy, further facilitating treatment options for hUCB-MSCs infusion in patients with RA in need.
Based on preclinical studies of MSC-based treatments in RA, MSC has consistently demonstrated therapeutic benefit. The findings suggest
that differences in different animal models and treatment protocols need to be considered in future studies using MSC to treat human RA to
maximize the benefits of treatment in the era of precision medicine. The ability of MSCs to modulate the immune response is a safe and
feasible strategy for the treatment of RA. Despite significant differences in tissue source, MHC environment, route of administration, and
animal models used, MSC-based treatments have consistently shown therapeutic benefits in modulating arthritic inflammation. The
optimal time for MSC infusion to achieve high efficacy appears to be in the early stages of inflammation, and further elucidation of this
critical aspect warrants further investigation. MSC-based therapies are rapidly evolving as promising treatment tools for patients with RA
who do not respond to or are intolerant to current treatments, but the evaluation of their long-term efficacy in RA will also need to be
addressed shortly \(^\text{112-113,114}\).

4.2.2.2.3 Induced pluripotent stem cell transplantation

iPSCs are derived from pluripotent stem cells and are commonly used in clinical trials. The iPSCs used for clinical trials can be
classified as autologous iPSCs (derived from the patient's somatic cells), universal iPSCs (generated by genetic manipulation of the HLA
gene) \(^\text{115}\). HLA-matched homozygous iPSCs \(^\text{116}\) and HLA-unmatched homozygous iPSCs \(^\text{117}\). Autologous iPSCs are probably the safest
option, as they should not trigger an immune response. Since iP cells can multiply indefinitely and give rise to all other types of cells in the
body (such as neurons, heart cells, pancreatic cells, and liver cells), they can be used to replace those lost due to injury or disease. iPSCs are
artificially generated from somatic cells by transduction of reprogramming factors, and the advantages of induced pluripotency include the
potential generation of unlimited numbers of desired cells, derivation of cells from difficult-to-obtain tissues, propagation of disease models,
bypassing ethical issues regarding the use of embryonic stem cells, and importantly providing an autologous cell therapy strategy
eliminating the need for immunosuppressive drugs \(^\text{118}\). This means that iPSCs can be induced directly from adult tissues, and they can not
only bypass the need for embryos, but can also be made in a patient-matched manner, which may mean that everyone can have their own
pluripotent stem cell line. This unlimited supply of autologous cells can be used to perform transplants without the risk of immune rejection.
We are now at a stage where PSC-based therapies are in clinical trials, but these are still in their early stages and safety and efficacy remain
key issues \(^\text{119}\).
Autoimmune diseases with limited therapeutic options are potential targets for clinical applications of stem cell and iPSC technologies. iPSCs offer three potential approaches for the treatment of autoimmune diseases; (i) providing pure replacement of lost cells (immune reconstitution); (ii) immunomodulation through in vivo disease processes; and (iii) for in vitro disease modeling. For iPSC treatment of autoimmune diseases, the following aspects can be considered: (i) application of iPSC technology for organ replacement; (ii) for complex autoimmune diseases, unique immunomodulatory therapeutic strategies using cellular components that can be manufactured by iPSC technology; (iii) iPSC technology allows us to generate, differentiate and genetically modify a large number of immune cells that can be used therapeutically; (iv) iPSC technology allows to mimic the growth and development of normal and diseased (based on genetic and epigenetic modifications) cells, the effect of mutations on functional and clinical phenotypes. In the era of personalized medicine, iPSC technology is likely to become a key therapeutic tool for autoimmune diseases 118. For SLE and RA, the mainstay of treatment is the use of immunosuppressive drugs, but true immunomodulation is difficult to achieve in the absence of toxicity. Many important cell populations influence the course of systemic autoimmune diseases, of which iPSC technology can potentially help mimic their effects and ideally contribute to restoring self-tolerance, such as Tregs and dendritic cells. Targeting specific cell lineages, rather than their end products, may also be beneficial for the treatment of other autoimmune diseases 118.

4.3 Advantages and disadvantages

The present study has several unique advantages. First, this paper is the first to systematically analyze the research on cell therapy in RA using a bibliometric approach, which can guide scholars who are concerned with related research. Second, three bibliometric tools were used simultaneously for the survey, and VOSviewer can display large bibliometric maps in an easily interpretable manner 5. CiteSpace's understanding of how transient articles change the dynamics of the knowledge landscape in science is of practical importance to scientists across disciplines 7. The R package is useful in bibliometrics 9. Unlike other techniques, bibliometrics provides a more objective and reliable analysis. A large amount of new information is derived from bibliometrics by providing structured analysis of large amounts of data. Themes of research can also be inferred over time, changes in disciplinary boundaries can be identified to discover the most prolific scholars and institutions, and the "big picture" of existing research can be presented, so our data analysis process is objective and realistic 120. The third, bibliometric analysis provides a more complete insight into hot spots and frontiers than traditional reviews. Fourth, the data sources were all completed within a single day on August 21, 2022, which minimizes the bias caused by frequent database updates. There are some shortcomings in this study. First, the data for this study were only from the WoSCC database, while other databases were ignored and some relevant studies may have been missed. Second, we screened for studies published in English, and studies published in non-English may have been overlooked.

5. Conclusion

Cell therapy has important research value and application prospects in RA. The consistently fluctuating growth in the number of publications indicates that cell therapy in RA research has been receiving attention from scholars worldwide and may continue to remain more or even surpass in the future. The leading countries are the United States and China. However, cooperation and communication between various countries still need to be strengthened, and it is hoped that each country will actively develop an international cooperation network, which will benefit the research of cell therapy in RA. On the one hand, studying the mechanisms of various factors (such as immune cells, immune molecules, cytokines, and inflammatory responses) in the occurrence and development of RA can help us analyze the causes of immune imbalance in RA and facilitate the development of new cellular therapies and the treatment of cell therapy in RA. On the other hand, cell therapy has great advantages over traditional drugs in the treatment of RA, so studying the therapeutic strategy of cell therapy will have important application value for the future precision treatment of RA. It is worth mentioning that, in addition to basic research on cell therapy in RA, its related clinical studies are gradually appearing with some good feedback, and it is reasonable to believe that there should be more and more clinical studies about it in the future.

Abbreviations

RA—Rheumatoid arthritis
WoSCC—Web of Science Core Collection
DMARDs—disease-modifying anti-rheumatic drugs
FLS—fibroblast-like synoviocytes
MSCs—mesenchymal stem cells
iPSCs – induced versatile stem cell
VEGF – vascular endothelial growth factor
TNF – tumor necrosis factor
MTX – methotrexate
HLA – human leukocyte antigen
Treg – Regulatory T cells
Th 17–IL-17 helper T
Bregs – Regulatory B cells
CAR-T – chimeric antigen receptor T
HDACs – histone deacetylases
BTK – Bruton tyrosine kinase
JAK – Janus kinase
HSCT–Hematopoietic stem cell transplantation
BMT–bone marrow transplantation
hUCB-MSCs–human umbilical cord blood mesenchymal stem cells

Declarations

Ethical Approval and Consent to participate
Not applicable.

Consent for publication
Not applicable.

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

Funding
This work was supported by grants from the National Natural Science Foundation (81871292) and the Key Research and Development (R&D) Projects of Shanxi Province (201803D31136).

Authors' contributions
All authors contributed to the study's conception and design. LYM, KX and LXQ had the idea for the article, and material preparation and data collection were performed by LYM and XYH. The first draft of the manuscript was written by LYM and XYH. YLJ, MMZ, YTH, and YNG performed the literature search, XYH and LYM drew the figures, and LYM and KX drafted and critically revised the work. All authors commented on previous versions of the manuscript and approved the final manuscript.

Acknowledgments
We thank all authors who participated in the study of cell therapy in RA.

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**Figures**
Figure 1

Flowchart of publication screening

Retrieval mode: Basic Search
Retrieval database: WeSCC
Retrieval time span: 2007-2022
Retrieval date: August 21, 2022
Retrieval strategy: TS=(cell therapy) AND TS=(rheumatoid arthritis) AND LA=(English)

Exclusion criteria:
- Proceedings of the conference (188)
- Editorial material (128)
- Summary of the meeting (117)
- Book chapters (41)
- Retracted publications (4)
- Letter (47)
- Recension (3)
- Reprint (3)
- Data paper (1)
- Publish online (43)

Step 1: Data collection
A total of 9398 records were identified

Step 2: Data screening
8822 publications were included in our final analysis

Step 3: Bibliometric and Descriptive analysis
The following tools were used:
- VOSviewer, Citespace, R package "bibliometrix" and Microsoft Office Excel 2019

Analysis of publication outputs
Analysis of Journals and Co-Cited Journals
Analysis of the Country and Authors
Analysis of the Corresponding Author’s Country
Analysis of Most Relevant Affiliations
Analysis of the Co-Cited References
Analysis of the Reference with Citation Bursts
Analysis of keywords
Figure 2

Annual production of cell therapy studies in RA
Figure 3

Visualization of journals (A) and co-cited journals (B) on cell therapy research in RA
Figure 4

Biplot coverage of journals in cell therapy studies for RA

Figure 5

visualization of countries on the research of cell therapy in RA
Figure 6

Top 16 countries in terms of publications of papers on cell therapy in RA

Figure 7
Top 9 affiliations of publications and cell therapy in RA by topic

Figure 8
## Visualization of co-cited references for cell therapy studies in RA

**Figure 9**

Top 15 references with strong citation burst

<table>
<thead>
<tr>
<th>References</th>
<th>Year</th>
<th>Strength</th>
<th>Begin</th>
<th>End</th>
</tr>
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Figure 10

Keyword clustering of cell therapy in RA VOSviewer(A), Citespace(B)